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STATE-OF-THE-ART PAPER

Anemia as a Risk Factor and Therapeutic Target in Heart Failure

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Anemia has recently been recognized as an important comorbid condition and potentially novel therapeutic target in patients with heart failure (HF). Anemia is common in HF patients, with a prevalence ranging from 4% to 55% depending on the population studied. Multiple potential mechanisms of interaction exist between anemia and the clinical syndrome of HF, including hemodilution, inflammatory activation, renal insufficiency, and malnutrition. A growing body of literature from observational databases and clinical trials suggests that anemia is an independent risk factor for adverse outcomes in patients with HF. Although preliminary data suggest that treatment of anemia may result in significant symptomatic improvement in HF, aggressive treatment of anemia may also be associated with increased risk of hypertension or thrombosis. Multiple ongoing studies will provide definitive data on the balance of risks and benefits of anemia treatment in chronic HF. (J Am Coll Cardiol 2004;44:959–66) © 2004 by the American College of Cardiology Foundation

> "There are, in truth, no specialties in medicine, since to know fully many of the most important diseases a man must be familiar with their manifestations in many organs."
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> —William Osler, *The Army Surgeon*, Medical News, Philadelphia, 64:318, 1894.

Chronic heart failure (HF) is a rapidly growing public health problem. Despite the significant successes of pharmacologic blockade of neurohormonal activation in HF, the negative or neutral results of multiple recent trials suggest that we have reached a "ceiling of benefit" with regard to this approach (1). This has led to the search for novel mechanisms by which to address the persistent morbidity and mortality associated with HF. Anemia has recently been demonstrated to be a common comorbid condition in patients with HF, and multiple observational studies have demonstrated an independent association between lower hemoglobin (Hb) and adverse clinical outcomes in this syndrome. Although these findings have generated substantial interest in anemia as a potentially important therapeutic target in patients with HF, current HF guidelines provide no specific recommendations for evaluation or treatment of anemia (2,3). The purpose of this review is to outline the current understanding of the association between anemia and HF and assess the existing and emerging data on anemia as a potential treatment target, including the potential benefits and risks of treating anemia in the setting of HF.

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SEARCH STRATEGY AND SELECTION CRITERIA

A search of published literature was performed using the MEDLINE database using the following search terms: anemia, hemoglobin, heart failure, oxygen delivery, cardiomyopathy, and erythropoietin. Studies were included if they evaluated the role of Hb concentration in the pathophysiology or outcomes of patients with HF. Reference lists from identified studies were also reviewed to identify other potentially relevant references. Given the rapidly evolving literature in this area, abstracts from recent scientific meetings were also reviewed for potentially relevant studies that have not yet been published.

SCOPE OF THE PROBLEM

Published estimates of the prevalence of anemia in patients with HF vary widely, with ranges from 4% to 55% (4–10). Reasons for this wide variation include differences in the HF population studied, in study methods, and in the definition of anemia used. Although the most commonly accepted definition of anemia is that of the World Health Organization (Hb <13 g/dl in men or <12 g/dl in women), studies have varied considerably in the criteria used to classify patients as anemic. In general, the prevalence of anemia is greater in less-selected populations (such as claims data) and lower in highly selected populations such as patients enrolled in clinical trials. Anemia appears to be more common in patients with more severe disease, with a reported prevalence in patients with New York Heart Association (NYHA) functional class IV populations as high as 79% (6). Patients hospitalized with HF have significantly higher rates

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ESRD = end-stage renal disease
Hb = hemoglobin
HF = heart failure
NYHA = New York Heart Association
rHuEPO = recombinant human erythropoietin
TNF = tumor necrosis factor

of anemia than outpatient populations. The prevalence of anemia in selected HF studies is shown in Table 1.

ETIOLOGY AND PATHOPHYSIOLOGY OF ANEMIA IN HF

Although anemia is common in HF, it remains controversial whether its high prevalence in HF patients is directly related to HF itself or is primarily due to other comorbid conditions. Heart failure is a disease of the elderly, a population where the prevalence of anemia is high irrespective of cardiac status (11). Multiple comorbid conditions are common in HF patients, in particular renal insufficiency, which is closely associated with the development of anemia (12,13). Although many studies have identified a high prevalence of anemia in patients with HF (Table 1), few have carefully examined the relationship between the burden of comorbidity and the prevalence of anemia. Hussein et al. (14) recently presented data on the attributable cause of anemia from a retrospective cohort study of 699 consecutive outpatient visits to a HF clinic. An explanation for anemia other than heart failure was identified in 98% of the study patients, with the most common etiologies being renal insufficiency (defined as creatinine clearance <60 ml/min/m^2) and iron, folate, or B12 deficiency. Although limited by its retrospective design, this study suggests that mechanisms other than HF may be responsible for anemia in a significant proportion of HF patients. A prospective ongoing study including both specialty and community sites, the Study of Anemia in a Heart Failure Population (STAMINA-HFP) registry, is evaluating the prevalence, etiologies, and mechanisms of anemia in a broad population of HF patients (15).

