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Anaemia and Heart failure

Review Article

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Abstract: Anaemia is one of the most frequent co-morbidities in patients with heart failure. Its prevalence increases from 4% to7% in subjects with asymptomatic left ventricular dysfunction to >30% in patients with severe heart failure. Renal insufficiency, activation of inflammatory mediators and treatment with renin-angiotensin antagonists seem to be its main determinants. The results of many studies agree in providing evidence that anaemia is a powerful independent determinant of survival in patients with heart failure. However, the mechanisms of this relation are still not fully understood. Moreover a favourable effect of the correction of anaemia on prognosis has not yet been shown . Also In addition to this, controlled studies assessing its effects on exercise tolerance have yielded controversial results. Further research is needed to assess the effect of correcting anaemia in chronic heart failure (CHF) patients; ongoing reduction of events with RED-HF (Darbepoetin alpha in heart failure) trial will help define the role.

Keywords: *Anaemia • Heart failure • Erythropoietin*

1. Definitions And Epidemiology

There is not a universally recognized definition of anaemia. The World Health Organization (WHO) defines anaemia as a decrease in haemoglobin (Hb) values below 13 gm/dl in men and 12 gm/dl in women [3]. The National Kidney Foundation defines anaemia as Hb values <13.5 gm/dl in adult men and <12 gm/dl in women (values based on the average of the lower quintile of the standard population) [1]. The third US National Health and nutrition Examination Survey and the Scripps- Kaiser data-base gives this definition of anaemia: haemoglobin < 13.7 and 12.9 mg/dl in white and black men, respectively, and 12.2 and 11.5 mg/dl in white and black women, respectively. The prevalence of anaemia in patients with heart failure (HF) ranges from 7%-10% to 70%-80%. The wide range of reported anemia prevalence is partly attributable to inconsistencies among reports in the definition of anemia and differences in the clinical characteristics (HF severity, demographic variables and comorbidities of the patients) of the population under study [2-4](Table 1).

Almost all currently available data indicate that anemia is common in HF population, with the majority of studies indicating prevalence >20%, and many studies indicating prevalence of nearly 50%. In studies that reported subgroup data, anemia appears to be consistently more highly prevalent in HF patients with advanced age, HF patients with more severe limitations in functional capacity, and HF patients with greater severity of co-morbid chronic kidney disease. These generalizations appear to be consistent in both acute and chronic HF populations, and in patients with impaired or preserved systolic function. Anaemia seems to have more prevalence in patients with heart failure and preserved ejection fraction (HFPEF)[5]. A report from Olmsted County reviewing the trends in the prevalence of anaemia in heart failure between 1979 and 2002 documented an increase in the prevalence of anaemia correlated to the prevalence of heart failure with preserved systolic function.

In a retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD), Al-Ahmad et al. [6] have shown that the prevalence of anaemia could change from 22% to 4% according to differences in the hematocrit threshold value (≤0.39%, corresponding to serum haemoglobin of 13 mg/dl and <0.35%, corresponding to 12 gm/dl, respectively).

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Table 1. Prevalence of anaemia in chronic heart failure.

Author / study(publication year)	Number of patients	Characteristics	Anaemia definition	Anaemia prevalence (%)
Al-Almed / SOLVD (2001)	6.360	CHF, LVEF <35%,Age from 21 to 81 yrs	Hct < 35%	4 to 22
Horwich (2002)	1.061	Heart transplantation evaluation	Hb<12,3g/dl	30
Tanner (2002)	193	CHF	Hb<12 g/dl	15
Kosiborod (2003)	2.281	HF ,age>65 yrs	Hct < 37%	48
Mozaffarian / PRAISE (2003)	1.130	LVEF<30% and NYHA III- IV	Hct < 37,6%	20
Sharma (2004) / ELITE II	3.044	LVEF<40% and NYHA II to IV	Hb<13 g/dl	16,9
Anand (2004) / RENAISSANCE	912	LVEF<30% and NYHA II to IV	Hb <12g/dL	12%
Ezekowitz (2005)	791	CHF	WHO	39
Maggioni (2005) / IN-CHF	2.411	HF	M: Hb<12g/dL F: Hb<11g/dL	15.6
Maggioni (2005)/ Val-HeFT	5.010	CHF, NYHA >II	M: Hb<12g/dL F: Hb<11g/dL	9.0
Kosiborod (2005)	50.405	HF, age>65 yrs	M: Ht <40% F: Ht <37%	M: 61.F: 52.
Go (2006)	59.772	CHF	WHO	42.6
Varadarajan (2006)	2.246	CHF (48% with normal LVEF)	Hb <12g/dL	> 50
Baggish (2007)	690	HF	WHO	44
Tang (2008)	6.159	CHF	M: Hb<12g/dL F: Hb<11g/dL	17. 2

CHF: chronic heart failure, HF: heart failure, NYHA: NewYork heart association class, WHO: World Health Organization, LVEF: left ventricular ejection fraction , M: men, F: female

1.1. Predisposing factors

The prevalence of anaemia increases with HF severity [6]. Left ventricular ejection fraction (LVEF), blood pressure, Brain Natiuretc Peptide (BNP) or NT-proBNP plasma concentrations, are associated to the prevalence of anemia [2-4,7]. LVEF has a reversed behaviour comparing to the others parameters in a wide case study, including patients with preserved left ventricular systolic function. In the CHARM study LVEF has an inverse relationship with serum Hb levels [8].

The patients' demographic characteristics also correlated to the prevalence of anaemia, since it is more frequent in the elderly, female and black patients [9,10]. Comorbidities, namely renal failure and diabetes, are frequently and independently related to anaemia [2-4,7,8,11].

