Anemia and Cardiovascular Risk: The Lesson of the CREATE Trial

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Anemia has received increasing attention as an independent cardiovascular risk factor in patients with chronic kidney disease (CKD); a number of studies have highlighted its clear relationship with CKD mortality, because its impact on cardiac function leads to the development of left ventricular hypertrophy. However, despite the association between higher hemoglobin levels and better outcomes, a number of clinical studies have failed to demonstrate that fully correcting anemia has a positive effect on morbidity and mortality in patients with CKD. The Cardiovascular Reduction Early Anemia Treatment Epoetin β (CREATE) study was designed from the hypothesis that, as anemia develops early in the course of CKD and nearly at the same time as cardiovascular disease, its earlier correction may provide better protection against the development of cardiovascular abnormalities. This randomized, multicenter, open-label, parallel-group trial involved 603 patients who had moderate anemia (hemoglobin 11 to 12.5 g/dl) and stage 3 to 4 CKD (estimated GFR 15 to 35 ml/min) and were randomly assigned to attain complete or partial anemia correction. The final results are due to be published within a few months, but the preliminary analyses do not show that complete anemia correction leads to any cardiovascular advantage, although the cardiovascular event rate was half that expected, possibly as a result of patient selection, trial effect, and improved medical care. The baseline findings also indicated that the burden of cardiovascular disease already is very high even in relatively early stages of CKD.

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Despite the many advances in our understanding and management of the cardiovascular risk factors that are related to chronic kidney disease (CKD), cardiovascular disease (CVD) still is the leading cause of death and hospitalization among patients with ESRD (1,2). The prevalence of this complication already is high at the start of renal replacement therapy (3,4), thereby indicating that the processes that contribute to its pathogenesis are closely related to those that occur during the course of even the earliest stages of CKD. This also is supported by the observation that the proportion of patients who have CKD and progress toward ESRD is much lower than that of patients who die, largely as a result of CVD, before ESRD is reached (5,6).

There is concern, therefore, about the devastating impact of CVD during the early stages of CKD on the long-term clinical outcome of patients, and this underlines that the nephrologic treatment of patients with CKD should be focused mainly on strategies that aim to prevent the development of cardiovascular complications, rather than only slow the progression of renal impairment. In addition to hypertension, anemia has attracted increasing attention in the past 10 yr as one of the major factors that contribute to the development of cardiovascular abnormalities in patients with CKD.

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Association between Anemia and CVD: Observational Studies

A number of studies have described a clear relationship between anemia and mortality in patients with CKD, and it has been hypothesized that it may be due to the impact of chronic anemia on cardiac function: Vasodilation and increased cardiac output (as a result of the consequent increase in cardiac contractility), plasma volume, and venous tone, finally leading to compensatory left ventricular hypertrophy (LVH) (7).

Earlier studies considered lower reference hemoglobin (Hb) values than those that are recommended today (8,9); subsequently, observational studies of large patient cohorts considered reference Hb values of between 10 and 12 g/dl. Locatelli *et al.* (9) in the Lombardy Registry and Ma *et al.* (10) in a large number of prevalent hemodialysis patients with Medicare insurance studied extensively the association between the risk for mortality and hematocrit levels and found a clear association between lower probabilities of death and higher hematocrit levels. To clarify the relationship between survival and higher hematocrit levels, Collins *et al.* (11) studied a large cohort of incident hemodialysis patients ($n = 66{,}761$) and, after 1 yr of follow-up, found that high hematocrit levels were associated with a lower risk for death from all causes, although there was no significant difference in the risk between patients with hematocrit values of 33 to <36% and those with higher levels. A similar pattern was observed in the case of cardiac causes of death and hospitalization, except for the patients with hematocrit values of 36 to <39%, who were at significantly lower risk for cardiac-cause hospitalization than those with hematocrit values of 33 to <36%.