Although the causal relationship between HF and anemia remains poorly defined, there are multiple potential mechanisms by which the HF syndrome could contribute to the development of anemia. These include hemodilution, renal dysfunction, proinflammatory cytokines, malnutrition due to right-sided HF, decreased perfusion to the bone marrow, and drug therapy (such as angiotensin-converting enzyme [ACE] inhibitors). In reality, it is likely that several of these mechanisms are active simultaneously, and that anemia in HF is the result of a complex interaction between cardiac performance, neurohormonal and inflammatory activation, renal function, and bone marrow responsiveness. This interplay has been termed the "cardio-renal-anemia syndrome" (16). A conceptual model for these interactions is shown in Figure 1.

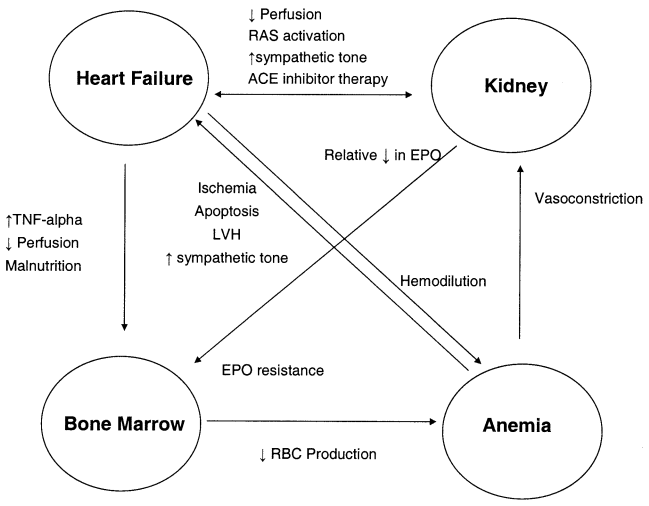

Figure 1. A conceptual model of mechanisms involved in the interaction between heart failure, renal function, bone marrow, and anemia. ACE = angiotensin-converting enzyme; EPO = erythropoietin; LVH = left ventricular hypertrophy; RAS = renin-angiotensin system; RBC = red blood cell; TNF = tumor necrosis factor.

Expansion of plasma volume is a characteristic of the HF syndrome, and, therefore, some anemia may be dilutional rather than due to a true decrease in red blood cell mass (17). In a recently published study of 37 HF patients by Androne et al. (18), true anemia (i.e., a decrease in red blood cell mass) was present in 54%, and hemodilution was present in 46%. Notably, in this study both hemodilution and true anemia were associated with adverse survival, with the worst survival seen in patients with hemodilution.

Renal insufficiency is common in HF, with a prevalence from 30% to 50% depending on the definition used and

Table 1. Prevalence of Anemia in Selected HF Studies

Study	Population	n	Definition of Anemia	Prevalence
Al-Ahmad et al. (4)	LV dysfunction +/− symptoms, clinical trial	6,563	Hct < 35%	4%
Tanner et al. (7)	Tertiary care HF clinic	193	Hb < 12	15%
Ezekowitz et al. (8)	New HF diagnosis, claims data	12,065	MD defined (ICD9 codes)	17%
Mozaffarian et al. (5)	Severe chronic HF, clinical trial	1,130	Hct < 37.6%	20%
Horwich et al. (9)	Heart transplant referrals single-center	1,061	Hb < 13 men, <12 women	30%
Kosiborod et al. (10)	Medicare patients, claims data	2,281	Hct ≤ 37%	48%
Felker et al. (38)	Acute decompensated HF, clinical trial	949	Hb < 13 men, <12 women	49%
Silverberg et al. (6)	Chronic HF, single-center trial	142	Hb < 12	55%

Hb = hemoglobin; Hct = hematocrit; HF = heart failure; LV = left ventricular.

