Anaemia as a risk factor for chronic kidney disease

Walter H. Hörl

Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria

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Corresponding author:
Prof. Walter H. Hörl, MD, PhD, FRCP
Division of Nephrology and Dialysis
Department of Medicine III
Währinger Gürtel 18-20
1090 Vienna, Austria
Phone: ++43 1 40400 4390
Fax: ++43 1 40400 4392
E-mail:
walter.hoerl@meduniwien.ac.at

Abstract

Anaemia is a risk factor for progression of chronic kidney disease (CKD). There is also a clear and consistent association between anaemia and cardiovascular risk in patients with CKD. Complete correction of anaemia by treatment with erythropoiesis-stimulating agents (ESAs) has not been shown to improve these outcomes in non-dialysis CKD patients. Anaemia plays a causal role in the pathobiology of left ventricular hypertrophy (LVH), but the beneficial effect of ESA therapy seems to be limited to CKD patients with severe anaemia. At present, target haemoglobin levels between 10 and 12 g/dl are considered for non-dialysis CKD patients but also in the dialysis patient population. Anaemia is also of clinical relevance and prognostic significance in patients with heart failure, particularly in those with heart failure and CKD. However, the ideal threshold at which anaemia corrections should be started and the optimal target haemoglobin levels for heart failure patients need to be determined.

Key words: chronic kidney disease, anaemia, cardiovascular disease, left ventricular hypertrophy, heart failure, erythropoiesis stimulating agents.

Introduction

The number of patients with chronic kidney disease (CKD) is increasing markedly worldwide. Two major problems are associated with CKD patients: the high cardiovascular morbidity and mortality in this patient population due to traditional and non-traditional risk factors, and progression of CKD to end-stage renal disease (ESRD). Decreasing the morbidity and mortality associated with CKD and preventing its progression are key public health objectives. Among a long list of potential risk factors, anaemia contributes to both cardiovascular complications and CKD progression to ESRD. Correction of anaemia by treatment with erythropoiesis-stimulating agents (ESAs) may not only reduce these complications and delay progression, but may also cause harm. This article summarizes the present knowledge on anaemia as a risk factor for CKD and the potential benefits or deleterious effects of its correction.

Effects of anaemia and erythropoiesis-stimulating agent therapy on chronic kidney disease progression

Non-diabetic patients with chronic kidney disease

Many risk factors, such as quality of blood pressure control, the type of antihypertensive medication, the degree of albuminuria or proteinuria, smoking, quality of blood glucose control (in diabetic patients), lipid-lowering agents (e.g. statins) and/or underlying renal disease may influence

progression of CKD to ESRD. In addition, renal anaemia and its partial or full correction may influence CKD progression in this patient population.

Roth *et al*. [1] randomized 43 out of 83 CKD patients with anaemia and serum creatinine between 3 and 8 mg/dl to 48-week treatment with human recombinant erythropoietin (rhuEPO) with a target haematocrit of 35%, while 40 CKD patients were randomized to the untreated arm. The rate of decline of the glomerular filtration rate (GFR) served as the primary outcome variable. ^{125}I-iothalamate clearance decreased in the rhuEPO-treated group by 2.1 ±3.2 ml/min and in the untreated group by 2.8 ±3.5 ml/min (p = 0.376). The decline of GFR, however, was significantly reduced in the treatment group after target haematocrit was reached (weeks 16 to 48). A non-significant but numerically higher incidence of hypertension as an adverse event with rhuEPO as compared to no treatment (26 vs. 10%) was observed. Variations of blood pressure were controlled by adjustment of antihypertensive medication in this patient population [1].