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In addition to the data that come from large registries (*e.g.*, U.S. Renal Data System) (10,11), the Dialysis Outcomes and Practice Patterns (DOPPS) study provides another very useful source of information. This prospective observational study has the advantage that it analyzed very large populations of adult hemodialysis patients after adjustment for many case-mix characteristics. The DOPPS I data showed that, after adjustment for demographics and comorbidities, the relative risks for mortality and all-cause hospitalization were, respectively, 5 and 6% lower for every 1-g/dl greater Hb concentration (relative risk 0.95 and 0.94; $P \leq 0.003$ for both) (12). The analysis of 4591 prevalent hemodialysis patients from five European countries (Euro-DOPPS) (13) and 5517 prevalent hemodialysis patients from the United States who participated in DOPPS I (US-DOPPS) (14) led to similar findings.

Volkova and Arab (15) more recently undertook a systematic, evidence-based review of published observational studies to investigate anemia and mortality in dialysis patients and confirmed a consistent trend toward increased mortality with decreasing Hb levels. However, the association between high Hb values and survival advantage was inconsistent insofar as there was a nonsignificant association between lower mortality and Hb values of >11 g/dl in studies that used Hb 10 to 11 g/dl as the reference, whereas at least some of the studies that used the higher reference value of 11 to 12 g/dl found a significant decrease in mortality associated with higher Hb levels (15).

Anemia Correction and Outcome Improvement

Observational studies often are an essential means of generating and investigating new hypotheses and help investigators to select the interventions to be tested in randomized, controlled trials that are capable of providing the most robust evidence of treatment efficacy, a route that is followed by researchers who study the treatment of anemia in patients with CKD. Beginning with the clear association between higher Hb levels and better outcomes and the hypothesis that this may be due to the deleterious effect of anemia on the development of LVH or simply a marker of greater morbidity (mainly inflammation), a number of clinical studies were designed to test whether correcting anemia can reverse LVH and improve patient outcomes. Taking LVH as an intermediate outcome rather than a surrogate end point, data from mainly small and uncontrolled studies indicated that correcting anemia led to partial LVH regression (16–20), but larger randomized studies failed to confirm that randomization to the higher Hb levels that were obtained using recombinant human erythropoietin had a significant positive effect on patients who were not (21,22) and were (23) on dialysis.

Other clinical trials that investigated the optimal Hb target that is required to obtain better survival started from the assumption that complete anemia correction would give the best results in terms of decreased morbidity and mortality and improved quality of life. In this regard, Besarab *et al.* (24) were the first to test the effect of normalized Hb levels on hard outcomes in a high-risk population of 1233 hemodialysis patients who were aged >65 yr and had clinical evidence of congestive heart failure or ischemic heart disease and of whom a significant percentage had grafts as a vascular access for hemodialysis. The trial was halted prematurely for reasons of safety and futility because vascular access thrombosis in the patients who were randomly assigned to normal hematocrit had reached statistical significance, and the trends in mortality/acute myocardial infarction were such that it was unlikely that any benefit would be reached. However, it has been suggested that the study population was affected by too many comorbidities to benefit from full anemia correction; in particular, a high percentage of grafts in a population of patients with severe cardiac disease were believed to increase the occurrence of vascular access thrombosis (and therefore morbidity and mortality) in the experimental group.

This disappointing experience did not detract from the idea that less complicated patients may benefit more, but Furuland *et al.* (25) were unable to demonstrate a significant reduction in mortality after Hb normalization; however, this trial involved a heterogeneous population and was not designed primarily to study mortality. Parfrey *et al.* (26) more recently carried out a randomized, double-blind study to compare lower and higher Hb targets (9.5 to 11.5 and 13.5 to 14.5 g/dl) in 596 incident hemodialysis patients without symptomatic cardiac disease or LV dilation. After a mean follow-up of 74 wk, the percentage change in the LV volume index was not significantly different between the two groups. Mortality was a secondary outcome and although there were fewer deaths among the patients who were randomly assigned to complete anemia correction, this was not statistically significant probably because of the relatively low percentage of events in both groups. It also is worth noting that the patients in the higher target group experienced a higher number of cerebrovascular disorders.

These findings do not indicate any major effect of complete anemia correction on survival in patients with CKD, but most of the data were obtained from heterogeneous studies that were not designed primarily to analyze mortality. The only exception is the one by Besarab *et al.* (24), but the generalizability of the results is limited by the fact that the patients were very compromised and there was a very high percentage of grafts as vascular access.