1.2. Recent onset anaemia

New onset anaemia (NOA) frequently develops during the clinical course of HF. The Carvedilol or Metoprolol European Trial (COMET) [7] enrolled 3029 patients who were followed for 58 months. In this trial the incidence of recent onset anaemia was of 14% at 1 year and 27.5% at 5 years. At a multivariate analysis age, high furosemide dose, increase of serum creatinine, hyponatremia, hyperkaliemia, and lack of aldosterone-antagonist administration were predictive factors of recent onset anaemia. Thus other studies showed different predictive factors as low serum albumin, glomerular filtration rate, body weight, diastolic arterial pressure, and an increase in furosemide dose, C-reactive protein, BNP levels and LVEF. These studies also showed that carvedilol [7] and valsartan [11] therapy can be an independent predictor of new onset anaemia.

In a retrospective study [12] reviewing the records of 6159 ambulatory patients with HF, NOA developed in 16% of patients at 6-month follow-up, whereas 43% of patients with anaemia at baseline had resolution of their anaemia. In SOLVD trial [13], NOA developed in 9.6% of patients and was associated with a two-fold increase in the risk of death and in Valsartan heart failure trial (Val-HeFT)[14], NOA developed in 16.9% of patients, and the quartile of patients with the biggest decrease in hemoglobin had 1.6 fold increase in mortality [11].

2. Mechanisms Causing Anaemia In Heart Failure

The pathogenesis of anaemia in patients with HF is multifactorial. The main factors related to anaemia in patients with heart failure are demographic factor such as age, gender, race, water retention, iron deficiency, renal failure, chronic inflammatory activation and concomitant

Table 2. Main factors related to anaemia in patients with heart failure.

Demographic factors (age, gender, race)
Water and salt retention
Iron deficiency
Renal failure
Chronic inflammatory activation
Concomitant treatment
- Angiotensin Converting Enzyme Inhibitors
- Angiotensin receptor blockers
- Non selective beta-blockers (Carvedilol)

treatment with Angiotensin Converting enzyme inhibitors, angiotensin receptor blockers and non-selective beta-blockers (Carvedilol)(Table 2, Figure 1).

2.1. Hemodilution

Anaemia is correlated to HF severity. Patients with HF often show signs of congestion. Water retention and increase in plasma volume can cause"pseudo-anaemia" due to hemodilution [15]. Ritz and colleagues showed that in 97 patients with HF the reduction of glomerular filtration, erythropoietin (EPO) levels and expanded plasma volume were independent predictive factors of low Hb levels. Some studies [16], conducted using the radiolabeled albumin technique, have demonstrated that up to 46% of patients with HF and anaemia have hemodilution along with a normal red blood cells number. In these patients treatment should be diuretic therapy, while erythropoietin administration could increase total blood volume with possible adverse clinical consequences [3].

Westenbrink and colleagues [15] showed that anaemia was not just independently associated with impaired renal perfusion and blunted EPO production, but also with fluid retention. Also Adlbrecht and colleagues [17] conclude that haemodilution appears to be the most potent factor for the development of low haemoglobin levels in patients with a broad spectrum of severity of heart failure and, with minor influence, iron deficiency.

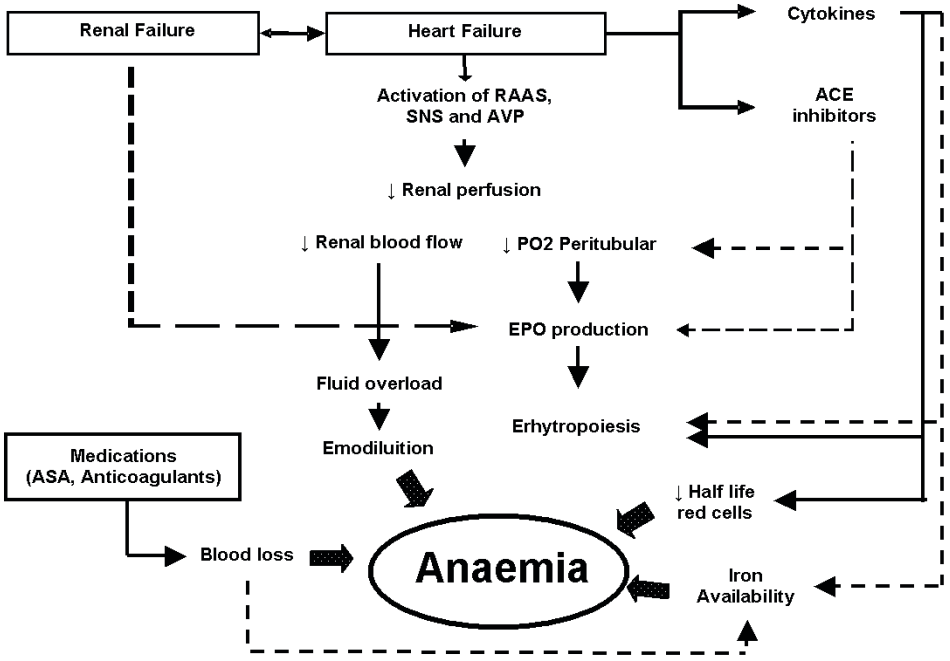
There is a relevant percentage of anaemic patients with HF but without haemodilution. In these patients, the cause is likely iron deficiency, chronic kidney disease, cachexia and angiotensin converting enzyme (ACE) inhibitors therapy

2.2. Iron deficiency

The prevalence of iron deficiency in patients with HF is variable from 30% to 73% [15].

In a recent study [18], 43% of patients had either low serum iron (<8 µmol/l) or ferritin (<30 µg/l), but microcytic anaemia was observed in only 6% patients. In contrast, Nanas et al. [19] found depleted iron stores in the bone marrow of 73% patients despite normal serum iron, ferritin, and erythropoietin. The mean corpuscular

Figure 1. Causes and mechanisms of anaemia in heart failure



RAAS: Renin-Angiotensin-Aldosterone System; SNS: Sympathetic nervous System; AVP Arginine Vasopressin; ACE: angiotensin converting enzyme inhibitor; PO2: oxigen partial pressure; EPO: erythropoietin; ASA: acetyl salicylic acid

Table 3. Effects of cytochines on iron metabolism and erythropoiesi.

