Myocardial Disease, Anemia, and Erythrocyte-Stimulating Proteins in Chronic Kidney Disease

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The combination of heart failure and chronic kidney disease (CKD) has received comparatively little attention in terms of clinical research versus investigations of each state individually. It has been known for over a decade that anemia, a cardinal feature of CKD, is associated with higher cardiovascular event rates in late-stage and end-stage renal disease. Although the biological mechanisms linking anemia, renal failure, and heart failure are incompletely understood, more prevalent anemia is consistent in patients with more severe heart failure and is associated with higher mortality rates. Impaired erythropoietin production and resistance to erythropoietin are major contributors to anemia in patients with heart failure. By targeting hemoglobin levels in anemic patients with CKD, through the use of recombinant erythropoietin (epoetin) therapy, it has been hoped that anemia, CKD, and heart failure outcomes can be improved. Darbepoetin alfa was engineered to contain more N-linked carbohydrate chains than erythropoietin, and has an approximately 3 times longer serum half-life. Several clinical trials have addressed the hypothesis that darbepoetin alfa can effectively treat renal anemia at dose frequencies of once per week, or less often, with positive outcomes.

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Heart failure and kidney failure frequently co-exist, and, in many ways, each condition could be considered an extension, in terms of severity, of the other. The combination of these disease states has received comparatively little attention, in terms of clinical research, versus investigations of each individually. Figure 1 summarizes findings from 2 PubMed searches performed on May 1, 2005, with total figures for 2005 projected from citation rates between January and April. The following terms were used in the initial

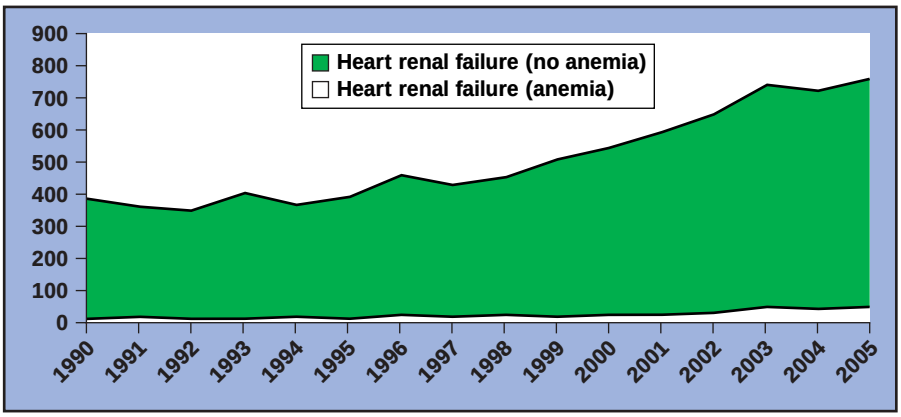

Figure 1. *Plot of annual citation rate against year of publication, from a May 2005 search of PubMed. The following search terms were used '(heart or cardiac) and (renal or kidney) and (failure)', with and without the additional term (and anemia). The figures for 2005 were projected, based on citations between January and April 2005.*

search: '(heart or cardiac) and (renal or kidney) and (failure)'. The search was then repeated with the addition of 'and (anemia)'. An impressive growth in overall research activity has been seen over the last 15 years. However, whereas overall citation rates doubled, the proportion of the overall heart failure publications also citing 'renal' or 'kidney' declined from 17.5% to 11.0%. Whereas citations containing the additional term 'anemia' increased 3.4-fold, they continue to represent a small proportion of the overall total.

Heart failure and kidney failure are public health problems throughout the world and both are predominantly diseases of older adults. The former condition has been estimated to account for annual incidence rates of 550,000 cases and annual costs of $56 billion in the United States.[1-3] Heart failure is now the foremost cause of hospitalization in older adults.[4] Despite dramatic changes in the management of heart failure in the last 2 decades, the outlook for patients with overt heart failure remains generally guarded; 5-year survival rates of no more than 40% are observed using current treatment paradigms.[5-7]

Chronic kidney disease (CKD) is also common in the general population. The National Health and Nutrition Examination Survey (NHANES) shows that approximately 1 in 20 contemporary US adults has a glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2, a widely accepted threshold value of clinically significant disease.[8] Diabetes mellitus, hypertension, and, most especially, older age are associated with the development of CKD.[9-10] Prevalence estimates of CKD are notably higher in older populations. For example, a recent study examined residents aged 65 years or older in 4 communities in the United States in 1989 and 1990 and found that 22% had GFR levels below 60 mL/min/1.73 m^2.[11] Many community-based studies have shown a graded association between declining GFR and cardiovascular-event and death rates, even when adjusted for classic risk markers.[11-16]

