Controversies in chronic kidney disease, anaemia and cardiovascular disease

Inclusion of chronic kidney disease within the primary care Quality and Outcomes Framework recognizes that most patients are diagnosed and managed in general practice. However, improved identification of patients with renal impairment also has important – and controversial – implications for hospital doctors.

In 2006, the status of chronic kidney disease as a major cause of morbidity and mortality was officially recognized when it became a clinical indicator in the Quality and Outcomes Framework (QOF), the annual reward and incentive programme in the general practice contract. As previously described (Moonie and Mooney, 2007), most biochemistry laboratories in the UK now routinely use the four-variable (or short) Modification of Diet in Renal Disease equation to report estimated glomerular filtration rate (eGFR) along with serum creatinine. Routine reporting of eGFR was a key quality requirement of the *National Service Framework for Renal Services* (Department of Health, 2005). This improves the recognition of impaired kidney function (*Table 1*), and in turn potentially allows better management of chronic kidney disease, an important public health problem that has major implications for patients, carers and the NHS.

Table 1. Classification of chronic kidney disease and associated complications

Stage	Description	Associated complications
1	Kidney damage* with normal or increased GFR (≥ 90 ml/min/1.73m^2)	Hypertension more frequent than among patients without chronic kidney disease
2	Kidney damage with mild reduction in GFR (60–89 ml/min/1.73m^2) and other evidence of chronic kidney damage*	Hypertension frequent, mild elevation of parathyroid hormone
3	Moderate impairment GFR 30–59 ml/min/1.73m^2: 3A: lower risk (GFR 45–59 ml/min/1.73m^2) 3B: higher risk (GFR 30–44 ml/min/1.73m^2)	Hypertension common, decreased calcium absorption, reduced phosphate excretion, more marked elevation of parathyroid hormone, altered lipoprotein metabolism, reduced spontaneous protein intake, renal anaemia, left ventricular hypertrophy
4	Severe impairment GFR 15–29 ml/min/1.73m^2	As stage 3, but more pronounced plus: metabolic acidosis, hyperkalaemia, decreased libido
5	Established renal failure GFR < 15 ml/min/1.73m^2 or on dialysis	As stage 4 with greater severity plus: salt and water retention causing apparent heart failure, anorexia, vomiting, pruritis (itching without skin disease)

*Other evidence of chronic kidney damage: persistent microalbuminuria, persistent proteinuria, persistent haematuria (after exclusion of other causes), structural abnormalities of the kidneys on radiological investigation, biopsy-proven chronic glomerulonephritis. GFR = glomerular filtration rate. From National Collaborating Centre for Chronic Conditions (2008); Scottish Intercollegiate Guidelines Network (2008)

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Benefits of early detection of chronic kidney disease

According to the most recent UK Renal Registry report, there were over 43 000 adult patients alive on renal replacement therapy (dialysis and transplantation) at the end of 2006, representing an increase in prevalence of 35% since 2000 (Ansell et al, 2008). The NHS already devotes 3% of its budget to kidney failure services (UK Transplant, 2007), and the projected increase in the patient population over the next 20 years (Roderick et al, 2004) has raised concern about the sustainability of the resulting expenditure.

Chronic kidney disease rarely becomes symptomatic until renal function has declined significantly, and earlier detection with eGFR could enable the use of interventions designed to slow progression to renal replacement therapy. There should also be benefits in reducing morbidity, mortality and associated costs among the 30% of patients with established renal failure who continue to be referred late (<90 days before start of dialysis) to nephrology services (Ansell et al, 2007). Late referral is particularly important for older patients – a group that is at higher risk of chronic kidney disease. The median duration of pre-dialysis care diminishes progressively with increasing age beyond the age of 45–54 years (Ansell et al, 2007).

Complex preparation for renal replacement therapy may be improved by earlier recognition of chronic kidney disease, but in fact progression to established renal failure occurs comparatively rarely (Hallan et al, 2006), especially for those individuals with stages 1–3 kidney disease.