Another very important point that needs to be taken into account when considering the results of the majority of these randomized, clinical trials is that the achieved Hb levels very often were in the lower or upper range of the experimental and control group targets, respectively, namely very close to or within the target range of Hb levels that are recommended by current international guidelines (27,28). This possibly has reduced the statistical power of the studies and may partially explain the negative findings. Figures 1 and 2 summarize the Hb targets and achieved values in studies of dialysis patients (Figure 1) and patients with CKD stage 3 to 4 (Figure 2).

Cardiovascular Reduction Early Anemia Treatment Epoetin β Trial

The hypothesis underlying the randomized, multicenter, open-label, parallel-group Cardiovascular Reduction Early Anemia Treatment Epoetin β (CREATE) study is that as anemia

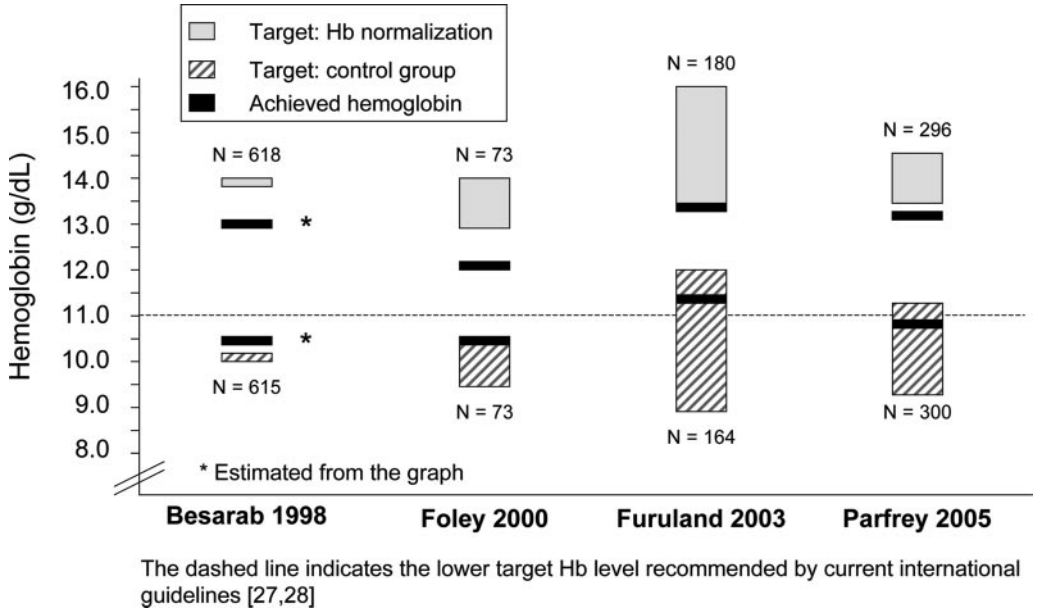

Figure 1. Target and achieved hemoglobin (Hb) levels in randomized, clinical trials: Dialysis patients. The dashed line indicates the lower target Hb level that is recommended by current international guidelines (27,28).