In a randomized, prospective controlled trial performed with anaemic CKD patients in Japan, time to doubling of serum creatinine (the primary endpoint of the study) was significantly lengthened in participants receiving 36-week rhuEPO treatment targeted to a haematocrit of 33-35% as compared to untreated anaemic control or low-grade anaemic control patients [2]. Both the latter groups showed a steady decline of haematocrit throughout the study period. The study was controlled for possibly confounding variables such as blood pressure, protein and salt intake, but partial correction of anaemia by rhuEPO appeared to be an independent parameter to retard CKD progression. The study participants, however, were not equally distributed between the treatment and the control groups. Although diabetic CKD patients were included in all three groups to a similar proportion, diabetes mellitus represents a possible confounding variable in this patient population [2].

Table I. Effects of partial or complete anaemia correction on progression of chronic kidney disease in patients with CKD stages 3-5

Authors [ref.]	*N*	Achieved haemoglobin [g/dl] or haematocrit [%]		Effect on progression
		"high"	"low"	
Roth *et al*. [1]	83	33	27	No effect
Kuriyama *et al*. [2]	73	32	25	Improvement
Jungers *et al*. [4]	63	11.3	9.5	Improvement
Furuland *et al*. [5]	72	14.3	11.7	No effect
Gouva *et al*. [6]	88	12.9	10.3	Improvement
Roger *et al*. [7]	155	12.1	10.8	No effect
Rossert *et al*. [10]	163	13.9	11.7	No effect
Drücke *et al*. [11]	605	13.2	11.5	Deterioration
Ritz *et al*. [19]	172	13.5	12.1	No effect

A meta-analysis including 12 trials with a total of 232 CKD patients assessed the effect of rhuEPO therapy on delaying the onset of dialysis treatment. Nine of these trials were of short duration (8-12 weeks), while three trials, including the two prospective studies mentioned above, ranged from 36 weeks to 1 year. RhuEPO-treated CKD patients did not differ from placebo-treated or untreated CKD patients for the proportion of patients commencing dialysis, for the decline in kidney function or the increase in serum creatinine levels [3]. In contrast, a beneficial effect of rhuEPO therapy on the rate of CKD progression was observed in a retrospective, single-centre study on 20 patients with advanced CKD [4]. Forty-three CKD patients with a comparable degree of CKD without rhuEPO therapy acted as controls. Mean haemoglobin levels at the start of dialysis differed between rhuEPO-treated and untreated CKD patients (11.3 vs. 9.5 g/dl). Ten responders in the rhuEPO treatment group showed a significantly lower decline in kidney function as compared to non-responders or untreated patients. Consequently, the time interval to initiation of dialysis was longer in rhuEPO-treated patients as compared to untreated CKD patients [4].

In a controlled trial, 416 Scandinavian pre-dialysis and dialysis patients with renal anaemia were randomized to reach a normal haemoglobin (13.5-16.0 g/dl, n = 216) or a subnormal haemoglobin (9.0-12.0 g/dl, n = 200) with or without rhuEPO [5]. Glomerular filtration rate in 46 pre-dialysis patients at baseline was 16 ±9 ml/min/1.73 m^2 (n = 24) and 17 ±6 ml/min/1.73 m^2 (n = 22) in the normal-haemoglobin and subnormal-haemoglobin groups, respectively. At week 48, GFR was 13 ±10 ml/min/1.73 m^2 (n = 19) in the normal-haemoglobin group and 16 ±7 ml/ min/1.73 m^2 (n = 21) in the subnormal-haemoglobin group (p = 0.43) (Table I).

Gouva *et al*. [6] reported that early initiation of rhuEPO therapy in non-diabetic CKD patients with a baseline creatinine clearance of 26.7 ±9.1 ml/min slows progression and delays initiation of renal replacement therapy when targeted to a haemoglobin concentration of 13 g/dl as compared to a deferred treatment group with a creatinine clearance of 22.3 ±6.0 ml/min starting rhuEPO therapy when haemoglobin levels reached a concentration ≤ 9 g/dl. The incidence of hypertension was similar between CKD patients with high and low haemoglobin levels (13 vs. 11%), and hypertension was well controlled in both the early- and deferred-treatment groups [6].