Table 2. Association of Anemia and Outcomes in Selected HF Studies

Study	Population	Outcome	Adjusted Hazard/ Odds Ratio	Unit Change
Al-Ahmad et al. (4)	LV dysfunction ± symptoms, clinical trial	Mortality	1.027	1% Hct
Ezekowitz et al. (8)	New HF diagnosis, claims data	Mortality	1.34	Anemic vs. not
Horwich et al. (9)	Heart transplant referrals, single-center	Mortality	1.13	1 g/dl Hb
Kosiborod et al. (10)	Medicare patients, claims data	Mortality	1.02	1% Hct
Mozaffarian et al. (5)	Severe HF, clinical trial	Mortality	1.03	1% Hct
Felker et al. (38)	Acute HF, clinical trial	Death or rehospitalization	1.12	1 g/dl Hb

Abbreviations as in Table 1.

population studied (12,19). In patients with advanced renal disease, progressive renal dysfunction leads to a decrease in circulating levels or erythropoietin, with a subsequent decrease in bone marrow erythrocyte production and Hb levels. It is well-established that anemia in patients with end-stage renal disease (ESRD) is associated with a variety of adverse cardiac consequences, including the development of left ventricular hypertrophy, left ventricular dilation, and frank clinical HF (20,21). As shown in Figure 1, there is a complex interaction between renal insufficiency, erythropoietin production, and HF. Indeed, despite the high prevalence of renal dysfunction, circulating levels of erythropoietin are generally normal-to-elevated in HF, with a correlation between the degree of erythropoietin elevation and worsening functional class (17). Increased renal production of erythropoietin may be driven by worsening cardiac performance and subsequent renal hypoperfusion and hypoxia, which is a powerful stimulus for erythropoietin production. In light of this elevation of erythropoietin levels in advanced HF, the high prevalence of anemia in this population is particularly notable. Anemia in HF may be a state of relative resistance to the effects of erythropoietin, with persistent anemia despite high normal or frankly elevated erythropoietin levels. Several potential explanations for erythropoietin resistance in HF have been proposed, including the influence of proinflammatory cytokines and malnutrition.

Chronic HF is known to be a state of persistent inflammatory activation, and higher levels of circulating proinflammatory cytokines are known to be associated with greater disease severity and worsened clinical outcomes (22–24). Proinflammatory cytokines such as tumor necrosis factor (TNF)-alpha and interleukin-6 also have direct effects on the bone marrow, and are implicated in the mechanism of anemia of chronic disease (25). Elevated levels of circulating proinflammatory cytokines lead to decreased erythropoietin production and resistance to the effects of erythropoietin on bone marrow production of red blood cells. Given that both proinflammatory cytokine activation and anemia are more pronounced in patients with more severe HF, it is attractive to hypothesize that inflammatory activation is a major contributor to anemia in this population. Recently presented data confirm the association between elevation of circulating inflammatory markers and anemia, with patients with anemia and HF demonstrating significantly higher levels of TNF-alpha and TNF soluble receptors 1 and 2 (26).

Other potential mechanisms may involve regulation of erythropoietin secretion from the kidney, either from the HF syndrome itself or from pharmacologic treatment. Autonomic dysfunction, which is known to be present in HF, may result in impaired renal production of erythropoietin even in the setting of significant stimuli for erythrocyte production (27,28). Therapy with ACE inhibitors is a mainstay of HF therapy, with clearly documented improvements in long-term survival (29–31). Some data have suggested, however, that ACE inhibitor therapy may reduce Hb concentration in patients with HF. Therapeutic doses of ACE inhibitors have been shown to decrease renal secretion of erythropoietin in patients with hypertension (32), renal insufficiency (33), polycythemia (34), and chronic HF (35). The mechanistic role these considerations may play in the development of anemia in patients with HF is not clear.

ANEMIA AND OUTCOMES

A variety of observational studies have found lower Hb or hematocrit to be associated with adverse clinical outcomes in HF (Table 2). This relationship persists whether considering Hb concentration as a continuous variable or anemia as a categorical variable. Anemia has been shown to be a risk factor for new cardiovascular events in the general population (36). Data from the Framingham study found that lower hematocrit was a significant risk factor for the development of symptomatic HF (37). Data from a large single-center cohort of patients with primarily NHYA functional class IV symptoms referred for cardiac transplantation identified an association between lower Hb and impaired hemodynamics, lower functional capacity, and decreased long-term survival (9). These findings persisted when patients were subdivided into a variety of subgroups based on gender, HF etiology, and age. Notably, this study identified a substantially increased risk even in patients with relatively mild anemia (Hb $<$12.6 g/dl for men and Hb $<$11.6 g/dl for women). In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study of patients hospitalized with decompensated HF, Hb levels were also found to be independently associated with adverse out-