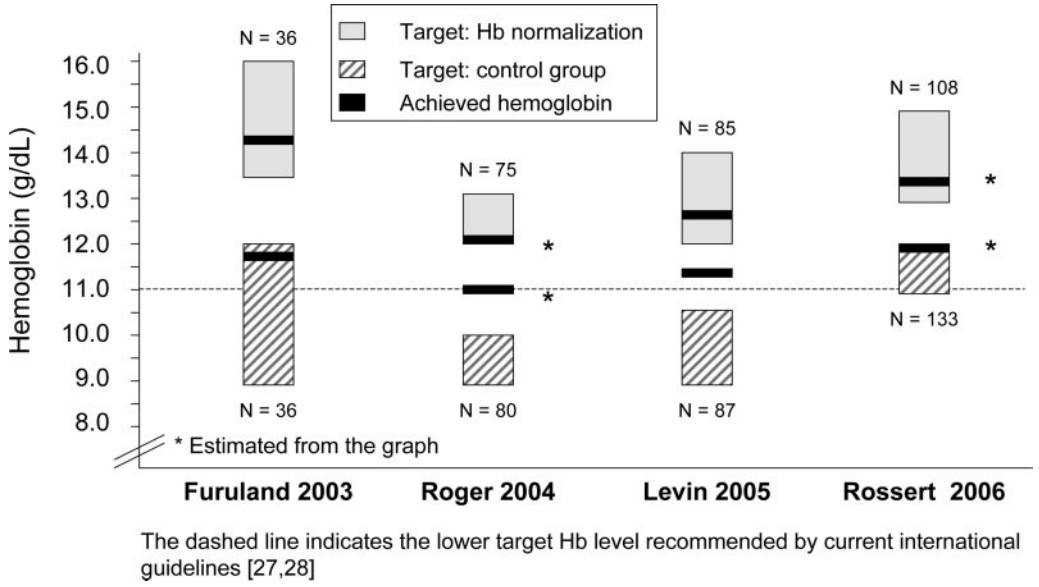

Figure 2. Target and achieved hemoglobin (Hb) levels in randomized, clinical trials: Patients with stages 3 to 4 chronic kidney disease. The dashed line indicates the lower target Hb level that is recommended by current international guidelines (27,28).

develops early in the course of CKD and almost at the same time as CVD, the earlier correction of anemia may provide better cardiovascular protection. The trial involved 95 nephrology units in 22 European, Asian, and Latin American countries, and its primary end point was the change from baseline in the LV mass index within 1 yr; if no differences were found at the time of the interim analysis, then the study was to have been stopped. The second primary variable was the time to the first cardiovascular event, including sudden death, fatal or nonfatal myocardial infarction, acute heart failure, angina pectoris or cardiac arrhythmias that required hospitalization, fatal or nonfatal stroke, transient cerebral ischemic attack, and peripheral vascular disease (amputation, necrosis). The secondary end points included CKD progression and quality of life.

Patients were eligible for inclusion when they had moderate CKD (estimated GFR 15 to 35 ml/min), mild to moderate anemia (Hb 11.0 to 12.5 g/dl) secondary to CKD, and no severe hypertension (BP $\leq$170/95 mmHg). Any patients with advanced CVD or severe chronic heart failure were excluded from the study, as were those who were expected to reach ESRD within 6 mo of the start of the study. A total of 603 patients satisfied the inclusion and exclusion criteria and were ran-

domly assigned to receive immediate treatment with epoetin β to obtain a target Hb level of 13 to 15 g/dl or to routine treatment with a target Hb of 10.5 to 11.5 g/dl (these patients received epoetin β only when their Hb levels decreased to $<$10.5 g/dl). The study ended as scheduled 2 yr after the final patient had been randomly assigned; the final results will be published soon, but the preliminary analyses did not show any cardiovascular advantage in complete anemia correction.

In addition to the expected data concerning the possibly positive effect of Hb normalization on patient morbidity and mortality, this trial provided an opportunity for collecting an enormous amount of information about the burden of CVD in patients with CKD. The preliminary baseline data indicate that the treatment groups were similar in terms of gender, age, Hb levels, renal function, baseline nephropathy, and BP (29). More interesting, there was a very high prevalence of hypertension as a qualitative variable in the population as a whole (nearly 80%), equally divided between the two groups; the same was true of the percentage of patients who were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at enrollment (nearly 60% in both groups). This is important when analyzing the results because it is widely known that hypertension can cause LVH and that therapy with angiotensin-converting enzyme inhibitors can both improve heart morphology and slow CKD progression.

Nearly half of the patients were affected by diabetic nephropathy or hypertensive renal disease. This is not surprising in itself because these two diseases are the leading causes of renal replacement therapy worldwide; however, it is notable because it underlines that this population is burdened by a particularly high cardiovascular risk not only because of CKD but also because of the frequent coexistence of diabetes and hypertension.

Although the study patients were selected deliberately on the grounds that they were in a relatively early phase of CKD, a significant percentage had clinically evident CVD at baseline: In addition to a high prevalence of hypertension, nearly one third of the patients already were affected by ischemic heart disease, congestive heart failure, valvulopathies, or electrocardiographic disturbances, and nearly 10% had cerebrovascular or peripheral vascular disease. The high prevalence of established CVD was reflected in their baseline LV geometry. Preliminary data showed that 64% had abnormal echocardiographic findings (29); in particular, nearly half of the population had an increased LV mass (28% had eccentric and 21% had concentric LVH), and an additional 15% had a normal LV mass but presented concentric remodeling. This is in line with other observations that showed a progressive increase in the frequency of LVH at more severe CKD stages (30).