Overt heart failure could be viewed as a state of incipient kidney failure, and vice versa. Many studies report that CKD is highly prevalent in patients with heart failure. For example, 1 group reported kidney function among participants in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) (N = 14,527). Patients with acute myocardial infarction complicated by clinically evident heart failure, left ventricular (LV) dysfunction, or both, were studied. Even though patients with serum creatinine levels above 2.5 mg/dL were excluded from the study, 22.2% had an estimated GFR of 45.0 to 59.9 mL/min/1.73 m^2 and 11.3% had levels below 45.0 mL/min/1.73 m^2; survival estimates paralleled GFR estimates.[15] Several other recent studies mirror this dual pattern of high prevalence and high associated mortality.[17-19]

Anemia, Kidney Disease, and Heart Failure: Associations With Outcomes

It has been known for over a decade that anemia, a cardinal feature of CKD, is associated with higher cardiovascular event rates in late-stage and end-stage renal disease.[20,21] Like CKD and heart failure, anemia is also a common condition that occurs with increasing prevalence as patients age. Recent estimates suggest that approximately 3.4 million Americans are anemic.[22] Although anemia is clearly more prevalent in people with heart failure than in the general population, estimates of the actual prevalence of anemia among patients with heart failure have varied widely, from 4% to 55%, in recent studies,[23-39] partly reflecting a heterogeneity of definition. Nonetheless, the following associations have been consistently observed in populations with heart failure: anemia is more prevalent in

Prevalence estimates of CKD are notably higher in older populations.