What has become apparent is that chronic kidney disease is a marker for increased vascular risk, not only in renal replacement therapy patients but also at relatively minor levels of renal impairment (Go et al, 2004). In the general population, each 5 ml/min/1.73m^2 decrease in glomerular filtration rate (GFR) is associated with an increased cardiovascular risk of 26% – a risk that remains after adjustment for other established risk factors (Henry et al, 2002) – and renal impairment is also a graded and independent predictor of long-term risk of death in patients with known or suspected coronary artery disease (van Domburg et al, 2008). The reasons for the link

between cardiovascular disease and chronic kidney disease are complex. Not only are traditional cardiovascular disease risk factors highly prevalent in people with chronic kidney disease (Sarnak et al, 2003), but unique factors related to chronic kidney disease are also important in pathogenesis (*Table 1*).

Complications related to chronic kidney disease are more commonly associated with patients receiving renal replacement therapy, but abnormalities of erythropoesis and of mineral metabolism can be present relatively early in the course of chronic kidney disease. There is a significant decline in haemoglobin (Hb) at estimated creatinine clearances <70 ml/min in men and <50 ml/min in women (Astor et al, 2002). Anaemia predicts increased left ventricular mass, left ventricular dilatation, heart failure and death, and is associated with increased hospitalization and increased mortality (Joint Specialty Committee et al, 2006). Serum parathyroid hormone (PTH), 1,25-dihydroxy vitamin D_3, and calcium and phosphate levels may also be abnormal in early chronic kidney disease (Craver et al, 2007). These abnormalities of mineral metabolism are associated with vascular calcification and remodelling (Guérin et al, 2000), and may represent a non-traditional risk factor for cardiovascular disease. There is also increasing interest in the contribution of persistent inflammation, endothelial dysfunction and oxidative stress to cardiovascular risk in chronic kidney disease, but their causal relationship with cardiovascular disease remains unclear (Stenvinkel et al, 2008).

Two aspects of medicines management may also be influenced by eGFR reporting in the future. Currently most drug-dosing information is based on the Cockcroft and Gault estimation of creatinine clearance. This takes into account body size and to some extent GFR, but is inaccurate at low GFR values. The future role of eGFR in this context remains unclear. Second, it may inform medicines-related risk. For example, a person with stage 3 chronic kidney disease (eGFR 30–59 ml/min/1.73m^2) may have a stable but potentially nephrotoxic drug regimen. Trivial volume disturbance may then result in a major perturbation of biochemistry, and what was a safe regimen becomes harmful. These areas require further study.

Disadvantages of routine eGFR reporting

In spite of its potential advantages, the introduction of routine eGFR reporting has been criticized. Moonie and Mooney (2007) outlined eGFR's well-accepted limitations, which often relate to issues with the measurement of serum creatinine. However, the disadvantages of eGFR as a tool are outweighed by its simplicity in providing an approximate percentage of normal kidney function to guide referral and management. For example, it has been reported that there are fewer late referrals to specialist renal services of patients who will require renal replacement therapy (Bebb and Burden, 2007), and eGFR also provides opportunities to improve cardiovascular outcomes (Taal and Tomson, 2007; Richards et al, 2008a).

Despite that, some authors have suggested that routine measurement of eGFR has effectively resulted in a screening programme that will overload specialist nephrology services and cause anxiety and harm to patients (Giles and Fitzmaurice, 2007). There is a potential risk of inappropriately 'medicalizing' people with early-stage chronic kidney disease. However, it is important to stress that recently published chronic kidney disease guidelines from the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guideline Network (SIGN) build on normal practice in recommending testing of serum creatinine in patients at risk and do not advocate mass screening. In addition, patients with eGFR 60–89 ml/min/1.73m^2 without other evidence of renal impairment should not be regarded as having chronic kidney disease and not subjected to further investigation unless otherwise indicated (National Collaborating Centre for Chronic Conditions, 2008; SIGN, 2008).

The classification of chronic kidney disease used by the *National Service Framework for Renal Services* (Department of Health, 2005) was not without issues, and modified schemes have been adopted by both NICE and SIGN. Since the risk of cardiovascular events and mortality increases considerably when GFR is <45 ml/min/1.73m^2 (National Collaborating Centre for Chronic Conditions, 2008), patients with chronic kidney disease stage 3 are now classified into lower- and higher-risk groups (*Table 1*). Similarly, since the presence of proteinuria is associated with a doubling of cardiovascular disease risk and mortality at all levels of GFR (National Collaborating Centre for Chronic Conditions, 2008), the suffix P should now be used to denote the presence of proteinuria when staging chronic kidney disease. Proteinuria is also important because it helps to guide the need for specialist referral and blood pressure targets, and predicts the effectiveness of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in terms of slowing disease progression (National Collaborating Centre for Chronic Conditions, 2008).