However, the 5.8% rate of cardiovascular events during follow-up was lower than the expected 15%, probably because of the positive patient selection, trial effects, and/or optimized care, including careful BP control and use of cardioprotective agents. Mortality in fact was much less than the need for dialysis, which is in contrast with epidemiologic data concerning the CKD population as a whole (5,6).

Conclusion

Anemia is a very common complication that often occurs early in the development of CKD, long before the need for renal replacement therapy. It not only affects patients' quality of life but also is associated with multiple comorbidities, including an increased risk for cardiovascular morbidity and mortality. However, the data from randomized, controlled trials do not indicate a major effect of complete anemia correction on LV mass and mortality. Interpreting the disagreement between the results of observational and interventional studies is difficult, but what is certain is that the possible effect of anemia correction on survival has not been studied extensively in the early stages of CKD. Nevertheless, such patients are likely to benefit more from the intervention and also are less likely to experience adverse events.

This formed the basis of the rationale of the CREATE study, which compared the effects of early and complete Hb normalization with those of partial anemia correction in a large sample of patients with stages 3 to 4. CKD. The preliminary baseline data of this study confirm the high burden of CVD in the conservative phase of CKD, thus emphasizing the importance of global medical care in this high-risk population.

References

1. Collins AJ, Kasiske B, Herzog C, Chavers B, Foley R, Gilbertson D, Grimm R, Liu J, Louis T, Manning W, Matas A, McBean M, Murray A, St Peter W, Xue J, Fan Q, Guo H, Li S, Li S, Roberts T, Snyder J, Solid C, Wang C, Weinhandl E, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Johnson R, Sheets D, Forrest B, Berrini D, Constantini E, Everson S, Frederick P, Eggers P, Agodoa L; United States Renal Data System: Excerpts from the United States Renal Data System 2004 annual data report: Atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 45[Suppl 1]: A5–A7, 2005
2. Rayner HC, Pisoni RL, Bommer J, Canaud B, Hecking E, Locatelli F, Piera L, Bragg-Gresham JL, Feldman HI, Goodkin DA, Gillespie B, Wolfe RA, Held PJ, Port FK: Mortality and hospitalization in haemodialysis patients in five European countries: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 19: 108–120, 2004
3. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 47: 186–192, 1995
4. Locatelli F, Marcelli D, Conte F, Del Vecchio L, Limido A, Malberti F, Spotti D, Sforzini S, the Registro Lombardo Dialisi e Trapianto: Patient selection affects end-stage renal disease outcome comparisons. *Kidney Int* 57[Suppl 74]: S94–S99, 2000
5. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 164: 659–663, 2004
6. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, Collins AJ: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in

