Anaemia and metabolic bone disease are complications of chronic kidney disease that can appear relatively early in the course of the condition. What is the best way to manage these complications?

**Chronic kidney disease**

**managing the complications**

By Reena Popat, MSc, MRPharmS

For most people with chronic kidney disease (CKD), complications of the condition progress as renal function declines. Cardiovascular disease is the most common complication, but anaemia and bone and mineral disorder also occur regularly (which also contribute to cardiovascular risk). These complications can manifest even in those with moderate renal function (ie, pre-dialysis) and are associated with increased rates of hospital admission and mortality if not treated appropriately.

Patients with CKD will require a large number of medicines by the time they reach end-stage renal disease (ESRD) and the pharmacist’s role in medicines management is essential to optimise patient care.

**Anaemia**

Anaemia is a lack of circulating red blood cells — defined by the World Health Organization as a haemoglobin (Hb) concentration of less than 13g/dl for men and post-menopausal women and 12g/dl for pre-menopausal women. Common symptoms include fatigue, depression and weakness often accompanied by dizziness.

If left untreated, anaemia can have serious consequences, impairing quality of life and increasing the risk of cardiovascular complications (eg, left-ventricular hypertrophy). It has also been shown that a lower Hb level when dialysis is first started substantially increases the risk of cardiovascular disease and death in the first year of dialysis; early intervention may prevent such complications.

In the UK, CKD is the most common cause of anaemia. Deficiency of the hormone erythropoietin (EPO) in CKD is the most likely reason for anaemia to develop. EPO is predominantly produced by the peritubular cells in the kidney and is responsible for the proliferation and differentiation of erythroid progenitor cells in the bone marrow, which are responsible for the production of red blood cells. Hence, loss of peritubular cells leads to inappropriately low levels of circulating EPO.

Other factors that contribute to anaemia in patients with CKD include:

- Blood loss (specifically iron loss) during dialysis
- Shortened life span of red blood cells
- Impaired iron haemostasis
- Secondary hyperparathyroidism
- Inflammation

**Diagnosis** The following diagnostic tests should be carried out when assessing anaemia in CKD:

- Full blood cell count
- Red blood cell indices — for example mean corpuscular volume and mean corpuscular haemoglobin
- Reticulocyte count
- Iron studies — including serum iron, total iron binding capacity, percentage transferrin saturation, serum ferritin and percentage of hypochromic red blood cells

Further tests, for example measuring vitamin B₁₂, folate and parathyroid hormone levels, may be required based on clinical and laboratory findings.
The National Institute for Health and Clinical Excellence and the UK Renal Association recommend that treatment of adults with CKD-related anaemia should be considered when their Hb level is less than or equal to 11g/dl. Treatment should aim to maintain stable Hb levels of 10.5–12.5g/dl for adults.1

**Erythropoiesis-stimulating agents** Erythropoiesis-stimulating agents (ESAs) are biological medicines that stimulate EPO, thereby increasing the production of red blood cells. ESAs have been shown to improve survival, reduce cardiovascular morbidity and enhance quality of life for people with anaemia and CKD.

Generally, treatment with an ESA begins with an intensive correction phase, which is then followed by maintenance treatment. The dosage and frequency of administration depends on the preparation, route, treatment phase and type of patient being treated. Both subcutaneous (SC) and intravenous (IV) routes are effective; although, some evidence suggests that SC administration is more effective, allowing lower doses to be administered, which is also less expensive. However, for patients undergoing haemodialysis, IV administration during dialysis ensures adherence with therapy and may improve outcomes. ESA therapy is ineffective for patients with high C-reactive protein and, additionally, some patients are resistant to ESA treatment; these patients are dependent on blood transfusions.

Several ESA preparations are available (see Box 1). The first ESAs available were epoetin alfa and epoetin beta, which were both licensed to be given IV or SC, two to three times a week. The next ESA on the market was darbepoetin, which can be administered by IV or SC routes. It has a larger molecular weight and longer elimination half-life than those previously mentioned and different receptor binding affinity it can be administered once weekly and, for some patients, may require fortnightly administration when treatment is initiated.

Recently, “biosimilar” versions of ESAs have become available in the UK. Unlike generic medicines, biosimilars are similar to, but not the same as, the innovator medicine. Like other biological medicines, biosimilars are manufactured through biological processes involving recombinant DNA. Often the protein structure is both more complex and larger than that of the innovator drug. Also, the proteins are highly sensitive to manufacturing changes. Concerns around long-term safety and efficacy of ESA biosimilars have somewhat limited their use in the UK. This may change as more data become available.