Cause	Mechanism	Effects
↑TNF-α, IF-γ, IL-1	↓proliferation and differentiation e ↑ progenitors cells apoptosis; toxic effects induced by free radicals; ↓erythropoietin receptor expression	Erythropoietin resistence; ↓erythropoiesis
↑TNF-α, IL-6, IF-γ, LPS, IL-10	↑ ferritin transcription	↑ferritin
↑TNF-α, IL-6, IF-γ, LPS, IL-10	Red cells demage (free radicals?) ↑red cells fagocitosis by macrophages	↓ half life red cells ↑ storage and iron retention in macrophage ↓sideremy
IL-6	↑Epcidin: ↓iron enteric uptake	↓sideremy
IF-γ, LPS	↑Divalent Metal transporter 1 (DIMT 1), ↓ ferroportin	↓sideremy, ↓ iron availability for progenitor cells

TNF= Tumor Necrosis Factor; IF = interferon; IL = interleukin; LPS= lipopolysaccharides.

volume was at the lower limit of normal, suggesting that microcytic anaemia was not present in all patients.

The reduction of iron absorption was correlated with the inflammatory response in patients with HF and anticoagulant and/or antiaggregant therapy could causes gastrointestinal bleeding. On the other hand, the iron resources in anemic patients with HF could be normal or high because of increased iron uptake and storage in macrophages (reticuloendothelial system) with a consequent reduction of its availability for haematopoiesis [20,21]. Intravenous iron therapy has been shown to increase serum Hb levels (from 11.2±0.7 to 12.6±1.2 gm/dl, p=0.0007) as well as to improve exercise tolerance, quality of life and functional class [22]. B_{12} vitamin and folate deficiency has not a significant role in pathogenesis of anaemia in patients with HF [18].

2.3. Renal failure

Moderate to severe chronic renal failure (glomerular filtration rate <60 ml/min) is one of the main determinants of anaemia [2,3,6,18,24], but also in patients with HF an inverse correlation between serum creatinine and plasmatic Hb has been reported.

Erythropoietin is produced primarily in the kidney by specialized peritubular fibroblasts in the cortex and outer medulla. Low partial pressure of oxygen (PO2) that activates hypoxia-inducible factor-1 in the peritubular fibroblasts is the primary stimulus for erythropoietin production, which induces transcription of the erythropoietin gene [23]. Chronic kidney disease causes anaemia through a reduction in erythropoietin production, although patients with HF can show increased levels of erythropoietin [24-26]. In these patients the main cause of anaemia, similarly to other chronic diseases associated to inflammatory processes, is resistance to erythropoietin effects [20].

2.4. Cytokines

Reduced body mass and cardiac cachexia have been shown to be important predictive factors for anemia in patients with HF [3,8]. The activation of pro-inflammatory cytokines (TNF-α, interleukine-6, interleukine-10, interferon-γ, lipopolysaccharides) is important for both anaemia and cardiac cachexia pathogenesis. Pro-inflammatory cytokines could have many effects: stimulation of erythropoietin, inhibition of gut iron absorption, inhibition of the proliferation of progenitor red cells and increase of apoptosis, red cells damage, erythrophagocitosis, uptakes and storage of iron into macrophages, resistance to erythropoietin. All these effects may ultimately lead to a reduction in erythropoiesis. (Figure 1, Table 3) [27]. Chronic inflammation causes reduced iron availability, that is stored by macrophages of the reticulo-endothelial system [13,28].

2.5. Concomitant therapy

Neuro-hormonal antagonist, ACE-inhibitors and angiotensin II receptors blockers are important causes of anaemia in patients with HF. An analysis of the SOLVD study [13] has shown as enalapril is an independent predictive factor for low Hb levels. The Valsartan Heart Failure (VAlHeFT) trial [14] has confirmed these data for angiotensin II receptors blockers. Angiotensin II increases erythropoietin secretion through hypoperfusion and renal hypoxia and, thus, can directly stimulate erythropoiesis [29]. Antagonists of renin-angiotensin system, blocking the effects of angiotensin II, also reduce erythropoiesis. Moreover, ACE catalyzes the demolition of *N*-Acetil-seril-lisil-proline (Ac-SKPD), a tetra peptide inhibitor of the proliferation of haematopoietic stem cells. ACE inhibitor administration causes an increase in the plasmatic concentrations of this substance with a consequent development of anaemia [30].

Differences between beta-blockers may also be important. An analysis of the Carvedilol or Metoprolol European Trial (COMET)[7] has shown as carvedilol

Table 4. Negative effects of anaemia on outcome in patients with heart failure.

Myocardial hypertrophy
Reduced oxygen uptake in peripheral tissues
Increased cardiac output
Neuro-hormonal activation
Worsening renal failure
Edema and fluid retention induction

therapy is associated with a slight but significant Hb decrease (0.2 gm/dl) compared to metoprolol therapy. Renal cells secreting erythropoietin or progenitor red cells have sympathetic innervation with beta-1, beta-2, and alpha-adrenergic receptors [31]. Beta-2 receptors have the most important role and carvedilol could cause a decrease in Hb levels through its non-selective action on beta-2 adrenergic receptors.

2.6. Compensatory mechanisms and pathophysiological consequences of anaemia

Non-hemodynamic responses to anaemia include increase in erythropoiesis to enhance oxygen carrying capacity, and increase in red blood cells (RBC) 2,3-diphosphoglycerate that shifts the hemoglobin-oxygen dissociation curve to the right and improves oxygen delivery to the tissues. Because erythropoiesis is defective in HF, hemodynamic responses may predominate. In chronic severe anaemia, low Hb reduces systemic vascular resistance (SVR) as the result of decreases in blood viscosity and enhanced nitric oxide-mediated vasodilation [32,33]. Low SVR reduces blood pressure (BP) and causes baroreceptor-mediated neurohormonal activation as in low output HF [34]. The increased sympathetic and renin-angiotensin activity decreases renal blood flow (RBF) and glomerular filtration rate, resulting in salt and water retention by the kidneys and expansion of the extracellular and plasma volumes. The combined effect of volume expansion and vasodilation increases the cardiac output, which may help to increase oxygen transport [35]. Correction of anaemia in patients with normal LV function causes a rapid and complete regression of the syndrome of high output HF [36]. Although these hemodynamic and neurohormonal responses were observed in patients with severe anaemia, it is unclear whether these mechanisms are also operative in HF patients with less severe anaemia.