Defining significant proteinuria has also resulted in a divergence of opinion. The latest NICE guidance focused on urinary albumin:creatinine ratio (ACR) but accepts that urinary protein:creatinine ratio (PCR) may also be utilised to quantify proteinuria. For example, significant proteinuria is defined as an ACR ≥30 mg/mmol (approximating to PCR ≥50 mg/mmol or proteinuria ≥0.5 g/day (National Collaborating Centre for Chronic Conditions, 2008)). SIGN recommends both ACR and PCR: the former to exclude, detect and monitor nephropathy in people with diabetes, and the latter to exclude chronic kidney disease and predict the risk of progressive disease in patients without diabetes. The Scottish guidelines also differ from NICE in defining P (significant proteinuria) as >1 g/day (approximating to PCR >100 mg/mmol or ACR >70 mg/mmol) (SIGN, 2008).

There are also concerns about the diagnosis of chronic kidney disease in the elderly population. Neither NICE

nor SIGN recommends age-adjusted reference ranges, since declining eGFR in the elderly is associated not only with the complications shown in *Table 1*, but also with reduced physical function and activity, and cognitive impairment (Roderick et al, 2008). End-stage renal failure is also more common in older people, yet they are more likely to be subject to delayed recognition, referral and management (Ansell et al, 2007). In addition, since older people are the main recipients of prescribed medication, they stand to benefit most from improved dosing of renally excreted drugs and avoidance of nephrotoxic medication such as non-steroidal anti-inflammatory drugs.

All doctors wish to avoid over-diagnosis and inappropriate treatment, especially in older people, many of whom have eGFR <60 ml/min/1.73m^2 (Roderick et al, 2007). However, the fact that chronic kidney disease has one of the highest exception reporting rates in the 2006/7 QOF (Information Centre Prescribing Support Unit, 2007) at least suggests that GPs are able to identify patients in whom review or intervention is inappropriate. There is concern that the QOF encourages the use of ACE inhibitors or ARBs in these patients. While these drugs are valuable in the amelioration of the progression of chronic kidney disease and as cardiovascular disease modification, patients with stable – that is non-proteinuric – chronic kidney disease are less likely to benefit, and the QOF has been modified in light of recently published recommendations from NICE and SIGN (see below).

Table 2. Guidelines for referral of patients with chronic kidney disease

National Institute for Health and Clinical Excellence (England and Wales)	The following groups should normally be referred for specialist assessment:	Stage 4 and 5 chronic kidney disease (with or without diabetes)
		Heavy proteinuria (albumin:creatinine ratio ≥ 70 mg/mmol, equivalent to proteinuria 1 g/24 hours) unless otherwise explained by diabetes and already appropriately being treated
		Proteinuria (albumin:creatinine ratio ≥ 30 mg/mmol, equivalent to proteinuria 0.5 g/24 hours) and haematuria
		Rapidly declining estimated glomerular filtration rate (> 5 ml/min/1.73^2 in 1 year, or >10 ml/min/1.73^2 within 5 years)
		Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses
		People with, or suspected of having, rare or genetic causes of chronic kidney disease
		Suspected renal artery stenosis
Scottish Intercollegiate Guidelines Network (Scotland)	Nephrology referral	Patients with clinical features suggestive of a primary renal diagnosis, e.g. glomerulonephritis present with nephrotic syndrome or renal disease secondary to vasculitis presenting with haematuria and proteinuria
		Rapidly progressive decline in kidney function
		Renal biopsy
		Unclear clinical picture
	Urology	Possible tumour
		Cystoscopy

From National Collaborating Centre for Chronic Conditions (2008); Scottish Intercollegiate Guidelines Network (2008)

