Role of Iron Deficiency and Anemia in Cardio-Renal Syndromes

Philipp Attanasio, MD,* Claudio Ronco, MD,† Stefan D. Anker, MD, PhD,‡ Mariantonietta Cicoira, MD,§ and Stephan von Haehling, MD, PhD*

Summary: Chronic heart failure is a common disorder associated with unacceptably high mortality rates. Chronic renal disease and anemia are two important comorbidities that significantly influence morbidity and mortality in patients with chronic heart failure (CHF). Progress in CHF again may cause worsening of kidney function and anemia. To describe this vicious cycle, the term cardio-renal anemia syndrome has been suggested. Iron deficiency is part of the pathophysiology of anemia in both CHF and chronic kidney disease, which makes it an interesting target for treatment of anemia in cardio-renal anemia syndrome. Recently, studies have highlighted the potential clinical benefits of treating iron deficiency in patients with CHF, even if these patients are nonanemic. This article summarizes studies investigating the influence of iron deficiency with or without anemia in chronic kidney disease and CHF and gives an overview of preparations of intravenous iron currently available.

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C hronic heart failure (CHF) is a common disorder. In industrialized countries the prevalence is approximately 1% to 2%, increasing to up to 10% and higher among persons aged 70 years or older. About 14 million patients in the European Union suffer from at least some degree of CHF. Patients with CHF still show unacceptably high mortality rates. To improve survival rates, the identification of comorbidities that add up to the overall mortality is crucial. Therefore, progress has been made in understanding the pathophysiology of CHF, which has evolved from simple pump failure to the concept of a complex disease that affects multiple body systems.

Co-involvement of the kidneys is particularly common because both the kidney and the heart play essential roles in blood volume homeostasis and blood pressure control. In a general adult population, the prevalence of chronic kidney disease (CKD) with a glomerular filtration rate less than 60 mL/min is about 5%, which increases to about half of all patients when CHF is present. Diagnosis and treatment of patients suffering from both CHF and CKD has to be modified and adapted because of interactions between the two organs. Therefore, the concept of cardio-renal or renocardial syndromes has evolved. Lately, the term cardio-renal syndrome (CRS) seems to be preferred over the other.

One common feature of CRS is the development of anemia. Although anemia is known to be one of the most important comorbidities of CKD, and diagnostic procedures in this regard are part of each patient’s initial work-up, anemia in CHF only recently has received systematic attention. This review focuses on the possible interplay between the heart and the kidneys in the development of anemia and the implications for diagnosis and treatment.

CRS

CHF leads to activation of a cascade of pathophysiological events, which, although initially meant to isolate and neutralize the insult that originally caused CHF, eventually may lead to an increase in mortality. Some of the common comorbidities in patients with CHF are caused by these mechanisms, or they trigger disease progression. Among these comorbidities are renal failure and the development of anemia. Renal failure again may worsen CHF and cause anemia, which leads to a vicious cycle that has been named CRS, or cardio-renal anemia syndrome (CRAS).

Classification of the CRS

It has been suggested to divide CRS or CRAS into 5 subgroups, differentiating acute and chronic forms (Table 1). The initial insult may target either the heart or the kidney, but the problem may spread to involve the other organ as well. Thus, cardiac dysfunction may lead to kidney injury and vice versa. According to the recently proposed classification, type 1 CRS is defined by a rapid...
worsening of cardiac function, leading to acute kidney failure. In type 2 CRS, CHF leads to worsening of kidney function, whereas in types 3 and 4 CRS the primary insult is an impairment of renal function that leads to worsening of cardiac function. Type 3 is characterized by acute worsening of renal function, type 4 is characterized by CKD. Type 5 CRS is caused by an acute or chronic systemic disease that involves the heart and kidneys (Table 1).

Anemia usually is diagnosed by measuring the hemoglobin concentration or hematocrit level. Yet, much debate exists with regard to cut-off values because those proposed by the World Health Organization (hemoglobin level, <13 g/dL in men and <12 g/dL in nonpregnant women) do not consider important aspects such as aging or race.13 In patients with CKD, anemia is known to be a very common comorbidity with severe prognostic implications. Anemia occurs early in the course of the disease and worsens as kidney function declines.14 Kidney function may be classified by practice guidelines published by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation. According to the glomerular filtration rate CKD is divided into 5 stages (Table 2).15

Table 1. Suggested Classification of 5 Types of CRS

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acute heart failure resulting in acute kidney injury</td>
</tr>
<tr>
<td>2</td>
<td>Chronic cardiac dysfunction (eg, CHF) causing progressive CKD</td>
</tr>
<tr>
<td>3</td>
<td>Abrupt and primary worsening of kidney function causing acute cardiac dysfunction</td>
</tr>
<tr>
<td>4</td>
<td>Primary CKD causing or contributing to cardiac dysfunction</td>
</tr>
<tr>
<td>5</td>
<td>Acute or chronic systemic disorders (eg, diabetes mellitus) that cause both cardiac and renal dysfunction</td>
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Data from Ronco et al.8