3. Anaemia and Clinical Outcomes

Many retrospective analyses of clinical trials have shown that reduced Hb levels are independently associated with an increased risk of hospitalisation and mortality in patients with HF [2-4,7-11,16,37-39].

A recent re-analysis of SOLVD trial shows that anaemia is also an independent risk factor related to new onset kidney disease [40]. Some studies have demonstrated that anaemia was an independent predictor for HF mortality but not for sudden cardiac death [7]. Anaemia is associated with poor outcome not only in patients with LV systolic dysfunction, but also in patients with asymptomatic LV dysfunction [6,41] or with preserved LVEF [8,42].

Anemia in patients with LV systolic dysfunction is associated with impaired exercise capacity [4,29,43], worse NYHA functional class [9] and renal function [44]. Patients with anaemia with moderate or severe HF show shorter distances in the 6-minute walk test [45], and they achieve lower peak oxygen consumption than patients without anaemia [9,45], even if the LVEF is similar in both groups. In some studies, including sub analyses of large clinical trials (the Evaluation of Losartan in the Elderly II [ELITE II], the Prospective Randomized Amlodipine Survival Evaluation [PRAISE], the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines [RENAISSANCE], and SOLVD), anaemia has been identified as a powerful independent risk factor for increased hospitalization and mortality [9,10,37,42,46].

There is a linear relationship between reduced Hb serum levels and increased mortality risk: a 1-mg/dl decrease Hb levels has been associated to an increase in mortality of 13% (relative risk [RR], 1.13; 95% confidence interval [95% IC], 1.045-1.224) [3].

Similar results were reported in a study by Mozaffarian and colleagues [10], who showed that patients with anaemia with severe HF (hematocrit ≤0.375) had an approximately 60% higher risk of death compared with patients who did not have anaemia. This relation between anaemia and increased mortality has not only been observed in patients with severe HF but also in those with asymptomatic, mild to-moderate HF and new-onset HF [47].

There is usually a linear relationship between high Hb levels and reduced mortality and morbidity risk. However, Sharma et al. [37] in the "Evaluation of Losartan in the Elderly II" (ELITE II) trial showed a U-shaped relation between Hb concentration and mortality risk. The lowest mortality risk was observed in the Hb range of 13 to 16 g/dl and the risk increased with Hb concentrations below

Table 5. Summary of the studies with erythripoiesis stimulating agents.

Author,Year	StudyDesign	InclusionCriteria	Patients(n)	Base-line Hb (g/dl)	Achie-ved Hb (g/dl)	Agents andDose Used	Outcomes
Silverberg , 2000	Single-center,uncontrolled, open-label	EF <35, Hb<12 g/dl	26	10.2	12.1	S/C epoetin alfa (mean 5,277 IU/week) + IV iron sucrose (mean 185 mg/ month)	↓NYHA class (3.7 ± 0.5 to 2.7 ± 0.7, p < 0.05), ↑LVEF (28 ± 5% to 35 ± 8%, p < 0.001).Decrease in diuretic dose and hospitalizations
Silverberg, 2001	Single-center, randomized, no placebo, open-label	NYHA class III/IV, EF<40%, Hb 10–11.5g/dl	16 usual care, 16 EPO	10.3	12.9	S/C epoetin alfa (4,000 IU 1–3 x week) IV iron sucrose (200 mg/2 x weeks)	↓NYHA class, ↑LVEF +5.5%. Decrease in diuretic dose and hospitalizations
Mancini, 2003	Singlecenter, single blind, randomized, placebo-controlled	NYHA class II/IV, Hct <35%,	9 control, 17 EPO	11.0 ±0.6	14.3 ± 1.2	S/C epoetin alfa 15,000 to 30,000 IU/ week + oral iron 325 mg and folate 1 mg OD	↑ Peak VO2 11 ± 0.8 to 12.7 ± 2.8 ml/kg/ min(p < 0.05), ↑ 6MWDImprovement in MLHFQ
Palazzuoli, 2007	Singlecenter, randomized, doubleblind, placebo-controlled	NYHA class III/IV,EF<40%, Hb9.0–12.0 g/dl, Cr 1.5–3.0 mg/dl	25 control, 26 beta EPO	10.4 ± 0.6	12.4±0.8	S/C epoetin beta 6,000 IU/2 x week + oral iron 300 mg for 1 year	↑LVEF, ↓LV volumes, mass ↓PAP and BNPNo change in Cr
Ponikowski, 2007	Multicenter, randomized, double-blind, placebo-controlled	Hb 9.0–12.0 g/dl, peak VO2 <16ml/kg/min	22 placebo, 19 darbepoetin	11.8±0.2	13.9 ± 0.4	Darbepoetin alfa, 0.75μg/kg Q2W +200–300 oral iron if serum ferritin<800 ng/ml	Mean change in peak VO2 (45 ml/min, p = 0.27) ↑PGA(79% vs. 41%, p = 0.01) No change in KCCQ/MLHFQ. No change in BNP or Cr
Van Veldhuisen,2007	Multicenter,randomized, double-blind, placebo-controlled	Hb>9.0 and<12.5 g/dl, NYHA class II/III, CHF, LVEF <40%	55placebo, 110 darbepoetin (56 weight based, 54 fixed dose)	11.5	13.3	Darbepoetin weight adjusted 0.75 μg/kg vs. fixed dose 50 μg vs. placebo Q2W + oral iron (200 mg OD if serum ferritin<800 ng/ml)	Rate of rise Hb 1.87 vs. 1.64 g/dl in weight basedvs. fixed dose (p = 0.07), ↑ in KCCQ (p <0.03), no significant ↑ in 6MWD (p =0.074), patients global assessment (p = 0.057), NYHA class, LVEF, or MLHFQ score
Ghali, 2008 (STAMINA-HeFT)	Multicenter,randomized, double-blind, placebo-controlled	Hb>9.0 and<12.5 g/dl, NYHA class II/IV, CHF, LVEF _40%,	157 placebo, 162 darbepoetin	11.4	13.4 at 27 weeks,13.4 at 53 weeks	Darbepoetin dose 0.75μg/ kg Q2W vs. placebo + oral iron (200 mg OD if serum ferritin<800 ng/ml)	No significant difference in exercise duration,NYHA class or quality of life scores at 27 weeks but trend to a ↓ in combined end point of death and hospitalization for HF
Van Veldhuisen and McMurray 2007	Combined safety analysis	Hb >9.0 and<12.5 g/dl, NYHA class II/III, CHF, LVEF <40%	209 placebo, 266 darbepoetin	11.4 ±0.8	13.4	Darbepoetin 0.75μg/kg vs. placebo Q2W+ oral iron (200mg OD if ferritin <800ng/ml)	Trend to ↓combined endpoint of death and hospitalization for HF for darbepoetin vs. placebo OR 0.67 (0.44 to 1.03), p = 0.06