The next concern is one of capacity. Secondary care would clearly be unable to cope if all patients with eGFR <60 ml/min/1.73m^2 were referred. There is evidence that implementation of eGFR reporting will, in the short term, result in significant increases in nephrology referral and additional investigations of patients with newly diagnosed chronic kidney disease (Klebe et al, 2007). However, this burden is related to case finding of prevalent disease (Tomson et al, 2007), with true incident referral rates closer to previous baseline levels (Richards et al, 2008b). The picture is complicated by the lack of evidence to guide recommendations on which patients should be referred to nephrology services (National Collaborating Centre for Chronic Conditions, 2008), and NICE and SIGN differ in the specificity of their guidance (*Table 2*). However, both guidelines envisage that a minority of patients will need referral and management by nephrology services, and that most people with chronic kidney disease can be managed by their GPs with specialist advice and support based on locally formulated shared-care arrangements (Jones et al, 2006; National Collaborating Centre for Chronic Conditions, 2008; Richards et al, 2008a; SIGN, 2008).

GPs have already shown their expertise in achieving QOF targets, and in a practice of 10 000 delaying the need for dialysis by 1 year in one patient could recoup the increased financial resources needed for initial management of newly identified chronic kidney disease (Klebe et al, 2007). In many cases, this requires good quality support and education. Local experience in Derbyshire, using educational meetings delivered by nephrologists and a web-based system, limited the initial rise in new referrals to 60%, which is returning to baseline levels 2 years after implementation of eGFR measurement (R Fluck, M Taal, unpublished data, 2008).

A final area of concern is nomenclature. It is perhaps unfortunate that reduced eGFR has been designated a 'disease' rather than a risk factor, but any diagnosis should be given sensitively to avoid unnecessary alarm and to clearly explain the implications for the individual. Patients should be informed that chronic kidney disease is common and that they are unlikely to need dialysis or transplantation. It does increase their chance of cardiovascular disease, but they and their doctors can take steps to reduce this risk. A diagnosis of chronic kidney disease may make it more difficult or costly to obtain life insurance or other types of cover, and this also requires study.

Managing cardiovascular disease risk factors in chronic kidney disease

Both NICE and SIGN guidelines include evidence-based recommendations on interventions to reduce cardiovascular disease risk in adults with chronic kidney disease.

Although some of the details differ (*Table 3*), both guidelines highlight the benefits of treating traditional cardiovascular risk factors in chronic kidney disease patients. This includes lifestyle measures such as smoking cessation, weight loss and exercise for all chronic kidney disease patients, and the recommendation that blood pressure control should also be designed to slow deterioration of GFR and reduce proteinuria (National Collaborating Centre for Chronic Conditions, 2008; SIGN, 2008).

Previous guidance on the management of mineral metabolism was complex and contentious. The recommendation to carry out monitoring of PTH and vitamin D in primary care, without education or resource, caused confusion for general practices, since the guidance applied to stage 3 or worse. Both SIGN and NICE have recognized this issue and have modified national guidelines. SIGN recommends measurement of serum, calcium phosphate and alkaline phosphatase levels when rechecking serum creatinine and eGFR in patients with chronic kidney disease stages 3 and 4 (SIGN, 2008). In contrast, English and Welsh guidelines from NICE state that there is no need to routinely measure calcium, phosphate, PTH and vitamin D levels in people with chronic kidney disease stages 1, 2, 3A and 3B. Calcium, phosphate and PTH – but not vitamin D as most laboratories do not measure 1,25 dihydroxy-vitamin D concentrations – should be measured in chronic kidney disease stages 4 and 5 at intervals determined by the measured values and clinical circumstances (National Collaborating Centre for Chronic Conditions, 2008).