Roger *et al*. [7] performed a randomized controlled trial in 155 patients with CKD (creatinine clearance 15 to 50 ml/min) with entry haemoglobin concentrations of 11.0 to 12.0 g/dl in female patients or 11.0 to 13.0 g/dl in male patients. The patients were monitored for two years until they required dialysis. The patients were randomized to receive rhuEPO as necessary to maintain haemoglobin concentration between 12.0 and 13.0 g/dl (group A) or between 9.0 and 10.0 g/dl (group B). Haemoglobin concentration increased for group A from 11.2 ±0.9 g/dl (mean ± SD) to 12.1 ±1.4 g/dl and decreased for group B from 11.2 ±0.8 g/dl to 10.8 ±1.3 g/dl ($p < 0.001$, group A vs. group B). The decline in kidney function within two years, as assessed with nuclear estimations of GFR, did not differ between the groups (8 ±9 vs. 6 ±8 ml/min/1.73 m^2). However, haemoglobin levels in the low-haemoglobin group did not decrease as expected, resulting in a small difference between groups in mean haemoglobin level achieved (1.2 g/dl) (Table I). Although the decrease in GFR was not significantly different between groups, a significant correlation was observed between GFR decrease and haemoglobin level [7]. This finding is in agreement with data obtained in two other studies: Ravani *et al*. [8] reported a 23% reduction in progression to ESRD for each 1 g/dl increase in haemoglobin level, and Fliser *et al*. [9] reported that CKD patients who progressed to ESRD had significantly lower haemoglobin levels than those who did not.

In the study of Rossert *et al*. [10], 108 high-haemoglobin (13.0-15.0 g/dl) and 133 low-haemoglobin (11.0-12.0 g/dl) patients with CKD stage 4 entered the maintenance phase. Mean maintenance duration was 7.4 months for the high-haemoglobin group and 8.3 months in the low-haemoglobin group. GFR decrease was numerically, but not statistically significantly, lower in the high-haemoglobin group as compared to the low-haemoglobin group (0.058 vs. 0.081 ml/min/1.73 m^2 per month).

In the study of Drüeke *et al*. [11], 608 CKD patients with an estimated GFR of 15.0 to 35.0 ml/min/1.73 m^2 were assigned to a target haemoglobin value in the normal range (13.0 to 15.0 g/dl, group 1) or to subnormal range (10.5 to 11.5 g/dl, group 2). Subcutaneous rhuEPO was initiated at randomization in group 1, but only after the haemoglobin level fell below 10.5 g/dl in group 2. The mean estimated GFR was 24.9 ml/min/1.73 m^2 in group 1 and 24.2 ml/min/1.73 m^2 in group 2 at baseline and decreased by 3.6 and 3.1 ml/min/1.73 m^2 per year, respectively ($p = 0.40$). Dialysis was required in more CKD patients of group 1 than of group 2 (121 vs. 111 patients, $p = 0.03$) (Table I). However, because of the non-protocolized nature of dialysis start, and the fact that there were no differences in rate of decline of GFR between high-haemoglobin and low-haemoglobin groups, it was concluded that the finding that the number of CKD patients went onto dialysis was greater in the higher haemoglobin group should not be over-interpreted [12].

Johnson *et al*. [13] developed a risk score to predict the 5-year risk of renal replacement therapy. Using 6 characteristics in 9,782 CKD patients, i.e. age, sex, estimated GFR, diabetes, anaemia and hypertension, the risk score discriminated the highest risk patients effectively: 19% of CKD patients in the highest risk quintile experienced progression, but only 0.2% of the CKD patients in the lowest risk quintile experienced progression [13]. Lee *et al*. [14] determined serum creatinine and calculated renal parameters such as Cockcroft-Gault formula, Modification of Diet in Renal Disease (MDRD) study and abbreviated MDRD equations in order to evaluate kidney function and progression of CKD, defined as a GFR < 60 ml/min/1.73 m^2 in 121 normotensive non-diabetic elderly patients (mean age 71.8 ±3.8 years) at baseline and after 2 and 4 years. In this study, the prevalence of CKD significantly increased only in those with baseline haemoglobin concentrations of < 14 g/dl ($p \leq 0.03$). Baseline haemoglobin correlated with 4-year changes of MDRD and abbreviated MDRD GFR in univariate (both $p < 0.001$) and multivariate regression analyses (both $p < 0.05$).

