Leading with Innovation
Serving with Compassion
St. Michael's Hospital
A teaching hospital affiliated with the University of Toronto
Terrence Donnelly Heart Centre

Cardiology

University of Toronto

Special Feature
Visit us at www.cardiologyupdate.ca for PowerPoint teaching slides on this topic

AN EDUCATIONAL PUBLICATION FROM THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

Treating Anemia in the Setting of Heart Failure due to Systolic Left Ventricular Dysfunction: Controversies and Recent Data

Originally presented by: James Young, MD

A Review of a Presentation at a Satellite Symposium at the 56th Annual Scientific Session of the American College of Cardiology

New Orleans, Louisiana March 24-27, 2007

By JONATHAN HOWLETT, MD

It is widely known that heart failure, a chronic condition characterized by myocardial dysfunction, salt and water retention, and associated with significant morbidity and mortality, frequently coexists in the setting of multiple comorbid conditions. Many of these, such as chronic kidney disease (CKD), ischemic heart disease, and diabetes, are known to independently confer a worse prognosis. Less commonly discussed, however, is the presence of anemia. This issue of *Cardiology Scientific Update* presents new data regarding the management of anemia in heart failure and reviews the clinical implications.

Prevalence, associated conditions, and etiology of anemia in heart failure

A review of published clinical trials and observational registries indicates that the prevalence of anemia ranges from 10% (in the Valsartan Heart Failure Trial [Val-HeFT]) to over 50% in single-centre heart failure (HF) cohorts with advanced HF or hospitalized patients.[1-5] Several studies have demonstrated that patients with anemia suffer with worse signs and symptoms of HF, are older, are more likely to have coexistent CKD, have higher serum brain natriuretic peptide (BNP) levels, and lower systemic blood pressure (BP).[1-7] Interestingly, studies have not shown a consistent relationship between anemia and left ventricular ejection fraction (LVEF), suggesting that EF does not play a role in this condition. In general, the likelihood of anemia increases with higher levels of New York Heart Association (NYHA) functional class and serum creatinine.[1,4,7-11]

In most cases, the etiology of anemia is multifactorial. Many anemic patients have impaired renal function and suffer a relative lack of erythropoietin (EPO), while others have relatively normal levels.[6,10] Since EPO levels should be higher in the setting of anemia, this raises the possibility of EPO resistance, possibly due to the presence of oxidative stress. Data to support this notion come from the Vesnarinone in Heart Failure trial (VEST) database, in which patients with anemia were shown to have significantly higher serum levels of tumour necrosis factor (TNF), in addition to its soluble forms, as well as interleukin-6 and its soluble form.[12] Further data from the Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) database indicate that patients with anemia also exhibit a higher pro-anti-inflammatory ratio, again suggesting the role of oxidative stress.[1]

A recent, small, single-centre study from Greece suggests that iron deficiency may be much more prevalent than previously thought.[13] Iron deficiency has been commonly described in HF patients due, in part, to malnutrition, poor absorption, chronic gastritis, or even drug interactions. However, there is little in terms of large-scale systematic data to delineate the exact prevalence of substrate deficiency as a cause of anemia in the HF setting. Other substrate deficiencies (eg, B_{12} or folate) may also be present.[14] Finally, plasma expansion due to fluid retention may occur; however, once again, the exact importance of this finding has not been well-characterized.[15]

The prognostic implications of anemia in HF

Is it important to recognize anemia? Data from several clinical trials consistently reveal that HF patients with anemia suffer worse symptoms and quality-of-life than those without anemia.