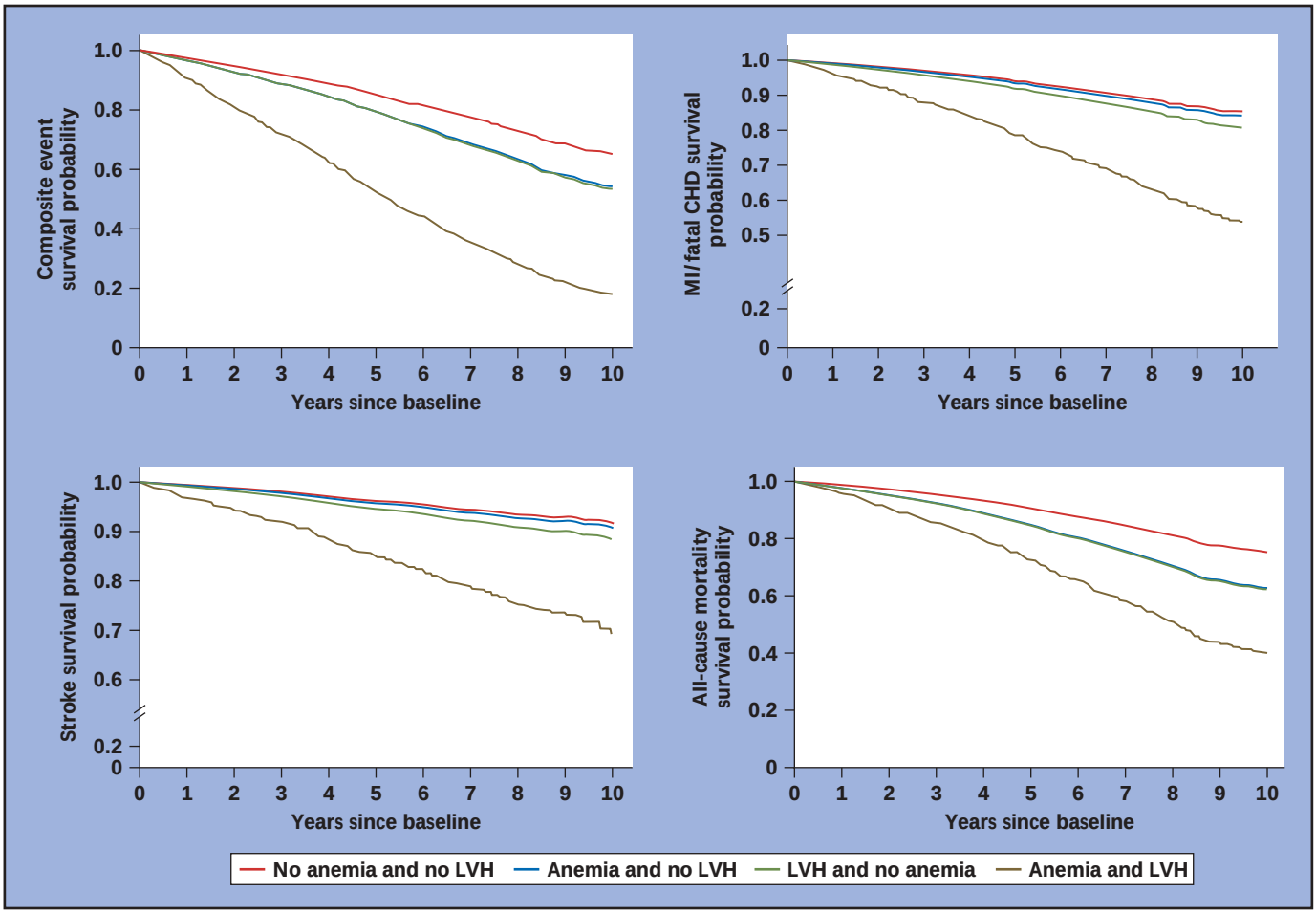

Figure 2. *Chronic kidney disease (CKD) patients with both anemia and left ventricular hypertrophy (LVH) have a nearly 4-fold increase in risk for adverse cardiovascular outcomes over a 10-year period. Data from an analysis of CKD patients in the Atherosclerosis Risk in Communities, Cardiovascular Health, Framingham Heart, and Framingham Offspring Studies. CHD, chronic heart disease. Reproduced with permission from Weiner DE, Tighiouart H, Vagopoulos PT, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease.* J Am Soc Nephrol. *2005;16:1803-1810.*

patients with more severe heart failure, reduced kidney function, and increasing age, and is associated with higher mortality rates.[40]

Left ventricular hypertrophy (LVH) is common in CKD, with an inverse relationship between LV mass and GFR. Anemia and LVH are associated with one another in CKD and both conditions exhibit multiplicative associations with cardiovascular events (see Figure 2).

Causes of Anemia in Heart Failure

The biologic mechanisms linking anemia, renal failure, and heart failure are incompletely understood. It is easy to imagine a scenario in which any one condition could cause the others. It is equally easy to imagine a scenario where all 3 conditions could reflect the presence of an unknown factor that leads to each independently. See Figure 3. With both scenarios, more severe anemia and worsening renal function and heart failure would occur in parallel. In the first scenario, interventions that change any one condition would be followed by changes in the other 2, a vicious circle; it has been hypothesized that such a scenario may exist as the 'cardio-renal anemia syndrome.'[25] It is worth pointing out an unfortunate prediction of genuine vicious circles. Even a small adverse change in one factor will lead to end-stage disease of all the component conditions. Given this idea, this scenario appears unrealistic. In the second scenario, all 3 conditions are caused by another unrecognized condition, condition X. Changes in X are accompanied by changes in hemoglobin and resultant changes in the severity of heart and renal failure. Thus, whereas hemoglobin level, heart function, and renal function change in parallel in response to changes in X, interventions that

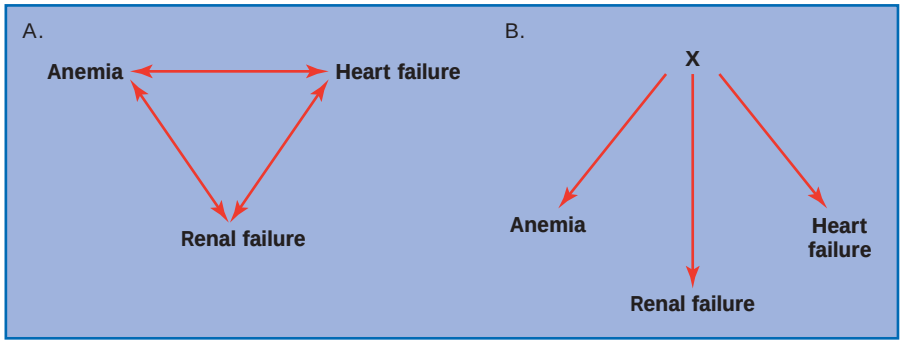

Figure 3. *Possible scenarios for the relationship between renal failure, heart failure, and anemia. The classic 'vicious circle'* **(A)**, *where a slight change in any one disease state leads quickly to end-stage in all 3, is less likely than the possibility of an 'X' factor* **(B)** *that affects each disease independently.*

change hemoglobin level, heart function, or renal function independently have no effect on the other conditions.