In stage IV CKD, more than half of the patients are anemic (cut-off hemoglobin values, <12.0 g/dL for men and for postmenopausal women [>50 years], and <11.0 g/dL for premenopausal women [<50 years]).16 Causes leading to anemia include iron deficiency, deficient erythropoiesis synthesis, as well as a decreased erythrocyte half-life.17

Prevalence of anemia in CHF has been examined in several studies. Because different cut-off values for hemoglobin or hematocrit have been used to define anemia and different patient populations have been studied, prevalence values range broadly between less than 10% to as much as 61%.18 Prevalence increases in patients with advanced disease, in those of older age, and when comorbidities such as diabetes mellitus or CKD are present.19-22 Interestingly, one recently published study investigating anemia among elderly patients with CHF found similar prevalence values in CHF with a reduced or preserved ejection fraction (19.0% versus 18.7%, \(P = .89\) for a left ventricular ejection fraction (LVEF) \(\leq 35\%\) versus LVEF \(>35\%\)).23 It is important to state, however, that the available results are all based on retrospective analyses. The first large-scale observational study in this regard, the Studies Investigating Co-morbidities Aggravating Heart Failure study, only recently has commenced recruiting,24 and the first results are expected in about 2013.

A recent study by Scrutinio et al25 found 24% of 528 patients with CHF and normal kidney function to be anemic. Patients who had a glomerular filtration rate of less than 60 mL/min/1.73 m2 (ie, Kidney Disease Outcomes Quality Initiative stages III-V), had a prevalence of anemia that increased to 48%. The pathogenesis of anemia in CHF seems to be somewhat similar to that of anemia of chronic diseases. It is thought to be of immunologic origin, with proinflammatory cytokines triggering deposition of iron in the cells of the reticuloendothelial system, leading to a relative iron deficiency for erythropoiesis.26 Other causes for anemia in CHF include absolute iron deficiency and decreased production of erythropoietin, especially if CKD is present.

**CLINICAL SIGNIFICANCE OF ANEMIA IN CRS**

Retrospective analyses showed that anemia has prognostic implications in patients with CHF. Recently published results from the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (SENIORS) study showed that the presence of anemia in elderly patients with CHF with preserved or depressed ventricular function is an independent risk factor for death from any cause or hospitalization for cardiovascular reasons.23 In a systematic review and meta-analysis, prevalence of anemia in a population of more than 150,000 patients with CHF was about 37%. Mortality after 6 months in anemic patients was 47% compared with 30% in nonanemic patients.27 Renal failure was present in 20% to 40% of patients included in this study.

In patients hospitalized with acute heart failure, moderate to severe anemia was shown to be an independent predictor of death. Anemic patients were older and more...
often displayed an impaired kidney function than non-anemic patients. Data from the Italian survey on acute heart failure found 31% of 2,318 patients to be anemic. The in-hospital mortality rate of anemic patients was increased: 12% compared with 5% in patients without anemia.

Also, changes in the hemoglobin value were found to be prognostically significant. In the Valsartan Heart Failure Trial (Val-HeFT), patients with a severe decrease in hemoglobin level during the first 12 months of the trial had a 60% increased risk of death compared with patients with stable hemoglobin values. In contrast, an increase in hemoglobin level lead to a decrease in mortality rate by more than 20%. In anemic patients with CHF and CKD the prognosis is even worse. An analysis from the US Medicare population examining more than 1 million patients showed a 2-year mortality risk of almost 46% in patients with the full clinical picture of CRAS, whereas the diagnosis of CKD alone, anemia alone, or CHF alone was associated with 2-year mortality rates between 17% and 26%.

With regard to morbidity, the exact role of anemia in CHF still has to be defined. Anemia in CHF seems to correlate with poorer quality of life and worse exercise capacity. In addition, the presence of anemia leads to an increased risk of hospitalization for cardiovascular reasons.

### Iron Deficiency and Anemia in CRS

In the largest study published on the topic to date, Ezekowitz et al showed that the cause of anemia in patients with CHF was anemia of chronic disease in 58% and absolute iron deficiency in 21%. As mentioned previously, anemia of chronic disease is characterized by trapping of iron within the cells of the reticuloendothelial system, leading to a relative or functional iron deficiency. The diagnosis of functional iron deficiency is made by low transferrin concentration and low transferrin saturation with normal or increased ferritin values in the presence of a chronic illness. It is important to note that functional iron deficiency may be present even in the absence of anemia. Apart from iron trapping caused by inflammation, the pathogenesis of iron deficiency in CHF patients is multifactorial and includes malnutrition, malabsorption caused by edematous bowel wall, and chronic aspirin use.