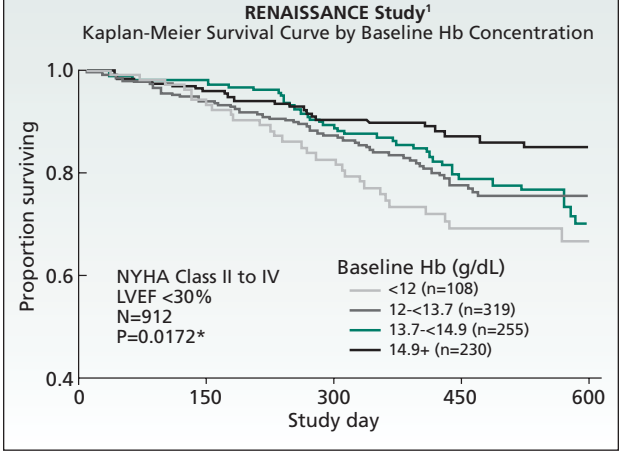
St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

In addition, anemia is an independent predictor of hospitalization and survival.[16] For example, in the RENAISSANCE trial,[1] patients with a hemoglobin (Hb) of <120 g/L at study entry had a 28% 1-year mortality, while those whose entry Hb was >149 g/L had a 16% 1-year mortality; this represented a 75% increase by log rank test (p<0.018) (Figure 1). In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study, patients were stratified by hematocrit quintiles. In the group whose levels were <37.6%, each 1% drop in hematocrit was associated with an 11% increase in 1-year mortality when corrected for other factors.[16] In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study,[17] patients whose baseline Hb levels were <110 g/L experienced nearly a 2-fold increase in the rate of death or hospitalization at 1 year versus those with normal Hb levels (47% vs. 25%).

The data are less dramatic, but still robust in observational cohorts. In one large cohort, Kosiborod et al reported that any increase in mortality related to anemia was largely explained by comorbid illnesses; however, these data were taken from the National Heart Care Project, which was not strictly a heart failure registry.[18] Ezekowitz et al also reported an increase in mortality in patients from Alberta with new-onset HF; this increase in mortality persisted after correction for comorbid conditions.[8] Finally, in the largest study of all (>90,000 patients), Alexander reported that the presence of anemia was associated with an independent and significant 16% increase in hospitalization at 1-year.[19] Other smaller observational studies reveal similar results. In 2005, Anand et al published an analysis of the Val-HeFT study that outlined outcomes related to change in plasma Hb between baseline readings and 12-month follow-up.[2] They found that patients whose Hb dropped by >8 g/L had the highest mortality (13.2%), when compared with those whose Hb dropped by less (9.9%; p=0.024), suggesting that changes in plasma Hb over a period of time is related to mortality.

Taken together, these data indicate that the correlates of anemia, including symptoms, morbidity, and mortality, are independent and significant and, thereby, represent a legitimate target for therapies that may affect the natural course of HF.

Figure 1: Anemia and mortality in heart failure patients[1]



*Log-rank test; 1-year mortality was 28% in anemic subjects (Hb <12 g/dL) vs. 16% in non-anemic subjects

How should we treat anemia of HF?

The recently published Canadian Cardiovascular Society Consensus Conference recommendations on HF, updated in 2007,[20] include a section entitled, "Heart Failure and Intercurrent Illness." This section includes recommendations regarding the management of anemia in the setting of HF (Table 1).[20] However, there is little randomized evidence to support the therapy that is reflected in the recommendations. In general, the investigation of anemia includes a careful history and physical examination, with particular emphasis on dietary intake of iron, B_{12}, and folate, enquiries about gastrointestinal blood loss, the presence of inflammatory and malignant diseases (eg, seropositive arthropathies), use of immune suppressive agents and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as routine blood analysis (complete blood count, serum ferritin, and transferrin saturation). Other special testing – up to and including endoscopy – may also be necessary, as clinically indicated.

Potential therapies for anemia of HF may include the provision of deficient substrates (usually elemental iron), reduction of volume overload, treatment of underlying causes (eg, gastrointestinal bleeding), and exogenous supple-

Table 1: 2007 CCS Consensus Conference heart failure recommendations for anemia

Recommendation

- Patients with HF and anemia (plasma hemoglobin <110 g/L or hematocrit <35%) should be carefully evaluated for underlying causes such as chronic blood loss or other inflammatory illness. Iron, vitamin B_{12}, or folate deficiencies should be treated (class I, level C).