the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 16: 489–495, 2005
7. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC: Pathogenesis of oedema in chronic severe anaemia: Studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *Br Heart J* 70: 357–362, 1993
8. Madore F, Lowrie EG, Brugnara C, Lew NL, Lazarus JM, Bridges K, Owen WF: Anaemia in hemodialysis patients: Variables affecting this outcome predictor. *J Am Soc Nephrol* 8: 1921–1929, 1997
9. Locatelli F, Conte F, Marcelli D: The impact of hematocrit levels and erythropoietin treatment on overall and cardiovascular mortality and morbidity: The experience of the Lombardy Dialysis Registry. *Nephrol Dial Transplant* 13: 1642–1644, 1998
10. Ma J, Ebben J, Xia H, Collins A: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10: 610–619, 1999
11. Collins AJ, Li S, St Peter W, Ebben J, Roberts T, Ma JZ, Manning W: Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol* 12: 2465–2473, 2001
12. Pisoni RL, Bragg-Gresham JL, Young EW, Akizawa T, Asano Y, Locatelli F, Bommer J, Cruz JM, Kerr PG, Mendelssohn DC, Held PJ, Port FK: Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 44: 94–111, 2004
13. Locatelli F, Pisoni RL, Combe C, Bommer J, Andreucci VE, Piera L, Greenwood R, Feldman HI, Port FK, Held PJ: Anaemia in haemodialysis patients of five European countries: Association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 19: 121–132, 2004
14. Robinson BM, Joffe MM, Berns JS, Pisoni RL, Port FK, Feldman HI: Anemia and mortality in hemodialysis patients: Accounting for morbidity and treatment variables updated over time. *Kidney Int* 68: 2323–2330, 2005
15. Volkova N, Arab L: Evidence-based systematic literature review of hemoglobin/hematocrit and all-cause mortality in dialysis patients. *Am J Kidney Dis* 47: 24–36, 2006
16. Portoles J, Torralbo A, Martin P, Rodrigo J, Herrero JA, Barrientos A: Cardiovascular effects of recombinant human erythropoietin in predialysis patients. *Am J Kidney Dis* 29: 541–548, 1997
17. Hayashi T, Suzuki A, Shoji T, Togawa M, Okada N, Tsubakihara Y, Imai E, Hori M: Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis* 35: 250–256, 2000
18. Frank H, Heusser K, Hoffken B, Huber P, Schmieder RE, Schobel HP: Effect of erythropoietin on cardiovascular prognosis parameters in hemodialysis patients. *Kidney Int* 66: 832–840, 2004
19. Ayus JC, Go AS, Valderrabano F, Verde E, de Vinuesa SG, Achinger SG, Lorenzo V, Arieff AI, Luno J; Spanish Group for the Study of the Anemia and Left Ventricular Hypertrophy in Pre-dialysis Patients: Effects of erythropoietin on left ventricular hypertrophy in adults with severe chronic renal failure and hemoglobin <10 g/dL. *Kidney Int* 68: 788–795, 2005
20. Hampl H, Hennig L, Rosenberger C, Amirkhalily M, Gogoll L, Riedel E, Scherhag A: Effects of optimized heart failure therapy and anemia correction with epoetin beta on left ventricular mass in hemodialysis patients. *Am J Nephrol* 25: 211–220, 2005
21. Roger SD, McMahon LP, Clarkson A, Disney A, Harris D, Hawley C, Healy H, Kerr P, Lynn K, Parnham A, Pascoe R, Voss D, Walker R, Levin A: Effects of early and late intervention with epoetin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4): Results of a randomized clinical trial. *J Am Soc Nephrol* 15: 148–156, 2004
22. Levin A, Djurdjev O, Thompson C, Barrett B, Ethier J, Carlisle E, Barre P, Magner P, Muirhead N, Tobe S, Tam P, Wadgymar JA, Kappel J, Holland D, Pichette V, Shoker A, Soltys G, Verrelli M, Singer J: Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. *Am J Kidney Dis* 46: 799–811, 2005
23. Foley RN, Parfrey PS, Morgan J, Barre PE, Campbell P, Cartier P, Coyle D, Fine A, Handa P, Kingma I, Lau CY, Levin A, Mendelsshon D, Muirhead N, Murphy B, Plante RK, Posen G, Wells GA: Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. *Kidney Int* 58: 1325–1335, 2000
24. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA: 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* 339: 584–590, 1998
25. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson BG: A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* 18: 353–361, 2003
26. Parfrey PS, Foley RN, Wittreich BH, Sullivan DJ, Zagari MJ, Frei D: Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol* 16: 2180–2189, 2005
27. National Kidney Foundation: K/DOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. *Am J Kidney Dis* 47[Suppl 3]: S16–S85, 2006
28. Locatelli F, Aljama P, Barany P, Canaud B, Carrera F, Eckardt KU, Horl WH, Macdougal IC, Macleod A, Wiecek A; European Best Practice Guidelines Working Group: Revised European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 19[Suppl 2]: 1–47, 2004
29. Macdougall IC; Steering Committee of the CREATE Trial, CREATE Study Group: CREATE: New strategies for early anaemia management in renal insufficiency. *Nephrol Dial Transplant* 18[Suppl 2]: ii13–ii16, 2003
30. Rossert J, Levin A, Roger SD, Horl WH, Fouqueray B, Gassmann-Mayer C, Frei D, McClellan WM: Effect of early correction of anemia on the progression of CKD. *Am J Kidney Dis* 47: 738–750, 2006