CHF : congestive heart failulre; EF : ejection fraction; EPO : erythropioetin; Hct : hematocrit; HF : heart failure; Hb : hemoglobulin; IV : intravenous; KCCQ : Kansas City Cardiomyopathy Questionnaire; LV : left ventricular; MLHFQ : Minnesota Living with Heart Failure Questionnaire; NYHA : New York Heart Association; OD : once daily; PAP : systolic pulmonary artery pressure; PGA : Patient's Global Assessment; Q2W : every 2 weeks; S/C : subcutaneous; 6MWD : 6-min walk distance.

or above this range. Therefore, there is a concern that excessive increases in haemoglobin may be associated with increased mortality [23]. Go and colleagues [4] in 59 772 patients with HF showed an increased mortality risk with Hb levels >17 gr/dl. However, other comorbidities (such as chronic obstructive pulmonary disease (COPD)) could have influenced the outcome, especially in the elderly patients.

Changes in Hb levels during the clinical course of HF could influence the prognosis. Results from COMET trial have shown that patients with a 2-3 gr/dL decrease in serum Hb have an increased mortality risk of 47% (RR, 1.466; 95%IC, 1.092-1.969; p=0.0109), while a Hb reduction ≥3 gr/dl was associated to a three fold greater mortality rate (RR, 3.37; IC95%, 2.464-4.611; p<0.0001) [7].

There are other haematological parameters that could be prognostic predictors despite anaemia; recently Pascual- Figaland and colleagues [48] in a study of 628 patients hospitalized with acute HF showed higher red blood cell distribution with (RDW) levels were associated with a worse long-term outcome, regardless of haemoglobin levels and anaemia status.

3.1. Negative mechanisms of anaemia in-patient with HF

Anaemia causes many negative effects on outcome in-patient with HF such as myocardial hypertrophy, neuro-hormonal activation, and fluid retention, reduces oxygen uptake in peripheral tissues and makes worse renal failure (Table 4).

3.2. Myocardial Hypertrophy

The increased myocardial workload, due to hemodynamic and neurohormonal alterations observed in chronic anaemia, could cause adverse LV remodelling. A sub-study of the RENAISSANCE trial reported that in patients with LV systolic dysfunction, an increase in haemoglobin over the 24-week study period was associated with a significant decrease in LV mass index (LVMI), whereas in those whose haemoglobin concentration either decreased or remained the same, an increase in LVMI was shown [42]. In this study, an increase in haemoglobin of 1.0 g/dL over a period of 24 weeks was associated with a reduction in LVMI of 4.1 g/m^2. These evidences are confirmed also in general population without cardiovascular disease or hypertension and anaemia has been linked to the development of LVH and to an increased LVMI [49-54].

Haemoglobin may be inversely related to EF [7,55], and whereas anaemia is related to brain natriuretic peptide (BNP), a marker of LV dysfunction, anaemia remains an independent predictor of adverse outcomes in the presence of BNP and EF, suggesting that these variables may have their effect through different mechanisms.

3.3. Oxygen uptake in peripheral tissues

The decreased availability of oxygen substrates to the peripheral tissues represents another effect of anaemia. In patients with anaemia and HF the reduced cardiac output cannot compensate for the reduced Hb levels and this could explain the more severe symptoms of anaemic patients, with a more severe impairment in exercise capacity and a greater risk of rehospitalisation [9]. A positive correlation has been shown between peak VO2 and serum Hb values [56,57]. The administration of erythropoiesis stimulating agents (ESA) has been related to an improvement in exercise capacity either in patients with renal failure [58] or in patients with HF [22,43,59].

The reduced peripheral oxygen demand can lead to an increased cardiac work with a consequent myocardial ischemia and LV remodelling increasing mortality and cardiovascular hospitalization [3,4].

3.4. Other Mechanisms

In addition, anaemia is often associated with poor nutritional status, low albumin [7,55], and cardiac cachexia [60], all of which could worsen outcomes. Finally, anaemic patients have worse neurohormonal and proinflammatory cytokine profile that may also contribute to worse outcomes. Thus, although anaemia may be related to a worse prognosis through multiple mechanisms, it is not clear whether anaemia is a mediator or just a marker of poor outcomes.

4. Treatment Approaches

4.1. Hemotrasfusion

According to the American Guidelines, blood transfusion is recommended for Hb levels in the range from 6 to 8 gr/dl thus the clinical utility of hemotrasfusion for higher Hb levels is not well defined. Generally, haemotransfusion is not considered for Hb values >10 gr/dl [61].

