Risk Factors in the Progression of Chronic Kidney Disease

a report by
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Chronic kidney disease (CKD) is a complex, progressive condition that develops slowly in some individuals, but rapidly in others. In addition to the underlying cause of renal failure, the rate of disease progression may be dictated by the presence of CKD risk factors. The principal outcomes of CKD include progressive loss of kidney function leading to end-stage renal disease (ESRD) and the development and progression of cardiovascular disease (CVD).

CKD is a major cause of cardiovascular morbidity and mortality and is considered a significant public health problem that places a burden on global healthcare resources. Notably, the incidence and prevalence of CKD have shown a dramatic increase over the past two decades. It was recently estimated that 11% of adults (19.2 million) in the US alone have early CKD that may progress to ESRD and require renal replacement therapy (RRT), such as dialysis or transplantation. Based on the US Renal Data System (USRDS), a national system that collects, analyses and distributes information about ESRD, it is estimated that the number of individuals receiving RRT will rise to more than 600,000 by 2010.

The observation that small reductions in the decline in renal function early in the disease process can provide marked benefits later, in terms of delaying progression to RRT, suggests that substantial benefits can be gained from the early identification and treatment of individuals at risk. In order to develop effective strategies to identify such individuals and delay or prevent disease progression, a comprehensive understanding of the complex interplay between risk factors influencing the disease process is required.

Risk Factors for CKD Progression

A number of primary non-modifiable risk factors for the progression of CKD have been identified, including age, ethnicity, gender and family history. Age was found to be a key predictor of CKD prevalence during an analysis of data from a subpopulation of 15,625 individuals enrolled in the third National Health and Nutrition Examination Survey (NHANES III). This analysis confirmed the frequent occurrence of CKD but also showed that there was a progressive decrease in glomerular filtration rate (GFR) with increasing age. In particular, 10.8% of individuals older than 65 years, but with no evidence of hypertension or diabetes, had CKD stage III or more, confirming age as a key predictor of CKD prevalence.

Gender was also confirmed as a key predictor of CKD prevalence in a similarly large meta-analysis of 68 studies involving 11,345 patients with non-diabetic CKD. This analysis found that men experienced a more rapid decline in renal function and worse outcomes than women.

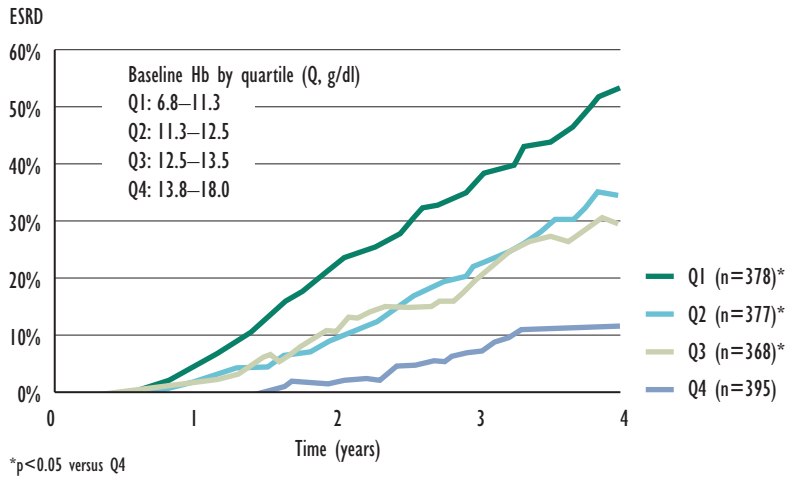
Perhaps more importantly from an interventional viewpoint, a number of independent risk factors have also been identified that may be modified by pharmacotherapy or lifestyle changes to reduce the rate of CKD progression. These modifiable risk factors, which are associated with both impaired renal and cardiac function, include diabetes, hypertension, smoking, inflammation and anaemia.

Hypertension and Smoking

In a prospective study of more than 33,000 men, a strong relationship was shown between hypertension and rate of progression to ESRD.