Practical tips

- Patients with severe anemia should be assessed by a physician experienced in the diagnosis and management of anemia, and underlying causes should be treated using intravenous means, if necessary.
- There is currently insufficient evidence to support the routine use of bone marrow-stimulating drugs to increase hemoglobin levels in HF patients.
- In general, plasma hemoglobin levels < 90 g/L are associated with increased symptoms of HF. In this setting, consideration may be given to blood transfusion or a bone marrow-stimulating agent if advanced symptoms are present and after substrate deficiencies have been corrected.

mentation of erythrocyte-stimulating agents (ESA), including recombinant erythropoietin or darbepoetin). Blood transfusions may be necessary, but are generally considered a last resort to control severe HF symptoms.

Therapy with erythrocyte-stimulating agents (ESAs) in HF

If anemia is related to increased symptoms and adverse outcomes in patients with HF, it would be expected that correction of anemia might reverse these findings. However, relatively few prospective studies evaluating the effects of ESAs on outcomes in HF patients with anemia have been performed. The literature contains 5 studies from 2 groups of investigators that included a total of approximately 200 patients.[21-24] In one study, Mancini et al randomized 23 patients with anemia, reduced LVEF, and advanced HF to single-blind EPO or placebo.[21] Over the study period, patients receiving EPO had a significant improvement in all endpoints compared with those receiving placebo, with up to a 20% treatment effect (6-minute walk test). The potential mechanisms for these effects are not known. However, preclinical work with ESAs has suggested that, in addition to improvement in tissue oxygen delivery, stimulation of erythrocyte progenitor cells may occur, limiting ischemic damage.[25-27] These effects may play a role in modulation of oxidative stress and myocardial apoptosis, although no direct human data are currently available.

In summary, earlier studies demonstrate that the addition of EPO is associated with improved LVEF, reduced symptoms, and lower risk of all-cause hospitalization. Small, open-label, randomized studies reveal similar results. As a result, interest in the use of ESAs in the treatment of anemia of HF has increased and is currently undergoing investigation.

Experience with ESAs in CKD and cancer patients: Is there a risk?

The concept that administration of ESAs corrects anemia is not new. This therapy has been primarily studied in 2 conditions, namely, stage 5 CKD, or in association with combination chemotherapy for malignancy. Use of these agents has been standard practice since early studies revealed that EPO improved plasma Hb levels, symptoms, and quality-of-life, and resulted in fewer blood transfusions in patients with severe anemia.[28-30] As a result, it is now a part of standard therapy to correct severe anemia to a target of approximately 100-110 g/L. Adverse events such has hypertension, platelet activation, and thrombosis have been reported with the clinical use of ESAs.

More recently, studies have focused on the use of ESAs for correction of anemia to a higher, versus a lower, target level. A study by Besarab randomized 1,233 patients to 2 regimens of EPO in order to achieve a target hematocrit of 42% vs 30%.[31] This study was stopped prematurely due to a trend towards an increase in the composite endpoint of death or myocardial infarction (MI). While there were no differences in blood pressure between the 2 groups, there was a noted increase in vascular access thrombosis, which has since been noted in other studies of higher-dose EPO. Singh et al, in the Correction of Hb and Outcomes In Renal insufficiency (CHOIR) study, randomized 1,432 patients to receive EPO in order to achieve either a standard target of just over 113 g/L versus >135 g/L.[32] In this study, the higher target group had a higher risk for the primary endpoint of death, MI, HF, or stroke (hazard ratio [HR] 1.34; 95% confidence interval [CI],1.04-1.71; 125 vs. 97 events). The increased event rate was largely attributed to an increase in death (52 vs 36) and hospitalization for HF (64 vs 47). In the Cardiovascular Risk reduction with Early Anemia Treatment by Epoetin beta (CREATE) study, 603 patients were randomized to either usual care or a strategy of normalization of plasma Hb.[33] In this study, a composite cardiovascular endpoint was not significantly different between the 2 groups and there was no blood pressure effect. Observers have speculated that several factors may have affected the results of these studies (eg, iron overload), although no data are currently available to definitively support this.