Few studies have systematically addressed the causes of anemia in patients with heart failure. One study used discharge diagnosis codes in 12,065 patients with new-onset heart failure between April 1993 and March 2001 in Alberta, Canada (a province with a total population of 3.06 million). Of these patients, 21% had iron deficiency, 8% had other deficiency states, and 13% had other identifiable causes of anemia. Thus, 58% had no identifiable cause of anemia, and were considered, by default, to have anemia of chronic disease.[27]

Erythropoietin is a glycoprotein produced by peritubular fibroblasts of the renal cortex, in response to low ambient oxygen tension; the latter reflects renal blood flow as well as oxygen utilization by the kidney. Oxygen utilization by the kidney is heavily influenced by tubule sodium reabsorption activity, and hence by the paracrine and endocrine systems, in particular the renin-angiotensin-aldosterone system.[41,42] Impaired erythropoietin production and resistance to erythropoietin are major contributors to anemia in patients with heart failure. Although impaired renal function is likely to be a principal cause of inadequate production, use of angiotensin-converting enzyme (ACE) inhibitors and the presence of pro-inflammatory cytokines have also been suggested to impair production.[43,44] Resistance to erythropoietin is also likely to play an important role in the pathogenesis of anemia in patients with cardiac and renal failure. Experimental studies in animals have shown that induction of heart failure lowers the pool size and proliferative capacity of pro-erythroblasts and increases the rates of pro-erythroblast destruction, an effect that is correlated with higher rates of tumor necrosis factor-mediated apoptosis.[45] To date, the role of inflammation in human subjects with heart failure remains poorly quantified.

Hemodilution is a cardinal feature of both decompensated heart failure and decompensated renal failure. One group studied the prevalence and clinical outcomes in 196 patients with heart failure. In addition, the prevalence of hemodilution was estimated in anemic patients with I131-tagged albumin. The prevalence of anemia increased from 33% in patients with New York Heart Association (NYHA) class II to 68% in class IV heart failure patients. Among patients with low hematocrit concentrations ($< 38\%$ in women and $< 41\%$ in men), 46% had hemodilution and 54% truly had low red blood cell mass.[33]

Hemoglobin Targets in CKD

Treatment Trials

Many factors beyond a direct causal link, could account for associations between anemia and outcomes in CKD populations. Randomized trials were necessary to evaluate the clinical effects of different hemoglobin targets.

Portoles and colleagues[46] reported on a prospective 6-month study of 11 predialysis patients receiving recombinant human erythropoietin (epoetin) treatment (initial dose, 1,000 U subcutaneously, 3 times per week). Clinical assessment and biochemical and hematologic measurements were made every 2 weeks in these patients, who were continuously monitored for blood pressure (BP) and echocardiography. Determination of neurohumoral mediators of hemodynamics were performed every 3 months. Adequate hematologic response was found (hemoglobin, 11.7 + 0.4 g/dL) without changes in the progression of renal disease. As anemia improved, a decrease in cardiac output and an increase in total peripheral resistance were seen. There was a trend toward decreased LV thickness, and a significant decrease in LV mass index (from 178.2 + 20.6 g/m^2 to 147.3 +/− 20.6 g/m^2) was observed. BP did not improve and in some patients an increase in systolic ambulatory BP occurred, while casual BP appeared to remain stable. The authors noted that sequential determinations of neurohormonal mediators of hemodynamic substances (endothelin, renin, norepinephrine, epinephrine, dopamine) failed to explain these results.

Additionally, Roger and associates,[47] reporting on effects of early and late intervention with epoetin alfa on LV mass among patients with

CKD (stage 3 or 4), presented results of a randomized, controlled, clinical trial in which 155 patients were monitored for two years or until they required dialysis. They were randomized to receive epoetin alpha as necessary to maintain hemoglobin concentrations between 120 and 130 g/L (group A), or between 90 and 100 g/L (group B). Hemoglobin increased for group A (112 + 9 to 121 + 14 g/L, mean + SD) and decreased for group B (112 + 8 to 108 + 13 g/L) ($P < 0.001$, group A vs group B). The intervention had no effect on LV mass index.