In a recent study, Jankowska et al showed that functional iron deficiency (defined as a ferritin level between 100 and 300 μg/L and transferrin saturation of <20%), or absolute iron deficiency (defined as ferritin <100 μg/L) was found in 37% of 546 patients with stable systolic heart failure. Absolute iron deficiency was even more common in a smaller study in which iron-deficiency anemia was confirmed by bone marrow aspiration. In this study, 73% of patients hospitalized for decompensated advanced CHF showed signs of absolute iron deficiency. Some of the patients showed iron-depleted bone marrow despite high ferritin levels. It is therefore important to state that absolute and functional iron deficiency in CHF are not separate entities but commonly both are pathophysiological important.

The cause of anemia in patients with CKD is multifactorial. Inadequate erythropoietin production is the most established cause, although iron deficiency in CKD is at least as common as in CHF. Data from the Third National Health and Nutrition Examination Survey confirmed iron deficiency (defined by a serum ferritin level <100 μg/L) in 46% of women and 19% of men with stage IV CKD.

In patients with CKD who are not yet on hemodialysis, iron deficiency often is caused by decreased oral iron intake from a decreased appetite for red meat or from the prescribed dietary protein restriction. If not present initially, iron deficiency often develops after initiation of therapy with erythropoiesis-stimulating agents because iron stores are depleted with the stimulation of new red blood cell production.

### Treatment Options

For treating moderate to severe iron-deficiency anemia of CHF or CKD, oral iron is presumed to be effective only in a minority of patients. In 2000, Silverberg et al were the first to study the effects of intravenous iron sucrose in combination with erythropoietin to treat anemia in 26 patients with advanced CHF in New York Heart Association (NYHA) classes III/IV with an LVEF less than 35%, and a hemoglobin level of less than 12 g/dL. Results were encouraging with mean NYHA class improving from 3.7 ± 0.5 to 2.7 ± 0.7, and hemoglobin values increasing from 10 ± 1 to 12 ± 1 g/dL (P < .001). After the identification of high prevalences of absolute or functional iron deficiency shown by Ezekowitz et al and Nanas et al intravenous iron has received even more research and clinical interest.

Although treatment of anemia in CKD with intravenous iron alone already had been proven to increase and maintain hemoglobin levels, the first study in CHF was conducted by Bolger et al in 2006. In this open-label study, 16 patients with stable CHF (NYHA classes II and III with a mean LVEF of 26 ± 13), a hemoglobin value of less than 12 g/dL, and a ferritin value of less than 400 μg/L received repeated doses of 200 mg intravenous iron sucrose (average total, 950 ± 137 mg). Results after a mean follow-up period of 92 ± 6 days showed an increase of hemoglobin values from 11.2 ± 0.7 to 12.6 ± 1.2 g/dL (P = .0007), and mean ferritin values from 87 to 217 μg/L. Patients also showed signs of improvement of functional capacity (walking distance assessed by a 6-minute walk test improved from 242 ± 78 to 286 ± 72 m; P = .01). Another smaller study was conducted in 40 anemic patients with CHF (LVEF, ≤35%), iron deficiency (transferrin saturation, <20%; ferritin, <100 mg/mL), and CKD (creatinine clearance, <90 mL/min). In this double-blinded study, patients received 200 mg of...
iron sucrose weekly for a total of 5 weeks. Hemoglobin and ferritin levels as well as cardiac biomarkers such as N-terminal pro-B-type natriuretic peptide and functional status (measured by a 6-minute walk test and the Minnesota Living with Heart Failure Questionnaire) improved significantly. Interestingly, an improvement in kidney function was shown in the intervention group (increase in the creatinine clearance from 39.8 ± 10.8 to 44.9 ± 11.0; \( P < .05 \)).46 Usmanov et al47 treated 32 patients with 150 mg iron sucrose two times daily for 3 weeks. They included anemic (Hb <11 g/dL) patients with NYHA class III to IV CHF and CKD. Results showed an improvement in cardiac hypertrophy, ventricular dilatation, and ejection fraction after correction of anemia over a 6-month period in all patients with NYHA class III. Left ventricular hypertrophy and LVEF did not improve in patients with NYHA class IV. This study failed to show a significant improvement of kidney function after treatment.