In 78 974 elderly patients hospitalised with acute myocardial infarction, blood transfusion was associated with a lower mortality rate at 30 days in patients with a hematocrit < 30% on admission [62]. Conversely, in 838 patients (26% with cardiovascular disease), stable Hb levels between 10-12 gr/dl did not provide additional benefits on mortality compared with Hb concentration of 7-9 gr/dL [63].

Moreover, the blood transfusion may be associated with some adverse effects such as suppression of the immune system, increased infection risk, iron overload and the sensitization to HLA antigens [64]. Transfusion may be considered only an acute phase treatment for severe anaemia and it is not available as a long-term therapeutic strategy.

4.2. Iron Therapy

It is commonly accepted that patients with chronic HF have relative iron deficiency [3,28]. Total body iron may be normal. However, iron is stored in the reticular endothelial system, being not available in tissue so that it could not be used for eythropoietic process.

Current guidelines from the National Kidney Foundation recommended the use of intravenous iron (because of the reduced enteric uptake) to maintain serum ferritin level from 100 to 800 ng/ml and a transferrin saturation from 20% to 50% to optimize the response to eythropoietic agents [1]. But iron therapy at high doses has severe side effects such as a greater oxidative stress on the endothelial tissue and the atherosclerosis progression [65].

In four small studies conducted on patients with systolic heart failure, intravenous iron replacement suggested a beneficial effect. Two open-label studies, one on 16 patients [22] showing improvement in symptoms and exercise capacity and the other on 32 patients with chronic kidney disease, demonstrated an improvement in cardiac remodelling and New York Heart Association (NYHA) class [66]. In two randomized studies, one on 40 patients [67] demonstrated an improvement in ejection fraction, NYHA functional class, exercise capacity, renal function and quality of life, and in the other randomized trial of 35 patients, there was evidence for an improvement in exercise capacity in anaemic patients without improvement in haemoglobin [68].

4.3. Erythripoiesis stimulating agents

The kidney produces erythropoietin, the primary regulator of erythropoiesis, and levels vary inversely with oxygen availability. In patients with HF serum erythropoietin levels may be increased, compared to normal values, and is correlated to a more severe outcome [24]. Infact anaemic patients with HF have erythropoietin values lower than patients without HF but same serum Hb values [15,28,69]. Besides, patients with HF develop a resistance to erythropoietin effects. This is mainly caused by the activation of many inflammatory molecules and treatment with inhibitors of Renin-Angiotensin system [29]. These data suggest an important role for therapy with exogenous ESA associated with iron supplementation in patients with anaemia and HF.

4.4. Available agents

There are three currently available eythropoietic agents for the treatment of anaemia: epoetin-α, epoetin-β (both of which are recombinant human erythropoietin, rHuEpo) and darbepoetin-α (analog of human erythropoietin). These agents can be administered either by intravenous or subcutaneous administration. Plasma half-life of epoetin-α and epoetin-β after intravenous dosing is 6 to 8 hours, after subcutaneous administration the plasma half-life is increased to more of 24 hours. Epoetin-α and epoetin-β are administered subcutaneously from once to three times per week. The Darbapoetin-α has a stronger affinity for erythropoietin receptors and longer plasma half-life of approximately 48 hours, with consequent longer dose intervals (1 to 2 weeks) during maintenance therapy [1,3].

4.5. Clinical efficacy: studies with rHuEpo

The effect of rHuEpo treatment in anaemic patients with HF was first reported by Silveberg et al. [44] in 2000. Twenty-six anaemic patients with advanced HF and haemoglobin <12 g/dl were treated with subcutaneous rHuEpo and intravenous iron sucrose, with seven months of mean follow-up duration. RHuEpo therapy increased mean haemoglobin from 10.2 g/dl to 12.1 g/dl, it was associated with an improved of New York Heart Association (NYHA) functional class, increased LVEF (28±5% at baseline to 35±8%, p<0.001), it reduced need of intravenous furosemide and hospitalization rate [70]. The same investigators reported that in a randomized open label trial (32 patients) rHuEpo therapy significantly decreased hospitalization days [69].

Mancini et al. [43] conducted a single-blinded, randomized, placebo-controlled trial of rHuEpo therapy in twenty-six patients with advanced HF and anaemia (hematocrit <35%). Patients received subcutaneous rHuEpo 5000 U three times per week and supplemental oral iron and folate, adjusted to raise hematocrit to >45%. Compared with the placebo group, rHuEpo therapy was associated with significant increase in Hb values from 11.0±0.5 to 14.3±1.0 g/dL, with a concomitant increases in treadmill exercise duration and peak oxygen uptake (11.0±1.8 to 12.7±2.8 ml/min per kilogram, p<0.05). The increases in Hb levels were linearly associated with the increase in peak oxygen uptake.

The Palazzuoli's study with a small number of patients with HF and anaemia demonstrated clinical benefits of rHuEpo therapy [70]. Forty patients with

severe HF were randomized to receive, in a double blind fashion, either subcutaneous rHuEpo for three months twice weekly, or placebo (saline solution). The treated group showed a significant increase in Hb values (from 10.4±0.6 to 12.4±0.8 g/dL, p<0.01), in NYHA functional class (from 3.5±0.6 to 2.8±0.5, p<0.05) and peak oxygen consumption (from 12.8±2.8 to 15.1±2.8 ml/Kg per minute, p<0.05). There was also a significant fall in plasma B-type natriuretic peptide levels, in serum creatinine and an increase in estimated creatinine clearance.