The prevalence of anaemia increases from 1% at eGFR 60 ml/min/1.73m^2 to 33% at eGFR of 15 ml/min/1.73m^2 (Astor et al, 2002). Anaemia is therefore uncommon in chronic kidney disease stages 1–3, except in diabetic patients and those with eGFR <45 ml/min/1.73m^2 (UK Consensus Conference on Early Chronic Kidney Disease, 2007). NICE has provided detailed guidance on anaemia management in chronic kidney disease, including use of erythropoiesis-stimulating agents (ESA), and the key implementation priorities are shown in *Table 4* (National Collaborating Centre for Chronic Conditions, 2006). There is no equivalent Scottish guidance, but SIGN chronic kidney disease guidelines agree that ESAs should be offered to all patients with anaemia of chronic

Table 3. Managing cardiovascular risk in chronic kidney disease

Risk factor		National Institute for Health and Clinical Excellence	Scottish Intercollegiate Guidelines Network
Blood pressure control	Target blood pressure	In people with CKD aim to keep systolic blood pressure <140 mmHg (target range 120–139 mmHg) and diastolic blood pressure <90 mmHg	Patients with ≥ 1 g/day of proteinuria (approximately equivalent PCR of 100 mg/mmol) should have a targeted maximum systolic BP of 130 mmHg
		In people with CKD and diabetes or ACR ≥70 mg/mmol, aim to keep systolic blood pressure <130 mmHg (target range 120–129 mmHg) and diastolic blood pressure <80 mmHg	
	Choice of treatment	In people with diabetes and ACR >2.5 mg/mmol (men) or >3.5 mg/mmol (women) offer ACEI or ARBs irrespective of the presence of hypertension or CKD stage	ACEI and ARBs are the agents of choice in patients without diabetes who have CKD and proteinuria
		In people with CKD without diabetes and ACR ≥30 mg/mmol offer ACEI or ARB	ACEI and/or ARB should be used as agents of choice in patients without or without diabetes with CKD and proteinuria ≥0.5 g/day (approximately equivalent to PCR of 50 mg/mmol) to reduce progression of CKD
		In people with CKD without diabetes but with ACR ≥70 mg/mmol, offer ACEI or ARBs irrespective of the presence of hypertension or cardiovascular disease	
		In people with CKD without diabetes but with hypertension and ACR ≤30 mg/mmol, offer a choice of antihypertensive treatment according to NICE guidance on hypertension* to prevent or ameliorate progression of CKD	Non-dihydropyridine CCBs should be considered in patients with CKD and proteinuria who are intolerant of ACEI or ARB
Lipids	Primary prevention	Use of statin therapy in people with CKD should not differ from its use without CKD and should be based on existing risk tables for people with/without diabetes (note: Framingham risk tables significantly underestimate the risk in people with CKD)	Statin therapy should be considered in all patients with CKD stage 1–3 with a predicted 10-year cardiovascular risk of ≥ 20%
	Secondary prevention	Offer statin therapy to people with CKD irrespective of baseline lipid levels	
Antiplatelet therapy		Offer treatment with antiplatelet drugs for secondary prevention of CKD. CKD is not a contraindication to low-dose aspirin, but be aware of the increased risk of minor bleeding in people with CKD given multiple antiplatelet drugs	Low-dose antiplatelet therapy should be considered in all patients with CKD stage 1–3 whose estimated 10-year cardiovascular risk is ≥ 20%

National Institute for Health and Clinical Excellence (NICE) provides the following approximate equivalent values for ACR, PCR and proteinuria: ACR 30 mg/mmol ~PCR 50 mg/mmol ~ proteinurea 0.5 g/day; ACR 70 mg/mmol ~PCR 100 mg/mmol ~ proteinurea 1 g/day. ACEI = angiotensin-converting enzyme inhibitor; ACR = albumin:creatinine ratio; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; PCR = protein:creatinine ratio. *National Institute for Health and Clinical Excellence (2006). From National Collaborating Centre for Chronic Conditions (2008); Scottish Intercollegiate Guidelines Network (2008)

kidney disease to improve their quality of life, although the target Hb range of 10.0–12.0 g/dl differs slightly from the NICE target of 10.5–12.5 g/dl (National Collaborating Centre for Chronic Conditions, 2006; SIGN, 2008).

Maintenance of Hb within a target range depends on regular maintenance dosing, but continuation of treatment may not be appropriate in some circumstances – for example, for some chronic kidney disease patients undergoing major orthopaedic surgery – and any concerns should be discussed with nephrology colleagues. As NICE emphasizes, patient concordance is also critical to maintaining Hb, and in most renal units specialist nurses play a crucial role in monitoring and educating patients, including training for self-injection, and advising them on dosage adjustment where necessary.