In a more recent prospective study, a predominantly Caucasian, community-based cohort of 25,534 men and women showed a similarly significant relationship between the development of CKD and hypertension (stages I–IV, as defined in the sixth report of the Joint National Committee, relative risk 5.7–8.8) and smoking (relative risk 2.6), irrespective of gender. Although the relative risk of CKD was highest in patients with more severe hypertension, overall, the attributable risk of CKD was greatest in patients with stage I hypertension, showing that patients with only modest hypertension comprise the bulk of the CKD burden. Thus, in contrast to the typical approach of only targeting patients with

Figure 1: Kaplan–Meier Curves Showing the Cumulative Incidence of ESRD by Quartile of Baseline Haemoglobin (Hb) in Patients with Type 2 Diabetes and Nephropathy



ESRD = end-stage renal disease, Hb = haemoglobin, Q = quartile.
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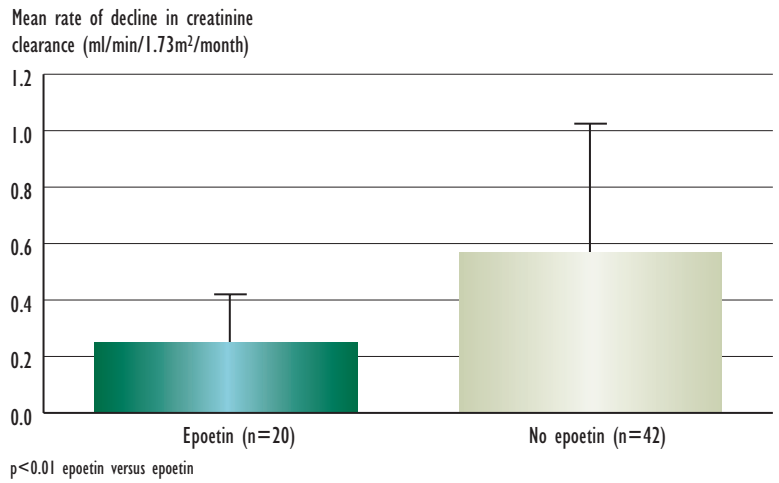
Figure 2: Mean Rate of Decline in Creatinine Clearance in Patients with CKD (Stages I–IV, Pre-ESRD/pre-dialysis) Receiving Either Epoetin or No Epoetin



CKD = chronic kidney disease, ESRD = end-stage renal disease.
Source: Jungers et al., Nephrol. Dial. Transplant. *(2001);16: pp. 307–312.*

stage III or IV hypertension, these findings suggest that optimal treatment of stage I hypertension will have a greater public health impact on reducing CKD.

Inflammation and CKD

Until recently, consideration of systemic inflammation as a modifiable risk factor for CKD progression received comparatively little attention. Cross-sectional studies show that patients with CKD have a pronounced inflammatory phenotype, including an elevated serum concentration of inflammatory markers, such as C-reactive protein (CRP) and interleukin (IL)-6, and decreased serum albumin levels.

A more recent retrospective analysis of data from 9,250 adults enrolled in NHANES II confirmed systemic inflammation as an independent risk factor for future development of CKD. After adjusting for age, race, gender, blood pressure, smoking and body mass index, a graded positive association was observed between increased total white blood cell count and risk of CKD ($p<0.001$ for trend; relative hazard: highest quartile (Q4) versus lowest quartile (Q1) = 2.34). This relationship remained after additionally adjusting for the presence of diabetes and CVD at baseline. A similarly strong and graded association was observed between decreased serum albumin levels and incident CKD ($p=0.02$ for trend; relative hazard: Q1 versus Q4 = 2.05).

Diabetes and CKD

Type 2 diabetes is one of the fastest growing epidemics worldwide. The number of individuals diagnosed with type 2 diabetes was estimated at 124 million in 1997, a number expected to reach 221 million by 2010. Significantly, the presence of diabetes has a considerable impact on the progression of CKD. Nephropathy, a major complication of diabetes associated with poor glycaemic control, occurs in approximately one-third of type 2 diabetic patients and is the single most important cause of ESRD in both the US and Europe. For example, approximately 24% of all patients in Europe beginning dialysis had diabetes in 1999.

Large, pivotal intervention trials provide evidence of a causal relationship between diabetes and CKD, showing that intensive glycaemic control in both type 1 and type 2 diabetic patients prevents the development and slows the progression of diabetic kidney disease by 25–50%. Despite this, however, there is little awareness of the risk of CKD development and progression associated with diabetes.

This situation in patients with CKD is compounded further in that CVD develops earlier and is more prevalent and more severe when diabetes is also present. In fact, in CKD patients with diabetes there is an approximate three-fold increase in the incidence of cardiovascular events and cardiovascular-related mortality compared with non-diabetic patients with CKD.