4.6. Studies with Darbapoetin-α

In patients with and anaemia, darbapoetin-α produced a stable increase in Hb concentration. Ponikowski's randomized, placebo-controlled trial [59] showed in 41 patients with HF anaemia after the treatment with darbapoetin-α, once every 2 weeks for 26 weeks an increase in Hb values from 11.8±0.2 to 13.9±0.4 g/dl and from 11.6±0.2 to 12.3±0.4 g/dL in placebo group. Patients with darbapoetin-a treatment had also an improvement in quality of life, evaluated by patients' Global Assessment; peak VO2 was increased about 0.5 mg/Kg per minute in darbapoetin-a arm, versus 0.1 mg/Kg per minute in placebo group (p=0.40) and no significant correlation in Hb concentration and exercise tolerance was shown [59]. Thus these results study were in contrast with Mancini's data [43]. The different protocol used (single-blind in Mancini's study, double-blind in Ponikowski's study), the greater change in Hb concentration in Mancini's data, the homogeneity of the sample and severity of HF of patients enrolled in the Mancini's study conducted to different results according with other studies of rHuEpo treatment [44,69,70].

A combined analysis of two randomized double-blind, placebo-controlled trials (Van Veldhuisen, McMurray e al. [71]) with darbapoetin-α versus placebo on 475 patients not show a statistically significant improvement of NYHA class and Quality of Life. Despite small sample size, it is observed a trend in decreasing the risk of composite outcome (death or HF hospitalization) and mortality rate in darbapoetin-α group versus placebo group (39 of 266, 15% vs 46 of 209, 22%; HR 0.67, 95% CI 0.44-1.03, p=0.06) and a trend to a less mortality in the darbapoetin-α treated patients (6% vs 9%; HR, 0.76).

Van Veldhuisen et al. [72] in a study of 2007 randomized patients with CHF , LVEF <40%, and Hb 9.0 to 12.5 g/dL, who received darbepoetin alpha subcutaneously every 2 weeks for 26 weeks at a starting weight-adjusted dose of 0.75 mcg/kg (n =56) or a fixed dose of 50 mcg (n = 54), or placebo (n = 55), to gradually achieve and maintain a target Hb of 14.0+1.0 g/dL [72]. Rate of Hb rise was equivalent between darbepoetin alpha weight-based and fixed dosing groups, vs in the placebo group. Mean Hb concentrations by week 27 were 13.4 and 13.2 g/dL, in the weight-based and fixed dosing groups, respectively. There were non-significant improvements in the combined darbepoetin alfa group vs. placebo for 6 min walk distance (P = 0.074) and Patient's Global Assessment score (P = 0.057). There was a significant improvement in Kansas City Cardiomyopathy Questionnaire total symptom score (8.2 vs.1.5 points; P = 0.027) but no change in NYHA class, LVEF, and Minnesota Living With Heart Failure Questionnaire score. Six treatment-unrelated deaths occurred in the 110 darbepoetin alpha treated patients, and none in the 55 placebo treated patients. Other adverse events were similar between groups.

In conclusion in this study of patients with CHF and anaemia, treatment with darbepoetin alpha raised Hb using different dosing regimens. Darbepoetin alpha improved some quality of life indices, but its safety requires further exploration [72].

Also in the Study of Anaemia in Heart Failure Trial (STAMINA-HeFT) of 2008 [73], patients (N=319) with symptomatic HF, left ventricular ejection fraction <40%, and haemoglobin >9.0 g/dL and <12.5 g/dL were randomized (double-blind) to placebo (N=157) or darbepoetin alpha (N=162) subcutaneously every 2 weeks for 1 year (target haemoglobin, 14.0 ± 1.0 g/dL). The primary end point was change from baseline to week 27 in treadmill exercise time. Secondary end points were change from baseline in New York Heart Association class and quality of life at week 27. An additional prespecified efficacy analysis included the time to death by any cause or first HF-related hospitalization by 1 year. At baseline, the median (interquartile range) haemoglobin was 11.4 (10.9, 12.0) g/dL. At week 27, darbepoetin alpha treatment increased median (interquartile range) haemoglobin by 1.8 (1.1, 2.5) g/dL. Of the patients treated with darbepoetin alpha, 85% achieved 2 consecutive haemoglobin levels of 14.0 ± 1.0 g/dL during the study and experienced a haemoglobin increase of >1.0 g/dL from baseline. By intent-to-treat analysis, darbepoetin alpha treatment did not significantly improve exercise duration, New York Heart Association class, or quality of life score compared with placebo. A non-significant trend was observed toward a lower risk of all-cause mortality or first HF hospitalization in darbepoetin alpha–treated patients compared with placebo (hazard ratio, 0.68; 95% CI, 0.43, 1.08; P=. 10). Occurrences of adverse events were similar in both treatment groups [73](Table 4).

A large-scale and mortality trial with anaemia and HF (Reduction of Events with Darbapoetin-α in Heart

Failure, RED-HF) is on going to shown the effects of darboepoietin-α on outcome.

4.7. Optimal target level of Hb

On November 2006 were published two large-scale, controlled studies with erythropoiesis stimulating agents in patients with chronic kidney disease (CKD) (Correction of Haemoglobin and Outcomes in Renal Insufficiency [CHOIR] and Cardiovascular Risk reduction by Early Anaemia Treatment with Epoetin beta [CREATE]) [74,75]. They were prematurely stopped because of an increased mortality [71,76]. In CHOIR, 1 432 patients with Anaemia and renal insufficiency (23% patients with a history of HF), were treated with two different erythropoietin regimes to reach Hb target levels of 13.5 g/dl or 11.3 g/dl. During a median follow-up of 16 months, the higher Hb target group had an increase of composite endpoint (death, myocardial infarction, hospitalization for HF and stroke) (HR, 1.34; p=0.03). Besarab et al. [77] prematurely stopped their study because of a trend in increased risk of the composite end point (death or nonfatal myocardial infarction) in higher hematocrit group (HR, 1.3; 95% CI 0.9-1.9).

Differently, in CREATE study [74] (603 patients with anaemia and renal failure, 33% with HF), there was not an increase in cardiovascular events rate in patients with target Hb levels after epoietin- β treatment (target levels 13.0-15.0). More patients in the higher Hb values group required hemodialysis and showed higher blood pressure but they less frequently developed acute HF. Similarly, in another study on diabetic patients [46], the quality of life was improved in the higher haemoglobin treatment group [75].