Diabetes patients with chronic kidney disease

Diabetes has become the most common comorbid condition of ESRD. Anaemia and its correction in patients with early diabetic nephropathy may influence outcomes. At every level of renal function haemoglobin levels were found to be lower by an average of 1.0 g/dl in CKD patients with diabetes as compared to those without. Likewise, anaemia was found to occur at an earlier stage of CKD and to be of greater severity in diabetic than in non-diabetic patients [15]. In the Reductions of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) study, lower baseline haemoglobin concentration was associated with significant increase in risk for ESRD [16]. ACEI and/or ARB treatment may lower haemoglobin and thereby attenuate the renoprotective effects of these drugs. In the RENAAL study, there were significant relative risk reductions for losartan as compared to placebo for ESRD and for ESRD or death regardless of the baseline haemoglobin even in those patients with a baseline haemoglobin below 12 g/dl [17]. In a prospective study of patients with diabetes and persistent macroalbuminuria, baseline haemoglobin, even within the normal range, predicted time in doubling of serum creatinine or ESRD independently of other risk factors, such as baseline systolic blood pressure, albuminuria, glycaemic control

and/or GFR. In this study with type 2 diabetes patients and overt nephropathy, the lowest relative risk for the above-mentioned complications was observed at haemoglobin levels between 14 and 16 g/dl [18]. These data suggest that complete correction of anaemia could be helpful to retard progression of CKD to ESRD in type 2 diabetes patients. In the Anaemia CORrection in Diabetes (ACORD) study, however, early and complete anaemia correction had no effect on the rate of decrease in creatinine clearance (Table I) or in urinary protein excretion [19].

Conclusions

Taken together, anaemia is a risk factor for progression of CKD to ESRD. It should be corrected by ESA therapy with target haemoglobin levels between 10 and 12 g/dl, if necessary. Complete anaemia correction is not indicated either in non-diabetic or in diabetic CKD patients.

Effects of anaemia and erythropoiesis-stimulating agent therapy on cardiovascular events in chronic kidney disease

Cardiovascular disease

More patients with CKD will die, often from cardiovascular disease (CVD), than will advance to ESRD [20]. Cardiovascular disease still is the leading cause of death and hospitalization among patients with non-dialysis CKD [21]. The processes that contribute to its pathogenesis occur already during the course or even at the earliest stages of CKD. Treatment of patients with CKD should be focused mainly on strategies that aim to prevent the development of cardiovascular complications, rather than slow the progression of renal impairment. Besides many traditional and non-traditional risk factors responsible for CKD events, anaemia has been associated with adverse outcomes in CKD populations. Poor renal function in the general population is also associated with increased risk of cardiovascular disease among middle-aged persons. This risk is amplified by the presence of anaemia [22], since the available oxygen supply to tissues is reduced in anaemia. The ability to modify this parameter with the use of ESA should improve outcome. However, to date there does not appear to be support for targeting normal haemoglobin values in CKD patients [12].