Another study randomly assigned 1233 hemodialysis patients with symptomatic heart disease to hemoglobin targets of 14 g/dL (normal-hematocrit group) or 10 g/dL (low-hematocrit group), using epoetin alfa.[48] The primary study outcome was time to occurrence of death or myocardial infarction and the intended study duration was at least 3 years per patient. The trial was terminated at a median interval of 14 months, at which time 29.6% and 3.1% of the normal hemoglobin group had died or suffered a myocardial infarction, respectively, compared with 24.4% and 2.3% in the lower hemoglobin target cohort. When interim analyses were taken into account, no statistically significant differences in rates of the primary study outcome were seen. Although the higher target was associated with better quality of life, it was also associated with dialysis vascular access thrombosis and a decline in urea clearance during the dialysis procedure.

A Scandinavian trial included 416 patients with anemia and various degrees of CKD (including patients not on dialysis and patients on hemodialysis or peritoneal dialysis), randomly assigned target hemoglobin levels of 13.5 g/dL to 16.0 g/dL or 9.0 g/dL to 12.0 g/dL, over 48 weeks or more, using epoetin alfa.[49] Higher hemoglobin targets led to improved quality of life in dialysis patients and rates of change of kidney function were similar. Intention-to-treat analysis showed that survival rates were similar in the 2 hemoglobin target groups.

Current guidelines suggest that patients with CKD should be treated to target hemoglobin levels of 11 g/dL to 12 g/dL regardless of coexisting medical conditions, including heart failure.[50] Although these guidelines are reasonable based on current knowledge, the evidence base is not entirely adequate. There is a need for more hard outcomes trials in different stages of CKD, and in patients with or without cardiovascular disease. Thus, anemic patients with CKD usually belong to one of the following characteristic categories: GFR below 30 mL/min/1.73 m^2 (not on renal replacement therapy), hemodialysis, peritoneal dialysis, and transplant. In addition, previous hemoglobin target trials have distinguished between patients with and without overt cardiovascular disease. Finally, trials have typically considered 3 types of hemoglobin targets, low (typical hemoglobin levels < 9 g/dL), intermediate (9-12 g/dL) and high (> 12 g/dL).

When stage of CKD, presence or absence of cardiovascular disease, and type of hemoglobin target are considered, it is easy to consider $4 \times 2 \times 3$, or 24 clinically differentiated groups of patients. To date, one hard outcomes trial has been performed. This study, described above, compared intermediate and high hemoglobin targets in hemodialysis patients with symptomatic cardiovascular disease.[48]

Few controlled trials of anemia therapy have been performed in patients with heart failure. One study included 32 patients with NYHA class III to IV heart failure and ejection fractions below 40%, with hemoglobin levels between 10.0 g/dL and 11.5 g/dL.[51] Patients were randomly assigned to either no anemia treatment, or to anemia treatment with epoetin alfa and intravenous iron (target hemoglobin above 12.5 g/dL). Over 8.2 months of follow-up, treated patients were more likely to exhibit symptomatic improvement and an increase in LV ejection fraction and less likely to die from heart failure, require intravenous loop diuretics, show an increase in serum creatinine, or require hospitalization. Another study randomly assigned 26 anemic patients with heart failure to epoetin alfa or placebo therapy for 3 months. Active therapy led to improvements in NYHA symptom class ($P < .05$), peak VO_2, and exercise duration, without apparent effects on resting and hyperemic forearm vascular resistance or rates of muscle oxidative capacity. Although noteworthy, larger trials with hard outcomes, such as heart failure-free survival rates, are needed to address the hypotheses suggested by these studies.