comes, with a 12% increased risk of death or rehospitalization at 60 days for every decrease of 1 g/dl of Hb (38). Anemia also contributes to the exercise intolerance that is a major morbidity in chronic HF. A recently published study in 93 men with HF found that Hb was a significant independent predictor of maximal exercise tolerance as measured by peak oxygen consumption, even after controlling for ejection fraction, age, and renal function (39). Not all studies have supported the association of anemia and adverse outcomes in HF. A study by Kalra et al. (40) of 552 patients with new-onset HF found a significant incidence of anemia in this cohort (18% with Hb <11.5 g/dl) but no association between baseline Hb and survival after adjustment for other variables. The authors concluded that anemia early in the disease course was likely due to factors other than HF and therefore, was unlikely to be associated with prognosis.

When taken as a whole, the observational data appear to suggest a relationship between anemia and outcomes in patients with HF. However, such studies must be interpreted with caution due to their retrospective design, and should not be construed as demonstrating a causative, mechanistic link between anemia, HF, and outcomes. Whether such a link exists is not clear from the currently available data. Multiple theoretical reasons have been postulated to explain the observed association between anemia and outcomes in patients with HF. The presence of anemia may simply be a marker for greater severity of HF or greater burden of comorbidity. A recently presented study using data from the National Heart Failure Project found that, while lower hematocrit levels were associated with higher mortality, this association was related to a greater severity of illness and burden of comorbidity, and that hematocrit was not independently associated with one-year mortality (41).

Patients with anemia are more likely to have concomitant renal insufficiency, which has been shown to be a powerful predictor of worsened outcomes in HF (12,19). Multiple studies, however, have demonstrated an independent effect of anemia even after controlling for renal function (4,8–10), suggesting that lower Hb is not simply a surrogate for renal disease. Patients with greater severity of HF may have more volume retention and, therefore, more anemia due to hemodilution. Horwich et al. (9), however, reported that Hb was a predictor of adverse outcome even after adjustment for volume overload as measured by invasive hemodynamic monitoring. Alternatively, anemia may contribute directly to the pathophysiologic state in HF. Anemia results in decreased oxygen carrying capacity, which may be compensated for in the normal heart by increasing heart rate and stroke volume, resulting in an increase in cardiac output and maintenance of tissue oxygen delivery (42). These adaptive responses may be limited, however, in patients with coronary artery disease or HF (43). Subsequent myocardial or tissue hypoxia may result in increased sympathetic activity, neurohormonal activation, and cytokine release, leading to a vicious cycle of HF progression.

INTERVENTIONAL STUDIES

The consistent association of anemia with adverse clinical outcomes in HF has led to substantial interest in anemia as a potential therapeutic target. Potential treatments for anemia include the use of red blood cell transfusions and treatment with erythropoietin analogs to increase red blood cell production. The impact of red blood cell transfusion on cardiovascular disease is controversial. Although a "transfusion threshold" of maintaining the hematocrit >30% in patients with cardiovascular disease has been commonly accepted, this concept has been based primarily on expert opinion rather than on clinical trials (44). In addition to the potential risk of infectious transmission, concerns have been raised about the potential immunosuppressive effects of blood transfusion (45). A randomized controlled trial of a restrictive (7 g/dl) versus liberal (10 g/dl) transfusion strategy in critically ill patients (26% of whom had cardiovascular disease) reported no significant difference in 30-day mortality, although there was a trend towards reduced mortality in the restrictive transfusion arm (46). In contrast, a retrospective review of Medicare claims data in elderly patients with acute myocardial infarction found that transfusion in patients with admission hematocrit <0.30 was associated with improved 30-day mortality rates (47). Given the risks and costs of red blood cell transfusion and its uncertain benefit, it does not appear that transfusion represents a viable therapeutic strategy for the routine treatment of anemia in HF.