Chronic kidney disease, at mild and advanced stages, is a predictor of clinically important myocardial perfusion abnormalities. Further, anaemia appears to confer a similar, independent risk for myocardial perfusion abnormality. Together, CKD (defined as GFR ≤ 60 ml/min/1.73 m^2) and anaemia (defined as haemoglobin ≤ 13 g/dl) were found to be associated with high-risk myocardial perfusion stress imaging markers for worse outcome [23]. Jurkovits *et al*. [24] examined the joint association between anaemia, defined as haemoglobin less than 13 g/dl in men and less than 12 g/dl in women, and impaired kidney function with the risk of definite or probable myocardial infarction or coronary heart disease. Individuals with anaemia and CKD had a higher risk for coronary heart disease (RR 2.74; 95% CI 1.42-5.28), while individuals with CKD and no anaemia did not (RR 1.20; 95% CI 0.86-1.67). Muntner *et al*. [25] measured risk factors of coronary artery disease and estimated GFR in 807 participants of the Atherosclerosis Risk in Communities (ARIC) study with CKD and an estimated GFR between 15 and 59 ml/min/1.73 m^2. After adjustment for age, race, gender, and ARIC field centre, among individuals with CKD, the relative risk (95% confidence interval) of coronary artery disease was 1.65 (1.01 to 2.67) for smoking, 2.02 (1.27 to 3.22) for hypertension, 3.06 (2.01 to 4.67) for diabetes, and 1.96 (1.14 to 3.36) for anaemia. A total of 14,971 adults were followed up for 12 years as part of the ARIC study [26]. During follow-up, 10.9% of individuals had a coronary heart disease event. The adjusted relative hazard of all-cause mortality was increased with anaemia from 1.7 (95% CI 1.3-2.2) to 3.5 (95% CI 2.4-5.1) ($p = 0.001$). Anaemia, with haemoglobin level of 12.8 g/dl or less, increased risk for cardiovascular disease with an odds ratio of 1.45 ($p < 0.001$) in 37,153 participants of the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) [27]. Anaemia was associated with increased hazard ratios for atherosclerotic vascular disease (1.09), congestive heart failure (1.14), renal replacement therapy (2.61) and death (1.40) in 41,522 Medicare beneficiaries with CKD analyzed for events over a period of two years [28]. Among 853 male US veterans with CKD stages 3 and 5, lower haemoglobin levels were associated with increased risk for the composite endpoint mortality and risk for ESRD [29].

In the study of Rossert *et al*. [10], cardiovascular adverse events occurred in 25% of the high-haemoglobin and 18% of the low-haemoglobin non-dialysis CKD patients ($p = 0.137$). The Correction of Haemoglobin and Outcomes in Renal insufficiency (CHOIR) trial [30], performed in the USA, randomly assigned 1432 CKD patients with a GFR of 15-20 ml/min/1.73 m^2 to a haemoglobin target of either 13.5 or 11.3 g/dl. A significantly increased risk for the composite primary endpoint (death, myocardial infarction, hospitalization for congestive heart failure, and stroke) was found with the higher haemoglobin target as compared to the lower haemoglobin target. In addition, no significant difference in the likelihood of a first cardiovascular event was found between the high-haemoglobin and low-haemoglobin groups in

the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin beta (CREATE) study [11], but the point estimate favoured the lower haemoglobin target. Thus, the maintenance of haemoglobin concentrations above 13.0 g/dl appears to be unsafe in non-dialysis CKD patients. Higher haemoglobin target concentrations may increase mortality via cardiovascular endpoints. Therefore, part rather than complete correction of anaemia is appropriate for non-dialysis CKD patients [31]. The secondary analysis of the CHOIR trial showed that patients achieving their target haemoglobin level had better outcomes than those who did not. Interestingly, among CKD patients who achieved their randomized target, no increased risk associated with the higher haemoglobin goal was detected [32].

Taken together, there is a clear and consistent association between anaemia and cardiovascular risk in CKD. Anaemia correction with ESA treatment has not been shown to improve these outcomes [33]. Complete correction of anaemia might increase blood pressure, blood viscosity and the risk of thrombosis, and accentuate vasoconstriction [34].

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is recognized as a potent risk factor for cardiovascular death in CKD patients. It has been linked to progressive renal dysfunction and anaemia in prospective observational studies [35]. However, based on a nested analysis of a 2-year study involving 155 patients with CKD stages 3 and 4 and examining effects of haemoglobin change on LV mass in patients with and without LVH, it was concluded that haemoglobin concentration is not a predisposing factor to maintaining or achieving normal LV mass dimensions in this patient population [36]. An Australian study [7], a Canadian study [37] and a United Kingdom study [38] used left ventricular mass index (LVMI) as a surrogate endpoint and used doses of ESA similar to the CREATE study [11]. Like CREATE, none of these studies demonstrated a difference between high-haemoglobin and low-haemoglobin CKD patients in LVMI over the study period [12]. In CKD patients with diabetes and mild to moderate anaemia (ACORD study), correction of a haemoglobin target level of 13 to 15 g/dl by rhuEPO also did not decrease LVMI [19].