It should be noted that these studies were not placebo-controlled and, while patients with HF were not necessarily excluded, they were not well-characterized as a group. This prompts questions as to what their LV systolic function and underlying therapy were, especially in respect to antithrombotic agents that are frequently used in HF patients. Finally, over one-third of patients in the CHOIR study were, due to the study design, censored from the final analysis. This may have increased the number of patients lost to follow-up and the potential risk of drawing misleading conclusions regarding treatment effects on morbidity and mortality.

The successful use of ESAs for the treatment of chemotherapy-related anemia in malignancy has led to an interest in expanding this therapy for prophylactic use.[34] Several randomized, open-label, clinical studies (some placebo-controlled) have been reported in patients with several different malignancies, including non-small-cell lung, breast, and head and neck cancers.[35-38] Another study into the prophylactic use of ESAs was in patients undergoing spinal surgery.[39] All of these studies did not include treatment with anticoagulation or antiplatelet agents and all failed to meet their primary endpoint. Indeed, a signal for harm was seen with increases in fatal thrombotic events, progression of malignancy, and overall mortality. As a result, Health Canada has issued a safety update regarding the use of ESAs:

- Healthcare professionals are advised to titrate the dose of ESA that will gradually increase the Hb concentration to the lowest level sufficient to avoid blood transfusions. Hb levels

during ESA treatment should not exceed 120 g/L. (This may not be applicable to all surgery patients, see below).
- Patients treated with epoetin alfa prior to elective surgery, for the purposes of reducing the requirements for allogeneic blood transfusion, should receive adequate antithrombotic prophylaxis in order to reduce the incidence of deep venous thrombosis.

It is important to recognize that this advisory did not include any use where there are existing approved clinical indications, ie, all of these studies were performed outside the settings where ESAs have been approved for use. Nevertheless, it would be interesting to see if these cautions apply to the HF population, a setting where another ESA – darbepoetin alfa – is under active investigation.

Darbepoetin alfa therapy for treatment of anemia of HF

As mentioned above, earlier data from studies of EPO in patients with HF were small, nonrandomized, or not controlled. However, 3 phase II, double-blind, randomized, multi-centre, placebo-controlled studies were conducted using darbepoetin-alfa in patients with mild-to-moderate HF, LV systolic dysfunction, and anemia.

- In the first, which included 41 patients, a trend towards improved exercise tolerance and quality-of-life was seen at 6 months.[40]
- In the second, the Study of Anemia in Heart Failure (STAMINA-HF) trial, a similar trend towards improved exercise time, as well as reduced hospitalization at 12 months in 319 patients, was observed.[41]
- The third study examined 2 dosing regimens versus placebo in 165 patients and showed trends toward improvement in exercise tolerance and quality-of-life.[42]

None of the studies demonstrated improved mortality but, taken together, they provide a strong signal towards reductions in the composite of death or HF hospitalizations (HR 0.67; 95% CI, 0.44-1.03; p=0.06) and death alone (HR 0.76; 95% CI, 0.39-1.48). Table 2 shows the adverse event data from the 2 largest and longest trials of darbepoetin alfa.[40,41] It is also important to note there was no increase in adverse events or any signal of harm (Table 3) in the pooled analysis of all phase II patients with HF.[40,41]

Table 2: Pooled results from the two largest Phase 2 darbepoetin alfa HF studies: All-cause mortality and all-cause mortality and first HF hospitalization[40,41]

Outcomes measures	Hazard ratio (95% CI)
Composite morbidity and mortality	0.67 (0.44-1.03)
All-cause mortality	0.76 (0.39-1.48)
HF hospitalization	0.66 (0.40-1.07)

It is important to be aware that these preliminary data contrast with observations in patients with CKD and cancer and may be due to different target populations and baseline characteristics (eg, renal function or malignancy, use of a placebo control rather than active control, concomitant use of antithrombotic and anticoagulation therapies in the darbepoetin alfa studies, and the intervention, darbepoetin alfa, itself).