In chronic kidney disease patients, ESAs are preferably administered through a subcutaneous injection in a limb or the abdomen. Since the use of these drugs was last reviewed in this journal (Fluck, 2006), physicians and patients have a wider choice of therapies and dosing interval (*Table 5*). These include agents that are biologically similar to, but cannot be directly substituted for, existing ESAs. This is because biosimilars differ from generic pharmaceuticals in their complexity and so are unlikely to have an identical structure or formulation to that of the existing or reference biological product. The Medicines and Healthcare Products Regulatory Agency (MHRA) therefore advises that it is good practice to use the brand name when prescribing to prevent automatic substitution of a biosimilar product by the pharmacist (MHRA, 2008).

Future developments in anaemia treatment include synthetic erythropoiesis protein, which is unrelated to erythropoietin but is still able to activate the erythropoietin receptor and stimulate erythropoiesis with monthly dosing (Macdougall, 2008). Submission for licensing is expected in 2010 depending on results of a phase III clinical programme that began towards the end of 2007. In the more distant future, there is also the exciting possibility of oral dosing using small molecule ESAs which are currently in pre-clinical development (Johnson and Joliffe, 2000).

Table 4. Key priorities for implementation of National Institute for Health and Clinical Excellence guideline on anaemia management in CKD

When to begin treating anaemia	Consider management of anaemia when Hb ≤11 g/dl	
Who should receive ESAs	Offer ESA to people with anaemia of CKD who are likely to benefit in terms of quality of life and physical function	
Agree a plan for ESA treatment	Plan should be patient-centred and include:	Continuity of drug supply
		Flexibility of where drug is delivered and administered
		Lifestyle and preferences of the patient
		Cost of drug supply
		Desire for self-care if appropriate
		Regular review of the plan in light of changing needs
Aspirational range and action thresholds for Hb	Maintain stable Hb levels between 10.5 and 12.5 g/dl Achieve by adjusting treatment, typically when Hb rises > 12 g/dl or falls below 11 g/dl Take patient preferences, symptoms and comorbidities into account and revise aspirational range accordingly	
Age	Should not be the only determinant for treatment of anaemia	
Aspirational ranges for iron supplementation	In patients receiving ESA maintenance therapy, give iron supplements to maintain:	Serum ferritin levels between 200 and 500 mg/litre and either
		Transferrin saturation > 20% (unless ferritin > 800 mg/litre) or
		Percentage hypochromic red cells <6% (unless ferritin > 800 mg/litre)

CKD = chronic kidney disease; ESA = erythropoeisis-stimulating agent; Hb = haemoglobin. From National Collaborating Centre for Chronic Conditions (2006)

Controversies in anaemia treatment in chronic kidney disease

The introduction of ESAs was one of the most important medical advances in the treatment of kidney disease, abolishing the severe anaemia that was common in renal impairment, reducing the need for blood transfusion and significantly improving functional health and wellbeing (Fishbane and Nissenson, 2007). There has, however, been continuing debate about Hb targets in chronic kidney disease, in light of randomized studies demonstrating no value and indeed increased risk in normalizing Hb in dialysis patients with and without symptomatic cardiac disease (Besarab et al, 1998; Parfrey et al, 2005).

This controversy came to a head in 2006 with the simultaneous publication of the large, prospective randomized CREATE and CHOIR studies in people with chronic kidney disease. CREATE indicated that early and complete anaemia correction did not improve cardiovascular outcomes compared with later and incomplete correction, and that higher Hb was associated with a greater risk of starting dialysis (Drueke et al, 2006). CHOIR demonstrated that, compared to an Hb target of 11.3 g/dl, a target of 13.5 g/dl increased the risk of the composite endpoint of death, myocardial infarction, stroke and hospitalization for heart failure (Singh et al, 2006). The mechanisms underlying the adverse effects associated with normalization of Hb in these studies are poorly understood, and may relate to increased blood pressure, increased blood viscosity, direct effects of ESAs and oxidative stress from intravenous iron (Fishbane and Nissenson, 2007).