These data are in contrast to a Canadian cohort assembled almost a decade ago, which described LVH and LVMI differences in CKD patients with and without anaemia, and CVD events as well [35]. At that time, however, the use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) was not common in the CKD population, target blood pressures were different from current levels, and treatment of hyperphosphataemia, secondary hyperparathyroidism and other complications was not commonplace [12]. In contrast, more than 80% of the CKD patients of the ACORD study received ACEIs and/or ARBs, and target blood pressure values were approximately 134/78 mm Hg [19]. In addition, Pappas *et al*. [39] investigated the effect of rhuEPO on LV systolic and diastolic performance in 30 patients with CKD stages 3 and 4. After one year, ejection fraction, LVMI, Tei index (an index of global cardiac function) and indices of mitral annulus motion improved significantly in CKD patients with haemoglobin levels of 13.6 ±1.2 g/dl as compared to those with haemoglobin of 10.3 ±1.2 g/dl.

In a recent study with non-dialysis CKD stage 5 patients with severe anaemia (mean haemoglobin at baseline 8.5 ±0.8 or 8.2 ±0.8 g/dl, respectively) and LVH, both rhuEPO or darbepoetin α therapy resulted in a comparable reduction of LVH and increase in ejection fraction as soon as haemoglobin in the two treatment arms was corrected to 10.6 ±0.6 or 10.7±0.5 g/dl, respectively [40]. These data confirm earlier studies with non-dialysis CKD patients where correction of anaemia in the study of Portolés *et al*. (haemoglobin 11.7 ±0.4 vs. 9.0 ±0.3 g/dl) or in the study of Hayashi *et al*. (haematocrit 39.1 ±2.4 vs. 32.1 ±1.8%) resulted in a decrease in LVMI [41, 42]. Ayus *et al*. [43] found LVH to be present among 68.3% of CK patients with creatinine clearance between 10 and 30 ml/min (non-diabetics) or between 20 and 40 ml/min (diabetics). Partial correction of anaemia (haemoglobin 11.3 ±1.9 vs. 9.1 ±0.7 g/dl) by rhuEPO resulted in a significant (p = 0.007) reduction of LVMI (142 ±56 vs. 157 ±22) within 6 months in this patient population. Kidney function and haemoglobin were associated with LV morphology among African Americans in the ARIC study [44].

Taken together, these data suggest that anaemia plays a causal role in the pathobiology of LVH but the beneficial effect of ESA therapy seems to be limited to non-dialysis CKD patients with severe anaemia and anaemia correction to target haemoglobin levels between 10 and 12 g/dl.

Stroke

Anaemia amplifies the risk of incident stroke. Data obtained from the prospective ARIC study, a cohort of middle-aged, community-based individuals, indicated that anaemia modifies the increased risk of cerebrovascular disease. In the total sample of the ARIC study, CKD (defined as creatinine clearance < 60 ml/min) was associated with an increase in stroke risk (hazard ratio 1.81, 95% CI 1.26-2.02) after adjusting for other risk factors. The hazard ratio for cerebrovascular disease among individuals with CKD and anaemia was 5.43

(95% CI 2.04-14.41). In contrast, CKD was associated with only a modest, non-significant elevation in stroke risk (hazard ratio 1.41, 95% CI 0.93-2.14) when anaemia was not present [45].