The Reduction of Events with Darbepoetin alfa in HF (RED-HF) Study

Given the promising data for darbepoetin alfa in HF patients taken from the phase II studies, the RED-HF study[43] commenced in June 2006 and is actively recruiting in >60 countries worldwide, including Canada (with >30 sites). In RED-HF, 3,400 patients with HF, LV systolic dysfunction, and plasma Hb levels between 90 and 120 g/L (in the setting of adequate iron stores), will be randomized 1:1 to usual care or darbepoetin alfa in order to achieve a Hb target of >130 g/L (but not exceeding 145 g/L). All other HF therapies are allowed and there is a fully independent Data Monitoring Committee. The trial is 90% powered to detect a 15% reduction in the primary endpoint of death or HF hospitalization and will be event-driven, until 900 have occurred. It is expected to have ≥3 years of follow-up.

The RED-HF trial differs from other studies of ESAs in several ways[32,33,43,44] (Table 4). It is placebo-controlled,

Table 3: Pooled safety data from the two largest Phase 2 darbepoetin alfa HF studies[40,41]

	Placebo n = 209	Darbepoetin alfa n = 264
Any adverse events, n (%)	**184 (88)**	**231 (88)**
Serious adverse events, n (%)	**94 (45)**	**101 (38)**
Deaths, n (%)	**18 (9)**	**17 (6)**
Number of subjects with adverse events of special interest, n (%)	67 (32)	69 (26)
• Hypertension	12 (6)	15 (6)
• Deep vein thrombosis	2 (1)	0 (0)
• Pulmonary emboli	1 (<1)	0 (0)
• Worsening heart failure	53 (25)	50 (19)
• Cerebrovascular disorder	4 (2)	9 (3)
• Myocardial infarction	5 (2)	6 (2)
• Seizure	2 (1)	1 (<1)

No anti-erythropoietic protein neutralizing antibodies were detected

Table 4: Comparison of trials with erythropoietin

	CREATE n=603	CHOIR n=1432	TREAT n=4000*	RED-HF n=3400
Study population	CKD	CKD	CKD	CHF
Inclusion criteria GFR (ml/min/1.73 m^2) Hb eligibility (g/dL)	 15-35 11-12.5	 15-50 ≤11	 20-60 ≤11	 "Normal" 9-12
Target Hb (g/dL) in treatment arm	13-15	13.5	13.0	13.0
Study drug	Epoetin beta	Epoetin alfa	Darbepoetin alfa	Darbepoetin alfa
Control arm	Active	Active	Placebo	Placebo
Presence of diabetes	26%	49%	100%	(30?)**
Presence of heart failure	32%	23%	(30%?)**	100%
Presence of hypertension Baseline systolic BP (mm Hg)	90% 139	94% 136	(70%?)** (135-140?)**	(40%?)** (110?)**
Baseline GFR (ml/min/1.73 m^2)	24.5	27.2	(25?)**	(53?)**
No. of patients experiencing a primary cardiovascular endpoint	105	222	~900	~1450*