Anaemia, Diabetes and CKD

The compounding effect of diabetes on adverse clinical outcomes in patients with CKD is exacerbated further by anaemia. Anaemia occurs more frequently (two- to three-fold greater incidence), earlier and with greater severity in patients with both CKD and diabetes compared

with patients with CKD alone. This is particularly relevant as studies in patients with diabetic nephropathy show that the degree of anaemia further exacerbates the rate of CKD progression, i.e. the greater the degree of anaemia in these patients, the more rapid the progression to ESRD and RRT (see *Figure 1*).

Despite the strong relationship between anaemia in diabetes and adverse clinical outcomes in patients with CKD, there is still a general lack of awareness among physicians about anaemia and its implications for CKD patients with diabetes. In fact, up to 66% of such patients can have unrecognised anaemia.

Anaemia – An Underestimated Risk Factor for CKD Progression

Numerous studies suggest that anaemia together with diabetes presents a substantial risk for CKD progression. However, it is particularly notable that, although anaemia was reported to be an independent risk factor for the progression of both CKD and CVD nearly a decade ago, its importance as such is still underestimated by physicians and patients alike.

The assertion that anaemia represents an independent risk factor for CKD is based, in part, on data from NHANES III (1988–1994, n=19,215 nationally representative subjects). Here, a continuous relationship was observed in both men and women between low haemoglobin (Hb) levels and renal impairment, a relationship that was evident even at modest reductions in renal function.

A further study in a Canadian cohort of patients with CKD also showed that, for any given level of kidney function, the risk of progression to RRT increased with the severity of anaemia. Most importantly, this latter study found that the prevalence of anaemia (defined according to World Health Organization (WHO) criteria as Hb <13.5g/dl) was not only higher with advanced renal disease, but that 25% of patients had anaemia at a relatively early stage of kidney disease (i.e. GFR >50ml/min).

Left Ventricular Hypertrophy

Complementing these studies, other investigators observed that anaemia also contributed to the development of left ventricular hypertrophy (LVH) and chronic heart failure. Each 0.5g/dl decrease in Hb concentration was independently associated with a 32% increase in LV growth, i.e. an increase in LV mass. Given this, it is perhaps not surprising that LVH is typically found in approximately 50% of patients with CKD and 75% of patients with ESRD.

Epoetin

Clinical trials demonstrating the reno- and cardioprotective effects of treating anaemia with recombinant human erythropoietin (epoetin) also suggest that anaemia is an independent risk factor for the progression of CKD. It is well established that epoetin is highly effective for the treatment of anaemia in patients with CKD, improves quality of life and reduces the risk of morbidity and mortality from CVD. Several small studies have also shown that treatment of CKD-related anaemia with epoetin is associated with delayed onset of RRT.

A retrospective analysis of data from a clinical trial in predominantly non-diabetic patients with CKD (stages I–IV, pre-ESRD/pre-dialysis) found that while the rate of decline in mean creatinine clearance was unchanged in moderately anaemic patients who did not receive epoetin, the rate of decline decreased significantly in severely anaemic patients who received epoetin ($p<0.01$ versus no epoetin) (see *Figure 2*). Furthermore, in a study in children with pre-dialysis chronic renal failure, long-term administration of epoetin (mean 31 months) was associated with a delayed deterioration in renal function.

Moreover, this improvement was reflected in a significant delay of approximately six months in the initiation of dialysis in patients receiving epoetin

Nephropathy, a major complication of diabetes associated with poor glycaemic control, occurs in approximately one-third of type 2 diabetic patients and is the single most important cause of ESRD in both the US and Europe.

Early estimation of Glomerular Filtration Rate (eGFR) can offer patients at risk of Chronic Kidney Disease (CKD) the care they deserve

Patients with diabetes, hypertension and family history of kidney disease are at high risk for developing CKD

- 35% patients commencing renal replacement therapy have cardiovascular disease[1]
- Risk of diabetes in chronic kidney disease in patients is 2-4 times that of the general population[2]
- Compared to patients with normal GFR, patients with GFR <60mL/min/1.73m^2, are 6 times more susceptible to develop anaemia associated with CKD[3]