Darbepoetin Alfa

Recombinant erythropoietin, first approved for clinical use in 1988, with a half-life of 6 to 8 hours after intravenous administration,[52,53] increases red blood cell mass by inhibiting the apoptosis of bone marrow erythroid precursors.[54] Erythropoietin exerts its action on erythroid precursors through specific membrane-bound receptors. A direct relationship exists between the sialic acid-containing carbohydrate content of the molecule and its serum half-life and in vivo biological activity. An inverse relationship exists with its receptor-binding affinity.[55]

Darbepoetin alfa was engineered to contain more N-linked carbohydrate chains than erythropoietin, and has an approximately 3 times longer serum half-life.[56] See Figures 4 and 5. Several clinical trials have addressed the hypothesis that darbepoetin alfa can effectively treat renal anemia at dose frequencies of once per week, or less often. A randomized, double-blind, non-inferiority study tested whether darbepoetin alfa was as effective as epoetin in hemodialysis patients, when administered at a reduced dosing frequency.[57] Patients receiving epoetin therapy were randomly assigned to continue epoetin (administered intravenously 3 times weekly, n = 338) or change to darbepoetin alfa (administered intravenously, once weekly, n = 169), over a 6-month period. Hemoglobin levels were similar in both study arms, as were safety profiles. Another study examined 522 hemodialysis and peritoneal dialysis patients receiving epoetin therapy by either intravenous or subcutaneous routes. Patients on once-weekly epoetin changed to darbepoetin alfa once every 2 weeks, and those on epoetin more frequently changed to once-weekly darbepoetin alfa. Hemoglobin levels were similar with both strategies.

In a multicenter, randomized, open-label study to determine whether darbepoetin alfa is effective for the treatment of anemia at a reduced dosing frequency, relative to epoetin, in patients with chronic renal failure, but not yet on dialysis, Locatelli and colleagues[58] found among 166 epoetin-naïve patients with CKD not on dialysis that darbepoetin alfa and epoetin had similar safety profiles and no antibodies were detected to either drug. Their results demonstrated that darbepoetin alfa safely and effectively corrected and maintained hemoglobin concentrations at a reduced dosing frequency, relative to epoetin, in patients with CKD not on dialysis, proving a potential benefit.

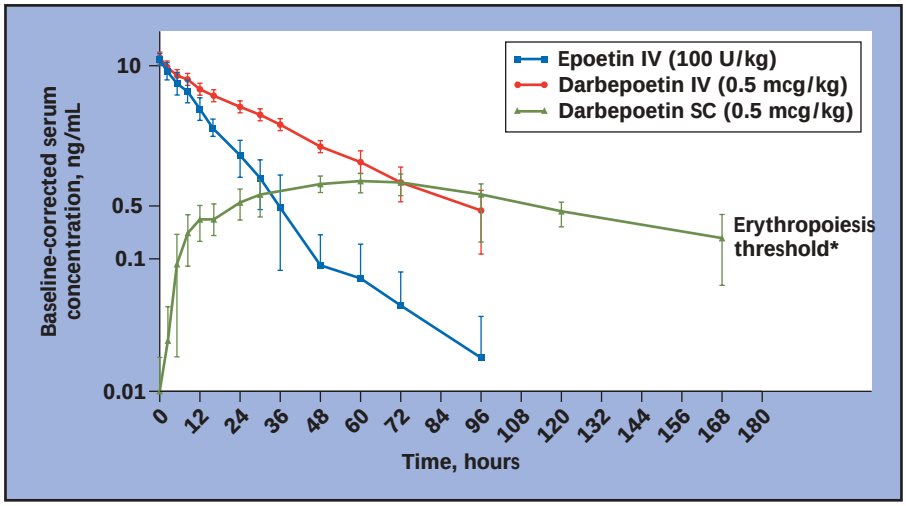

Figure 5. *Pharmacokinetics of darbepoetin alfa injected intravenously (IV) and subcutaneously (SC) versus IV injected epoetin. Reproduced with permission from MacDougall IC. Darbepoetin alfa: A new therapeutic agent for renal anemia.* Kidney International. *2002;61(suppl 80):S55-S61.*

In a multicenter, open-label study of 76 epoetin-naïve patients enrolled to receive darbepoetin alfa (0.75 mcg/kg) biweekly for up to 24 weeks, Suryani and colleagues[59] reported that 97% of the patients completing 24 weeks of treatment achieved a hemoglobin response. The median time to response was 5 weeks, and the median dose of darbepoetin alfa at the time of response was 60 mcg. It was safe and well tolerated, and no antibodies were detected. The authors concluded that the results demonstrated the utility of darbepoetin alfa administered once every other week in epoetin-naïve CKD patients, and this new treatment paradigm may allow for more widespread management of anemia in patients with CKD.