Since the publication of CHOIR and CREATE, regulatory authorities have reviewed the safety of ESAs and authorized indications have been changed to stipulate treatment only if symptoms are present, that target Hb should be 10–12 g/dl and concentrations higher than 12 g/dl avoided (MHRA, 2007). While the revised indications are unlikely to change UK clinical practice since

Table 5. Erythropoiesis-stimulating agents available in the UK

Product name (brand)	Renal indication	Subcutaneous maintenance dosing frequency in chronic kidney disease
Epoetinum alfa (Eprex)	Treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis	Three times weekly
Epoetin beta (NeoRecormon)	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	Once weekly, or in divided doses three/seven times weekly. Patients stable on once-weekly dosing may be switched to once every 2 weeks
Epoetin delta (Dynepo)	Treatment of anaemia in patients with chronic renal failure. It may be used in patients both on dialysis and not on dialysis	Twice weekly
Darbepoetin alfa (Aranesp)	Treatment of anaemia associated with chronic renal failure in adult and paediatric patients	Once monthly
Methoxy polyethylene glycol-epoetin beta (Mircera)	Treatment of anaemia associated with chronic kidney disease	Once monthly
Epoetin alfa (biosimilar) (Binocrit)	Treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adults patients with renal insufficiency and not yet undergoing dialysis	Not applicable: intravenous injection only in renal patients
Epoetin zeta (biosimilar) (Retacrit)	Treatment of anaemia associated with chronic renal failure in adult and paediatric patients on haemodialysis and adult patients on peritoneal dialysis Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adult patients with renal insufficiency not yet undergoing dialysis	Not applicable: intravenous injection only in renal patients

From Electronic Medicines Compendium. http://emc.medicines.org.uk/ (accessed 24 June 2008)

they are compatible with previously published NICE guidelines, concerns about the adverse effects associated with normalization of Hb should not deprive patients of the proven benefits of ESAs. Given the inverse relationship between Hb levels and risk of cardiovascular disease in patients starting dialysis (Levin et al, 1996), it is unlikely that maintenance of recommended Hb will increase chronic kidney disease patients' risk and there is unlikely to be a problem if Hb occasionally rises above 12 g/dl through normal biological variability. In practical terms, clamping the Hb in a relatively tight range can be a challenge. While an overshoot on an ESA may increase risk, one must consider that undershooting probably confirms a higher degree of hazard. Again, more sophisticated guidance on this area is awaited.

Conclusions

The introduction of routine eGFR reporting has been controversial, but it provides the opportunity to reduce patient cardiovascular and renal morbidity and mortality, and long-term costs for the NHS. It has allowed improved detection and focused attention on the treatment of complications of chronic kidney disease, and already there are signs that this results in better preparation of patients who will require dialysis. The synergy between cardiovascular disease and chronic kidney disease, in terms of management, requires development. Despite areas of contention, eGFR has led to better patient care. Further research and modification of eGFR reporting, the classification of chronic kidney disease and of management of both chronic kidney disease and cardiovascular disease will consolidate those improvements. **BJHM**

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KEY POINTS

- Chronic kidney disease is an important public health problem that has major implications for patients, carers and the NHS.
- Most patients are diagnosed and managed in general practice, but detection of chronic kidney disease has important implications for hospital doctors in terms of referral, prevention of complications, and medicines management.
- Chronic kidney disease guidelines do not advocate mass screening for chronic kidney disease, but build on normal practice by recommending testing of serum creatinine and routine reporting of estimated glomerular filtration rate in at-risk groups.
- The National Institute for Health and Clinical Excellence (NICE) recommends that treatment of anaemia in chronic kidney disease should be considered at haemoglobin levels ≤11 g/dl, and that erythropoiesis-stimulating agents should be used to maintain stable haemoglobin levels between 10.5 and 12.5 g/dl.
- Following large clinical trials that demonstrated potential adverse effects of higher target haemoglobin, European regulatory authorities recommend treatment with erythropoiesis-stimulating agents only if symptoms are present, a target haemoglobin of 10–12 g/dl and avoidance of concentrations >12 g/dl.
- Given pre-existing NICE guidance, recently revised erythropoiesis-stimulating agents indications are unlikely to affect UK clinical practice in chronic kidney disease.
- It is important that patients who are maintained within recommended haemoglobin ranges are not deprived of the proven benefits of erythropoiesis-stimulating agents because of concerns about the potential adverse effects of higher targets.