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Epoetin beta – 500, 1000, 2000, 3000, 4000, 5000, 6000, 10 000 prefilled syringes. 500 IU powder and solvent for solution for injection. 10 000, 20 000, 60 000 IU cartridges, 50 000 and 100 000 IU Multidose powder and solvent for injection (benzyl alcohol and benzalkonium chloride as preservatives). Indications: Treatment of anaemia associated with chronic renal failure (renal anaemia) in patients on dialysis. Treatment of symptomatic renal anaemia in patients not yet undergoing dialysis. For indications other than renal anaemia, please refer to full prescribing information.
Dosage: Chronic renal failure. NeoRecormon can be administered subcutaneously or intravenously. In case of intravenous administration, the solution should be injected over approximately 2 minutes. For non-haemodialysed patients, subcutaneous administration should be preferred. The aim of the treatment is to increase the packed cell volume (PCV) to 30-35%. A PCV of 35% should not be exceeded. In the presence of hypertension or existing cardiovascular, cerebrovascular or peripheral vascular diseases, the weekly increase in the PCV and the target PCV should be determined individually. In some patients the optimum PCV may be below 30%. Correction phase – subcutaneous administration: Initially 3 x 20 IU/kg body weight/week. Dosage may be increased every 4 weeks by 3 x 20 IU/kg/week if the increase in PCV is <0.5%/week. Weekly dose can also be divided into daily doses. Intravenous administration: Initially 3 x 40 IU/kg/week. Dosage may be increased after 4 weeks to 3 x 80 IU/kg/week and if further increments are needed by 3 x 20 IU/kg/week at monthly intervals. For both routes of administration the maximum dose should not exceed 720 IU/kg/week. Maintenance phase: To maintain a PCV of between 30 and 35% – initially reduce to half the previously administered amount. Then adjust the dose individually at 1 or 2 week intervals. In the case of subcutaneous administration, the weekly dose can be given as one injection per week or in divided doses three or seven times per week. Patients who are stable on a once weekly dosing regimen may be switched to once every two weeks administration.
Contra-indications: Poorly controlled hypertension or known hypersensitivity to the active substance or to any of the excipients of NeoRecormon (for Cartridges and Multidose: including benzoic acid, a metabolite of benzyl alcohol). Cartridge and Multidose presentations contain benzyl alcohol as a preservative and therefore must not be used in infants or young children up to three years old.
Special warnings and precautions: Use with caution in the presence of refractory anaemia with excess blasts in transformation, epilepsy, thrombocytosis and chronic liver failure. Folic acid and vitamin B12 deficiencies should be ruled out prior to therapy. Severe aluminium overload may compromise the effectiveness of NeoRecormon. Pure red cell aplasia caused by neutralising anti-erythropoietin antibodies has been reported in association with erythropoietin therapy, including NeoRecormon. These antibodies have been shown to cross-react with all erythropoietic proteins, and patients suspected or confirmed to have neutralising antibodies to erythropoietin should not be switched to NeoRecormon. Platelets should be monitored regularly in the different indications as specified in the SmPC as there may be an increase in platelet count. Occlusion of the dialysis system is possible if heparinisation is not optimised. Early shunt revision and thrombosis prophylaxis should be considered in chronic renal failure patients at risk of shunt thrombosis. Serum potassium levels should be monitored regularly as potassium elevation has been reported in a few uraemic patients. Misuse by healthy persons may lead to an excessive increase in haemoglobin. This may be associated with life-threatening cardiovascular complications. All presentations contain phenylalanine.
Drug interactions: None known from clinical studies.
Use in pregnancy and lactation: There is no adequate experience in human pregnancy and lactation therefore NeoRecormon should only be used in pregnancy and lactation if the potential benefit justifies the potential risks.
Undesirable effects: Cardiovascular system: In patients with chronic renal failure, treatment was most commonly associated with an increase in blood pressure or aggravation of existing hypertension, especially in cases of a rapid increase in PCV. If blood pressure rises cannot be controlled by drug therapy, a transient interruption of NeoRecormon therapy is recommended. Hypertensive crisis with encephalopathy-like symptoms may occur, even in individuals with otherwise normal or low blood pressure, and requires the immediate attention of a physician and intensive medical care. Sudden stabbing migraine-like headaches are a possible warning sign. It is recommended to monitor blood pressure. Blood: Shunt thrombosis may occur, especially in patinets who have a tendency to hypotension or whose arteriovenous fistulae exhibit complications. In isolated cases, neutralising anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA) associated with NeoRecormon therapy has been reported In case anti-erythropoietin antibody-mediated PRCA is diagnosed, therapy with NeoRecormon must be discontinued and patients should not be switched to another erythropoietic protein. Serum ferritin values can fall simultaneously with a rise in haemoglobin. Oral iron substitution dose of 200–300 mg Fe2+/day is recommended in all patients with serum ferritin values below 100 µg/l or transferrin saturation below 20%. Iron dosing should be modified according to the serum ferritin level and continued until signs of iron deficiency disappear. Other: Rarely, skin reactions such as rash, pruritus,
urticaria, injection-site reactions. Isolated cases of anaphylactoid reactions, flu-like symptoms. Please see full SmPC for incidences of undesirable effects in clinical trials.
Special precautions for storage: Store at 2°C–8°C.
Legal Category: POM
Marketing Authorisation Holder: Roche Registration Limited,
6 Falcon Way, Shire Park, Welwyn Garden City AL7 1TW
United Kingdom
Further information is available on request.
Full prescribing information should be viewed prior to prescription.
NeoRecormon is a registered trade mark.
Date of preparation: December 2005