After these evidences on 9 march 2007 Food and Drug Administration (FDA) avoid the achieve Hb levels >12 g/dl and to stop erythropoietin therapy with Hb values > 12 g/dl administering low dose of erythropoiesis stimulating proteins to hemotransfusions that were recommended with Hb values< 10 gr/dl [76]. The National Kidney Foundation recommends to achieve a value of serum Hb of 11-12 g/dl [1,76].

4.8. Adverse events of erythropoiesis stimulating agents administration

The increased cardiovascular events rates in patients with high level of Hb after erythripoiesis stimulating agents therapy may be due to increased blood viscosity and high blood pressure [71].

The increased blood viscosity associated with high hematocrit in patients with diffuse atherosclerosis and kidney disease, increases thrombosis events. Direct effect of erythropoietin on platelets and endothelium increases the thrombotic risk [78]. These evidences are not be confirmed in patients with HF because the frequent concomitant therapy with antiplatelet and anticoagulant medications may reduce prothrombotic effects of eythropoietic agents [71].

rHuEpo therapy causes an increased blood pressure by increased blood viscosity, altered neurohormonal system, and direct effects on microvascular structure and function. However, blood pressure was significantly increased in a single study [75] and in patients with HF no changes in blood pressure or in peripheral resistances are observed after erythropoietin therapy [76].

In a meta-analysis, Bo Jin and collegues [79] suggests a symptomatic improvement in anaemic patients with CHF receiving ESA and a non significant reduction in all-cause mortality in the ESA treatment group compared with the control group. These outcomes are in contrast with studies in cancer and kidney disease and support a large phase III morbidity and mortality trial in anaemic patients with CHF.

Several studies have confirmed that ESAs decrease experimental infarct size, reduce hypoxic injury, prevent myocyte apoptosis, and mobilize endothelial progenitor cells, independent of increases in Hb. It is therefore possible that the beneficial effects of ESA are related to their non hemopoietic effects and not to an increase in Hb.

In fact Erythropoietin (EPO) is not solely a hormone charged with regulating the proliferation and differentiation of erythroid cells. Indeed, EPO is synthesized locally by many cells, especially under conditions of stress or injury. In these paracrine/autocrine settings, EPO plays a crucial protective–restorative role, activating cytoprotection (e.g., in the brain, heart, and kidney), reducing inflammatory responses, preserving vascular integrity, and mobilizing stem cells, including proliferation and differentiation of endothelial progenitor cells. The following actions play a role in protection from acute cardiac injury and can exert a beneficial effect in HF: (a) antiapoptotic effect, (b) mobilization of endothelial progenitor cells from bone marrow, and (c) anti-hypertrophic effects [80].

4.9. Anaemia ed heart failure with preserve ejection fraction

Multiple previous studies have demonstrated a relationship between anemia and adverse outcomes in heart failure [81-88]. Such studies have generally used data from randomized trials or population-based studies using administrative databases. Two previous studies have included patients with heart failure in the setting of preserved LV function [85]. In a single center study of

anemia in an unselected heart failure population with a mean EF of 42%, anemia was found to be a significant predictor of adverse outcomes, but the data were not analyzed by EF [89]. In a large study of administrative data from heart failure hospitalizations, Kosborod et al. [85] found anemia to predict both rehospitalization and mortality. Thirty-six percent of patients in this cohort had an EF greater than 40%, but the role of anemia was not assessed by EF. A small study by Brucks et al. [90] of 137 patients with clinical heart failure and EF 50% demonstrated a prevalence of anemia of 42% and a non-significant trend toward worse survival in the anemia group. While the data of Felker et al. [91] describe an increase of mortality associated with anemia in the epidemiologically important population of patients with heart failure in the setting of preserved LV function. Also in retrospective studies of Tehrani et al. and Shamagian et al. [92,93] anemia is associated with an increased long-term mortality rates in patients who have diastolic heart failure and in addition, in the study of Tehrani anemia appears to be an independent predictor of worse outcome in elderly (age > 75 years) HF patients.

5. Reccomendations and Future Directions

The role of anaemia as an independent prognostic factor is accepted. Anaemia is frequent in patients with advanced HF and aetiology is generally multifactorial. It is not only related with impaired renal perfusion and kidney failure, but also it could be triggered by a hyperinflammatory state or by the RAA-system inhibitors therapy. The prognostic value of anaemia is not clear and there are no evidences about the correction of low Hb values and improving survival rate in patients with HF. The administration of Erithropoietic stimulating agents remains the more effective therapy to improve Hb serum level.

According to the 2008 Guidelines about the diagnosis and treatment of chronic HF of European Society of Cardiology (ESC), anaemia is an independent risk factor for hospital admission and mortality. Correction of anaemia has not been established, as routine therapy in HF. Simple blood transfusion is not recommended to treat the anaemia of chronic disease in HF. Among potential therapies, the use of erythropoietin- stimulating agents, usually together with iron, to increase red blood cell production represents an unproven option.

In HF patients with moderate-to-severe anaemia (Hb < 11 gr/dL), current guidelines of FDA and of National Kidney Foundation recommend treatment to target value of 10-12 gr/dl to improve the quality of life. However, there are no clinical data supporting the use of ESA to improve the outcome in HF patients. Large trials with long-term follow up are needed to determine the effects on morbidity and mortality [71].

There are several critical questions that need to be addressed, including the relevance of hemodilution as a cause, the ideal imitating as well as target haemoglobin levels. Preliminary evidence provides encouraging signals for the use of ESAs to correct anaemia in heart failure. RED-HF trial will help define that role.

ESA may have antiapoptotic and anti-ischemic effects with a pro-angiogenic activity on endothelial cells [4,94-97]. Cytoprotective and antiapoptotic effects have been shown [98,99] as well as a beneficial action on central nervous system injury and in experimental models of myocardial hypoxia. These evidences showed the possibility that derivatives of rHuEpo may be useful to protect cardiomyocites by ischemic injury and to improve the myocardial function in patients with HF, rather than reducing other co-morbidities.

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