Reporting on a multicenter, open-label study to determine the safety and efficacy of once-every-other-week administration of darbepoetin alfa for anemia and CKD in erythropoietin-naïve patients not on dialysis, Toto and associates[60] found the drug to be safe and effective for achieving and maintaining target hemoglobin levels in anemic patients with CKD. Of the 463 patients who completed treatment, with 95% achieving a hemoglobin response, the mean darbepoetin alfa dose at the time of response was 63.5 ± (SD) 16.9 mcg, and the

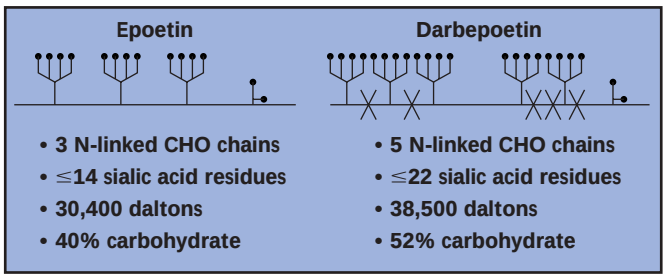

Figure 4. *Structure of recombinant human erythropoietin (epoetin, left) versus darbepoetin alfa (right). ×s marked on darbepoetin represent 5 amino acid exchange sites required to allow the attachment of 2 extra n-linked carbohydrate chains. Reproduced with permission from MacDougall IC. Darbepoetin alfa: A new therapeutic agent for renal anemia.* Kidney International. *2002; 61(suppl 80):S55-S61.*

mean time to hemoglobin response was 5.7 ± (SD) 4.5 weeks. Oral iron therapy was administered to 60% and intravenous iron to 16% of the participants. Darbepoetin alfa was well tolerated and adverse events were consistent with those expected in patients with CKD, and it was effective and safe for achieving and maintaining target hemoglobin levels in patients with CKD.

Additionally, Ling and colleagues[61] reported on a multicenter, open-label study of 97 patients with CKD not on dialysis and concluded patients with CKD who are clinically stable on darbepoetin alfa administered once every 2 weeks can be safely and effectively converted to darbepoetin alfa administered once monthly.

All things being equal, the ability to reduce dosing frequency, without compromising efficacy, would be an attractive feature of a new therapy, especially for treatments requiring intravenous or subcutaneous administration. It remains a fundamental truth that adequately powered, randomized, controlled trials are needed to evaluate the risks and benefits of all therapies, irrespective of their perceived benefits. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)[62] is an ongoing, double-blind trial of 4000 patients, examining the impact of anemia therapy with darbepoetin alfa on mortality and nonfatal cardiovascular events in patients with chronic kidney disease (CKD) and type 2 diabetes mellitus. The intervention being tested consists of random assignment to darbepoetin alfa, with a hemoglobin target of 13 g/dL, or to a placebo, with active rescue to maintain hemoglobin levels above 9 g/dL. This study, which addresses a clinically important issue, is expected to conclude in approximately 4 years. ■

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Main Points

- Although heart failure and kidney failure frequently co-exist, this combination of disease states has received comparatively little attention, in terms of clinical research, versus investigations of each individually.
- Although the biologic mechanisms linking anemia, renal failure, and heart failure are incompletely understood, the prevalence of anemia is consistently higher in patients with more severe heart failure and is associated with higher mortality rates in heart failure patients.
- Impaired erythropoietin production and resistance to erythropoietin both play an important role in the pathogenesis of anemia in patients with cardiac and renal failure; therapy with recombinant erythropoietin (epoetin alfa) has been used to raise hemoglobin levels in anemic patients, in hopes of improving outcomes for both disease states.
- Current guidelines suggest that patients with chronic kidney disease (CKD) should maintain hemoglobin levels of 11 g/dL to 12 g/dL regardless of co-existing medical conditions, including heart failure. However, the evidence base for these guidelines is not entirely adequate and requires more research of hard outcomes in patients with both diseases.
- Darbepoetin alfa was engineered to contain more N-linked carbohydrate chains than erythropoietin, and has an approximately 3 times longer serum half-life; several clinical trials have addressed the hypothesis that darbepoetin alfa can effectively treat renal anemia at dose frequencies of once per week, or less often, with promising results.
- The Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT) is an on going, double-blind trial of 4000 patients, examining the impact of anemia therapy with darbepoetin alfa on mortality and nonfatal cardiovascular events in patients with CKD and type 2 diabetes mellitus.

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