1. Jungers et al. Epidemiology of end-stage renal disease in the Ile-de-France area: a prospective study in 1998. Nephrol Dial Transplant 2000;15: 2000-2006
2. Stevens PE. Prevalence of Chronic Kidney Disease in the UK. Abstract EDTA-ERA 2004
3. NHANES III (Third National Health and Nutrition Examination Survey)

compared with those who did not (16.3 versus 10.6 months, respectively; p<0.01).

A similar study, also in non-diabetic pre-dialysis patients, showed that correction of anaemia using epoetin was associated with a significant improvement in cumulative renal survival compared with no epoetin therapy (p=0.0003). The fact that clinical factors known to modify renal function, such as blood pressure, angiotensin-converting enzyme (ACE) inhibitor therapy and amount of dietary protein, were rigorously controlled for led the authors of this study to conclude that anaemia *per se* is a key factor in CKD progression. In addition, in patients with moderate CKD, mild anaemia (mean Hb 10.4g/dl) and congestive heart failure, correction of anaemia using epoetin was associated with significant improvements in GFR, functional status and cardiac function.

The beneficial effect of initiating epoetin pre-dialysis, in terms of hard clinical outcomes, is supported further by observational data from the Health Care Financing Administration (HFCA). In this analysis, mortality risk was reduced by up to 40% in patients who received epoetin compared with those who did not.

These findings have since been confirmed in a recent prospective trial in non-diabetic pre-dialysis patients with non-severe anaemia (Hb level 9.0–11.6g/dl) randomised to early or deferred treatment with epoetin. Here, the early use of epoetin was associated with a 60% risk reduction for initiation of RRT and death.

Conclusions

In patients with CKD, the impact of multiple chronic risk factors may be compounded by amplifiers or a lack of inhibitors. Thus, different strategies will need to be developed to improve patient outcomes. Improved understanding and awareness of the risk factors for CKD progression, and of the effect of early management of modifiable risk factors on outcomes will go a long way towards achieving this goal.

Anaemia occurs early and is considered an independent risk factor for progression to RRT and cardiovascular complications in patients with CKD. In showing that initiation of epoetin therapy early in CKD provides significant benefit in terms of slowing disease progression, the described studies collectively suggest early treatment of anaemia should be included with established measures known to delay ESRD such as blood pressure control and protein restriction. The on-going Cardiovascular risk Reduction by Early Anaemia Treatment with Epoetin beta (CREATE) trial will further clarify this issue.

There are many studies showing that an effective disease management strategy for CKD should include early intervention for modifiable risk factors such as diabetes, hypertension, smoking, inflammation and anaemia. However, despite recent evidence to the contrary, the importance of anaemia in CKD is still frequently underestimated by both physicians and patients, with potentially serious implications.

The increased risk of anaemia-related cardiovascular events in patients with CKD is exacerbated if diabetes is also present. However, it remains unclear whether correction of anaemia in early diabetic nephropathy will have any impact on cardiovascular morbidity and mortality. It is anticipated, however, that on-going trials such as the Individualised Risk-profiling In DIabEtes Mellitus (IRIDIEM) and the Anaemia CORrection in Diabetes (ACORD) studies will clarify the benefits of anaemia correction with regard to cardiovascular risk.

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In summary, regular monitoring and prompt intervention to control key modifiable risk factors is important for the prevention of CKD progression and for the long-term clinical outcome of patients with renal anaemia.

A version of this article, with references, can be found in the Reference Section on the website supporting this business briefing (www.touchbriefings.com).

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