Interaction between chronic kidney disease, anaemia and heart failure

Chronic kidney disease, anaemia and declining kidney function are risk factors for adverse outcomes in patients with heart failure. Data from 48,612 patients at 259 hospitals of the Organized Program to Initiate Lifesaving Treatment in Patients with Heart Failure (OPTIMIZE-HF) Registry showed that half of the total cohort had low haemoglobin (< 12.1 g/dl) and that 25% were moderately to severely anaemic (lowest haemoglobin quartile, 5 to 10.7 g/dl). Anaemic patients had higher in-hospital mortality, longer hospital length of stay, and more readmissions by 90 days as compared to non-anaemic patients [46]. Luthi *et al*. [47] examined among patients with heart failure the association between CKD, anaemia and in-hospital mortality and early readmission. Among 955 eligible patients hospitalized with heart failure, creatinine and haemoglobin were associated with an increased risk of death at the hospital, and haemoglobin was related to early readmission. In the Studies of Left Ventricular Dysfunction (SOLVD), anaemia was associated with a rapid decrease in kidney function in patients with heart failure, particularly in those with underlying CKD [48]. In the Blue Mountains Eye Study cohort, a prospective Australian population-based study of 3654 residents, Leeder *et al*. [49] confirmed that CKD increases the risk for coronary heart disease events in people with anaemia. This effect was not evident in people without CKD. Interactions between anaemia and low GFR have been reported for mortality among patients with left ventricular dysfunction [50], and between anaemia and left ventricular hypertrophy for coronary heart disease incidence and related mortality among patients with CKD [51]. In contrast, Gurm *et al*. [52] reported no interaction between kidney function and anaemia with cardiovascular risk among 6000 patients undergoing percutaneous coronary intervention.

Vlagopoulos *et al*. [53] evaluated whether anaemia is a risk factor for adverse outcomes in people with diabetes and whether the risk is modified by the presence of CKD. Pooled data were obtained from four community-based studies with 3015 individuals. In a model with a CKD-anaemia interaction term, anaemia was associated with the following hazard ratios (95% CI) in patients with CKD: 1.70 (1.24 to 2.34) for the composite outcome myocardial infarction/fatal coronary heart disease/stroke/death, 1.64 (1.03 to 2.61) for myocardial infarction/fatal coronary heart disease, 1.81 (0.99 to 3.29) for stroke, and 1.88 (1.33 to 2.66) for all-cause mortality. In this study, anaemia was not a risk factor for any outcome in those without CKD [53]. Several small studies suggest beneficial effects of empirically treating anaemia in heart failure patients with ESAs and/or intravenous iron. However, the ideal threshold at which therapy should be initiated and the effect of correction considered safe and desirable in the individual patients with heart failure need to be clarified [54].

A total of type 2 diabetes patients were assessed for diabetic complications. A total of 294 patients (7.4%) developed cardiovascular events, particularly those with the lowest haematocrit (male 35.6 ±3.3, female 29.2 ±2.7%) and the lowest estimated GFR (62 ml/min/1.73 m^2) as compared to type 2 diabetes patients with normal haematocrit and normal estimated GFR (18.6 vs. 3.4%, $p < 0.001$). After stratifying by the presence of CKD, the reduction in the risk of developing cardiovascular events with increasing haematocrit was abolished in the cohort with CKD but persisted in the non-CKD cohort [55]. Diabetes is the single largest cause of chronic kidney failure in western countries. Joss *et al*. [56] identified 508 patients with diabetic nephropathy referred to renal services in Scotland. At referral, mean estimated GFR (calculated using the MDRD formula) was 34 ml/min/1.73 m^2 and 48% of patients were at CKD stages 4 and 5. Mean haemoglobin was 11.7 g/dl, but 21% had haemoglobin < 10 g/dl at referral. Older age and lower haemoglobin at referral predicted death on multivariate analysis [56].

Taken together, current literature suggests clinical relevance and prognostic significance of anaemia in patients with heart failure, particularly in those with concomitant CKD. Trials are ongoing to answer the question whether disease progression and increased mortality risk in heart failure patients can be reduced by anaemia correction with ESA therapy.

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