Recombinant human erythropoietin (rHuEPO) has become a mainstay in the treatment of anemia in patients with ESRD. In addition to well-documented improvements in quality-of-life and survival, data from patients with ESRD have suggested that rHuEPO treatment leads to an improvement in a variety of measures of cardiac performance, including reduced left ventricular hypertrophy and improved ejection fraction and cardiac output (48–50). Three small studies have been published directly examining the effect of rHuEPO therapy on clinical outcomes in patients with heart failure. In an uncontrolled study, Silverberg et al. (6) demonstrated an improvement in ejection fraction, NYHA functional class, and hospitalization after treatment with erythropoietin and intravenous iron in a group of 26 patients with NYHA functional class III to IV HF. In this study, the dose of rHuEPO was adjusted to maintain an Hb level of 12 g/dl. The same group subsequently conducted a small randomized trial of rHuEPO and intravenous iron in 32 patients with NYHA functional class III to IV HF, which demonstrated that treatment of anemia in this patient population resulted in improved functional class and a decrease in the need for hospitalization (51). Several features of these studies suggest the need for caution in the interpretation of these results. Both studies examined very

small numbers of patients. The initial study was not randomized and had no control group. Additionally, the randomized trial was significantly limited by its lack of a placebo control and the fact that neither patients nor investigators were blinded to treatment assignment. Given the subjectivity of assessments of functional class and in criteria for diuretic dosing or HF hospitalization, these end points must be interpreted very cautiously in the setting of an unblinded study.

A recent randomized, single-blind, placebo-controlled study by Mancini et al. (52) evaluated the effect of 3 months of erythropoietin treatment on exercise capacity in 26 patients with anemia and NYHA functional class III to IV HF. This study demonstrated significant improvements in peak oxygen consumption (VO_2 max) with erythropoietin treatment (from 11 ± 0.8 to 12.7 ± 2.8 in the rHuEPO-treated patients [$p < 0.05$] vs. no significant change in the control patients). A significant correlation was observed between elevations in Hb with rHuEPO treatment and increased VO_2. Notably, the improvement in exercise performance with rHuEPO treatment was observed whether the anemia was found to be from decreased red blood cell mass or from hemodilution. Although this study was randomized, placebo-controlled, single-blinded, and had an objective end point (VO_2 max), the small sample size suggests the need for larger confirmatory studies before these results can be widely accepted.

All three of these studies used rHuEPO in a regimen similar to the one used in patients with ESRD. Newer erythropoietin analogs have been developed (such as darbepoetin alfa) that have a longer half-life and require less frequent administration, potentially making them more attractive for HF therapy. An ongoing phase II study of darbepoetin in patients with HF and anemia will provide important preliminary data on the potential efficacy of this agent in the HF population.

Another area of ongoing investigation deals with direct effects of rHuEPO on the heart. Erythropoietin receptors are present in a variety of tissues, including the heart, and erythropoietin appears to have anti-inflammatory and anti-apoptotic properties (53). Recently published studies have demonstrated that treatment with rHuEPO favorably attenuated ischemia-reperfusion injury in a mouse model (54,55). Whether these findings will have physiologic relevance in humans remains unknown, but they do suggest an additional potential mechanism for beneficial effects of erythropoietin treatment in human HF.

POTENTIAL RISKS OF ANEMIA TREATMENT

As with all therapies, potential benefits must be balanced against potential risk (primum non nocere), and concern does exist about possible adverse effects of anemia correction in HF. In large part, these concerns are based on the results of a large randomized trial, the Normal Hematocrit Treatment trial, that demonstrated a non-significant increase in mortality in hemodialysis patients with clinical heart disease (heart failure or ischemic heart disease) who were treated with erythropoietin to a goal hematocrit of 42% as opposed to 30% (56). This trial was terminated prematurely when the Data Safety Monitoring Committee concluded that the trial would be unable to reach its prestated end point of demonstrating improved outcomes in the higher hematocrit group. Although not statistically significant, the relative risk of death or non-fatal myocardial infarction in the high hematocrit group was 1.3 (95% confidence interval, 0.9 to 1.9). Paradoxically, however, higher hematocrit values in this study were associated with a decreased mortality rate within each study group, suggesting that the higher hematocrit per se was not responsible for the increased mortality. These issues have led to significant controversy in interpreting these results (57). Other smaller studies have not replicated the results of the Normal Hematocrit Treatment trial. Data from the Canadian Multicenter study in 146 patients with asymptomatic left ventricular hypertrophy or left ventricular dilation found no evidence of improvement in echocardiographic parameters but did show improvements in quality-of-life with normalization of Hb (target, >13.5 g/dl) (58). There was no difference in rates of thrombosis between the two groups, but there was a greater need for antihypertensive therapy in the high Hb group. The Spanish Cooperative Quality of Life study group performed an uncontrolled trial in ESRD patients without HF, and found that normalization of hematocrit was associated with improved quality of life and functional status (59).