After a small pilot study, the Ferinject Assessment in Patients with Iron Deficiency and Heart Failure was conducted, which is the largest study of intravenous iron in patients with CHF published to date. In this study, 459 patients with symptomatic CHF (NYHA II-III) were assigned randomly, in a 2:1 ratio, to iron carboxymaltose or placebo. Inclusion criteria were absolute or functional iron deficiency, defined as serum ferritin level less than 100 \( \mu \text{g/L} \) or between 100 and 299 \( \mu \text{g/L} \), if the transferrin saturation was less than 20%. Patients did not have to be anemic because hemoglobin levels had to be between 9.5 and 13.5 \text{g/dL}.

Primary end points were changes in NYHA functional class and the self-reported Patient Global Assessment after 24 weeks of treatment. Secondary end points included improvements in 6-minute walk distance and health-related quality of life.51

In this study, a new intravenous iron preparation, iron carboxymaltose, was administered weekly until iron repletion was achieved, followed by monthly injections. Black syringes and curtains were used to ensure blinding. The iron dose required for iron repletion was calculated according to the Ganzoni formula.49,50 After 16 weeks, iron carboxymaltose yielded a significant increase in serum ferritin (\( P < .0001 \)) and transferrin saturation compared with placebo (\( P < .0001 \)).

Results for the primary end points showed significant improvement with iron carboxymaltose for NYHA class (odds ratio for improvement by one class, 2.40; 95% confidence interval, 1.55-3.71) and self-reported Patient Global Assessment (50% of all patients after 24 weeks compared with 28% of patients on placebo, odds ratio for improvement, 2.51; 95% confidence interval, 1.75-3.61). Interestingly, independently of whether anemia was present or not, all patients reported improvements in clinical symptoms.

Secondary end points also showed significant improvements in 6-minute walk distance and health-related quality of life at 4, 12, and 24 weeks (\( P < .001 \) for all comparisons). Again, iron carboxymaltose showed a favorable safety profile because side effects were similarly common as in those patients treated with placebo.

### Available Intravenous Iron Agents

Today a number of different intravenous iron agents are commercially available. They all consist of colloids of spheroidal iron-carbohydrate nanoparticles. Carbohydrates surround a core of iron-hydroxide where Fe(III) is stored and released. This way, it is possible to prevent immediate iron release and toxicity by the formation of highly reactive oxygen species. The preparations differ in core size and the carbohydrate shell surrounding them. Intravenous iron agents currently available in North America and most European countries use gluconate, dextran, and sucrose within the carbohydrate shell.52 Recently, carboxymaltose became available as a new chelating agent and is approved for more rapid administration of large iron doses.53

As the most dreaded side effect, anaphylactic reactions have been observed after the administration of intravenous iron agents. Anaphylactic shock has been reported primarily with iron dextran–containing formulations. This side effect is extremely rare with newer intravenous iron preparations and therefore the administration of a test dose is not necessary.

Recently, two novel intravenous iron formulations became available. These include iron isomaltoside and ferumoxytol. Iron isomaltoside is a modified isomalto-oligosaccharide. Iron is strongly encapsulated within the isomaltoside matrix, which guarantees slow iron release with little risk of free iron toxicity. Furthermore, iron isomaltoside is characterized by a low immunogenic potential. It is approved for administration in doses of up to 20 mg/kg.54 Ferumoxytol is a semisynthetic, polyglucose sorbitol carboxymethylene-ether-coated super-paramagnetic iron oxide nanoparticle that can be administered in a relatively large dose (510 mg, exclusive vial size) in fewer than 20 seconds. It also seems to cause less allergic reactions, and shows an improved safety profile compared with older intravenous iron preparations.55

### CONCLUSIONS

The triad of CKD, CHF, and anemia is a clinical entity with significant influence on morbidity and mortality in affected patients. In patients with CHF, the presence of CKD increases mortality rates significantly. When both CKD and anemia are present, mortality rates are multiplied excessively. Yet, CRAS remains clinically underrecognized. The available data suggest that the full picture of CRAS affects about 20% of all patients with CHF. Iron deficiency, whether absolute or functional, plays a significant role in the development of anemia in both CHF and CKD. In advanced stages, more than 50% of patients are affected. It is important to note that intravenous iron application is not a treatment of heart failure...
per se, but rather a treatment of a comorbid condition, namely iron deficiency. It remains a matter of debate why patients with iron deficiency benefit with regards to their clinical symptom burden, but because clinical benefit has been observed also in nonanemic patients it is tempting to speculate that intravenous iron application also improves oxygen use in skeletal muscle. The latter mechanism may involve iron use in mitochondria. Future studies are required to define the optimal hemoglobin value for patients with CHF, but also for those with CKD. In addition, we require more insight into iron storage and use in the human body after intravenous iron administration. Treatment of iron deficiency today, however, is safe and effective because new preparations of intravenous iron are available and several studies have shown promising results. Such treatment should be considered in highly symptomatic patients with iron deficiency with or without anemia.

REFERENCES