* Projected; study still ongoing; **assumptions; based on similar/earlier studies. Adapted from: *Eur J Heart Fail* 2007;9:110-112.
BP = blood pressure; CKD = chronic kidney disease; CHF = chronic heart failure, GFR = glomerular filtration rate

double-blind, randomized, and targets a well-defined HF population.[32,33,43,44] The dominant feature of this population is not CKD, as shown by the much higher mean glomerular filtration rate (GFR) at baseline. It will be powered to show a significant impact on morbidity and mortality. Concurrent therapies, especially anti-thrombotic and anticoagulation therapy, will be well-characterized. Lessons learned from the EUROPA[45] and PEACE[46] trials reveal that differences in target patient populations may result in significant differences in study outcomes. Similarly, the ELITE-I and II studies[47,48] remind us that properly-powered outcome studies are required to establish therapeutic efficacy. As such, one would expect the RED-HF study to provide the definitive answer to the issue of ESA use for treatment of anemia of HF.

Anemia and HF: Conclusions

Accumulated evidence suggests that anemia is an important comorbid condition in patients with HF that is independently related to adverse outcomes. The initial diagnosis of anemia and its evaluation should take into account the multifactorial nature of anemia of HF, recognizing that a significant number of these patients have CKD. Treatment should be tailored according to the underlying cause and frequently includes supplemental substrate administration, such as oral or intravenous iron. The current use of ESAs in HF patients with anemia should be limited to patients with severe anemia and significant symptoms, according to recently published CCS Heart Failure Consensus Conference recommendations.[20] Recently, data suggesting toxicity with ESAs has raised concern over their off-label use; however, such data were not derived from HF populations. While there is promising evidence that suggests administration of ESAs in mild- to moderately-anemic HF patients may improve morbidity and mortality, it is important to await the results of pivotal randomized trials in this area, such as the RED-HF trial.

References

1. Anand I, McMurray JJ, Whitmore J, et al. Anemia and its relationship to clinical outcome in heart failure. *Circulation* 2004;110:149-54.
2. Anand IS, Kuskowski MA, Rector TS, et al. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation* 2005;112:1121-7.
3. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003;24:442-63.
4. Maggioni AP, Opasich C, Anand I, et al. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail* 2005;11:91-8.
5. McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. *J Am Soc Nephrol* 2002;13:1928-36.
6. McCullough PA, Lepor NE. The deadly triangle of anemia, renal insufficiency, and cardiovascular disease: implications for prognosis and treatment. *Rev Cardiovasc Med* 2005;6:1-10.
7. O'Meara E, Clayton T, McEntegart MB, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 2006;113:986-94.
8. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12,065 patients with new-onset heart failure. *Circulation* 2003;107:223-5.
9. Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM. The prognostic importance of anemia in patients with heart failure. *Am J Med* 2003;114:112-9.
10. McCullough PA, Lepor NE. Piecing together the evidence on anemia: the link between chronic kidney disease and cardiovascular disease. *Rev Cardiovasc Med* 2005;6 Suppl 3:S4-12.
11. Vaglio J, Safley DM, Rahman M, et al. Relation of anemia at discharge to survival after acute coronary syndromes. *Am J Cardiol* 2005;96:496-9.

12. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation* 2001; 103:2055-9.
13. Bolger AP, Bartlett FR, Penston HS, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol* 2006;48:1225-7.
14. Parsi A, Kleber FX. Anaemia in heart failure: its diagnosis and management. *Eur J Heart Fail* 2003;5:3-4.
15. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. *Circulation* 2003;107:226-9.
16. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). *J Am Coll Cardiol* 2003;41:1933-9.
17. Anker SD, Coats AJS, Roecker EB, et al; The COPERNICUS Study Group. Hemoglobin level is associated with mortality and hospitalization in patients with severe chronic heart failure: results from the COPERNICUS study. *J Am Coll Cardiol* 2004;43(Suppl A):216A.
18. Kosiborod M, Curtis JP, Wang Y, et al. Anemia and outcomes in patients with heart failure: a study from the National Heart Care Project. *Arch Intern Med* 2005;165:2237-44.
19. Alexander M, Grumbach K, Remy L, Rowell R, Massie BM. Congestive heart failure hospitalizations and survival in California: patterns according to race/ethnicity. *Am Heart J* 1999;137:919-27.
20. Arnold JM, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: Prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. *Can J Cardiol* 2007;23:21-45.
21. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, Androne AS. Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. *Circulation* 2003;107:294-9.
22. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol* 2000;35:1737-44.
23. Silverberg DS, Wexler D, Blum M, et al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. *Nephrol Dial Transplant* 2003;18:141-6.
24. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol* 2001;37:1775-80.
25. Bahlmann FH, De Groot K, Spandau JM, et al. Erythropoietin regulates endothelial progenitor cells. *Blood* 2004;103:921-6.
26. Parsa CJ, Kim J, Riel RU, et al. Cardioprotective effects of erythropoietin in the reperfused ischemic heart: a potential role for cardiac fibroblasts. *J Biol Chem* 2004;279:20655-62.
27. van der Meer P, Lipsic E, Henning RH, et al. Erythropoietin induces neovascularization and improves cardiac function in rats with heart failure after myocardial infarction. *J Am Coll Cardiol* 2005;46:125-33.
28. Beusterien KM, Nissenson AR, Port FK, Kelly M, Steinwald B, Ware JE, Jr. The effects of recombinant human erythropoietin on functional health and well-being in chronic dialysis patients. *J Am Soc Nephrol* 1996;7:763-73.
29. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987;316:73-8.
30. Lim VS, DeGowin RL, Zavala D, et al. Recombinant human erythropoietin treatment in pre-dialysis patients. A double-blind placebo-controlled trial. *Ann Intern Med* 1989;110:108-14.
31. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584-90.
32. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.
33. Drueke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355: 2071-84.
34. Atabek U, Alvarez R, Pello MJ, et al. Erythropoetin accelerates hematocrit recovery in post-surgical anemia. *Am Surg* 1995;61:74-7.
35. http://clinicalstudyresults.org/documents/company-study_2157_o.pdf.
36. http://frejacms.au.dk/dahanca/get_media_file.php?mediaid=125.
37. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005;23:5960-72.
38. Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. *J Clin Oncol* 2007;25:1027-32.
39. http//download.veritasmedicine.com/PDF/DR004621_toplineresults.pdf.
40. Abraham WT, Klapholz M, Anand I, et al. Safety and efficacy of darbepoetin alfa treatment in anemic patients with symptomatic heart failure: a pooled analysis of two randomized, double-blind, placebo-controlled trials. *Euro Heart J* 2006;27(Abstract Supplement):166-167.
41. Coletta AP, Tin L, Loh PH, Clark AL, Cleland JG. Clinical trials update from the European Society of Cardiology heart failure meeting: TNT subgroup analysis, darbepoetin alfa, FERRIC-HF and KW-3902. *Eur J Heart Fail* 2006; 8:547-9.
42. Cleland JG, Coletta AP, Clark AL, Velavan P, Ingle L. Clinical trials update from the European Society of Cardiology Heart Failure meeting and the American College of Cardiology: darbepoetin alfa study, ECHOS, and ASCOT-BPLA. *Eur J Heart Fail* 2005;7:937-9.
43. Young JB, Anand IS, Diaz R, et al. Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) Trial. *J Card Fail* 2006;12:S77.
44. Mix TC, Brenner RM, Cooper ME, et al. Rationale—Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT): evolving the management of cardiovascular risk in patients with chronic kidney disease. *Am Heart J* 2005;149: 408-13.
45. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
46. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351: 2058-68.
47. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-7.
48. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-52.

Dr. Howlett declares that he has received research grants from AstraZeneca, Merck Frosst, and Novartis. He has also been a consultant and/or a member of the speakers bureau for the same companies, as well as, Pfizer, Servier, Boehringer Ingelheim, Abbott, Ortho Biotech, and Schering.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Amgen to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology, St. Michael's Hospital, and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.

Publications Post #40032303

SNELL

202-084