Table 3. Potential Benefits and Risks of Treating Anemia in Heart Failure

Potential Benefits	Potential Risks
Improved oxygen delivery	Increased thrombosis
Improved exercise tolerance	Platelet activation
Attenuate adverse remodeling	Hypertension
Antiapoptotic	Endothelial activation
? Improved QOL	
? Decrease in hospitalizations	
? Improved survival	

QOL = quality of life.

Several mechanisms could theoretically result in harmful effects from increasing Hb in HF patients. Erythropoietin therapy is associated with worsening hypertension in 20% to 30% of patients on hemodialysis (60). Additionally, erythropoietin use may be associated with increased risk of thrombosis, especially of vascular access grafts (61–64). These effects may be due to an increase in platelet activation, increased blood viscosity, or effects on the levels of proteins C and S (65–67). Finally, erythropoietin therapy may be associated with endothelial activation and the release of endothelin, a circulating peptide that has been shown to be associated with adverse outcomes in HF (68,69). A summary of the potential risks and benefits of erythropoietin therapy in HF is shown in Table 3.

Given the potential risks associated with erythropoietin therapy, caution seems well-justified until more definitive data on the potential clinical benefits of anemia therapy in HF

are available. Many important questions remain unanswered, including the optimal Hb target and appropriate rate of rise of Hb. Importantly, the ultimate benefit of a therapy is related to the relative balance of risks and benefits in a given patient population. Thrombolytic therapy, for example, carries a finite risk of intracranial hemorrhage, but this risk is outweighed by the clinical benefits in appropriately selected patients with acute ST-segment elevation myocardial infarction. Such a balance of risks and benefits can only be established in appropriately designed, randomized, controlled trials. Such studies, several of which are ongoing, will provide substantially greater understanding of balance of risks and benefits of pharmacologic treatment of anemia in patients with HF.

CURRENT RECOMMENDATIONS/FUTURE DIRECTIONS

At present there is insufficient data to make a general recommendation for aggressive treatment of anemia in patients with HF. A diagnostic evaluation for potentially reversible causes of anemia (such as iron deficiency or occult blood loss) and subsequent treatment, if identified, is appropriate in all patients. Although pilot data on the treatment of anemic HF patients with erythropoietin analogs are promising, the studies published thus far have been significantly limited by very small sample size, lack of blinding, and the use of subjective end points. Treatment of mild anemia with erythropoietin analogs can, thus, not be considered a proven therapy for HF based on currently available data, and the results of larger, more carefully controlled clinical trials will be required before such treatment could be considered a viable therapy. The history of drug development in HF is notable for many therapies that appeared promising in small, early studies (such as chronic inotropic therapy or TNF-alpha blockade) only to be proven neutral or harmful when evaluated in large, carefully controlled trials (70,71). Such experience must serve as a cautionary tale and, therefore, it is crucial that appropriate caution be exercised until data from prospective, blinded, controlled trials of adequate size are available. Many such studies are currently being planned or are underway, including prospective studies addressing the prevalence and incidence of anemia in HF populations (15), the mechanisms of anemia in HF, and the effect of anemia treatment on quality of life, exercise tolerance, morbidity, mortality, and costs. Given the history of drug development in HF, a mixture of optimism and caution would appear to be the appropriate attitude towards anemia therapy in HF at present.

CONCLUSIONS

Anemia is increasingly recognized as an important comorbid condition in patients with HF. Although the exact mechanism is not well-defined, it appears that anemia in HF patients is the result of a complex interaction of cardiac performance, renal homeostasis, bone marrow responsiveness, and concomitant drug therapy. Multiple observational studies have confirmed the substantial prevalence of anemia in a variety of HF populations. Observational data has also suggested a significant independent association of lower Hb levels with adverse clinical outcomes. Although preliminary and limited, several pilot studies have demonstrated the potential for therapies targeted at anemia to impact clinical outcomes in HF. Given the potential risks of worsening hypertension and thrombosis, larger, carefully controlled studies will be required before such therapy can be accepted. Such studies must also address important questions about mechanisms and the cost-benefit of this type of therapy. Given the therapeutic ceiling that seems to have been reached with current modalities of neurohormonal modulation, anemia may represent an important novel target for addressing the substantial morbidity and mortality associated with the ongoing HF epidemic.

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