There is no strong evidence to suggest superiority of one ESA preparation over another. Choice is dependent on factors such as the patient’s dialysis status, the route of administration and the local availability of ESAs.2 Most hospital trusts have entered into purchasing agreements with particular manufacturers so they receive considerable bulk-order discounts — this largely dictates the type of ESAs available to patients in particular regions.

**Adverse effects** Although ESAs can be beneficial for patients with CKD-associated anaemia, evidence does show that patients should not be over-treated. The “Cardiovascular risk reduction by early anaemia treatment with epoetin beta” (CREATE)3 and the “Correction of haemoglobin and outcomes in renal insufficiency” (CHOIR)4 studies both showed that ESA treatment to Hb targets above those currently recommended can pose a safety risk.

The CREATE study tested whether complete correction of anaemia (to 13–15g/dl) in patients with stage 3 or 4 CKD would offer improved cardiovascular outcomes compared with partial correction (10.5–11.5g/dl). The results showed a quicker rate of progression to dialysis for the group aiming for the higher Hb target. There was also a non-significant trend towards a higher risk of cardiovascular events among this group.

CHOIR evaluated the effect of correcting Hb to a target of 13.5g/dl or 11.5g/dl in the pre-dialysis population. The primary endpoint was a composite of death, myocardial infarction, congestive heart failure, hospital admissions and stroke. This study was terminated early because of increased rates of the primary endpoint in the group aiming for the higher Hb target.

In the TREAT study,5 diabetic patients with CKD-related anaemia were randomised to receive darbepoetin (treatment to a target Hb of 13g/dl) or placebo (with rescue darbepoetin given if Hb fell below 9g/dl). Fatal or non-fatal stroke occurred in 101 patients assigned to darbepoetin and 53 patients assigned to placebo (hazard ratio 1.92, 95% confidence interval 1.38–2.68; P=0.001). The patients in the target-treated darbepoetin group also experienced higher rates of venous thromboembolic events (2.0% versus 1.1%; P=0.02). In addition, more patients with a history of malignancy at baseline died in the treat-to-target group than in the placebo/rescue group.

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**Box 1: Erythropoiesis-stimulating agents**

<table>
<thead>
<tr>
<th>PREPARATION</th>
<th>FREQUENCY</th>
<th>2–3 times a week</th>
<th>Weekly</th>
<th>Fortnightly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoetin alfa (Eprex, Binocrit*)</td>
<td>✓</td>
<td>✓</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Epoetin beta (NeoRecormon)</td>
<td>✓</td>
<td>✓</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Epoetin theta* (Eporatio)</td>
<td>✓</td>
<td>✓</td>
<td>☑</td>
<td>☑</td>
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</tr>
<tr>
<td>Epoetin zeta* (Retacrit)</td>
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<td>✓</td>
<td>☑</td>
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</tr>
<tr>
<td>Darbepoetin alfa (Aranesp)</td>
<td>✓</td>
<td>✓</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Methoxy polyethylene glycol-epoetin beta (Mircera)</td>
<td>✓</td>
<td>✓</td>
<td>⚫</td>
<td>☑</td>
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</tr>
</tbody>
</table>

* Denotes biosimilar products
As a result of these studies, many physicians have re-evaluated their approach to the treatment of anaemia, taking into account patient comorbidities and treating to the lower end of NICE targets.

There have been rare reports of antibody-mediated pure red cell aplasia (PRCA) associated with the use of ESAs, mainly with SC use. PRCA is a severe, non-regenerative form of anaemia, which involves selective erythroid aplasia of the bone marrow. Affected patients have a normochromic, normocytic anaemia, severely reduced reticulocyte count, normal white cell and platelet counts and practically no erythroid precursors in bone-marrow aspirates, leaving the patient dependent on blood transfusions.5

Other side effects associated with ESA treatment include hypertension, seizures and allergic reactions.

Iron
In addition to treatment with an ESA, most patients will also require iron supplementation. NICE guidance recommends that iron supplements are given with the aim of maintaining serum ferritin levels of 200–500µg/L in both haemodialysis and non-haemodialysis patients and either of the following:2

- Transferrin saturation level above 20% (unless ferritin is greater than 800µg/L)
- Percentage hypochromic red cells less than 6% (unless ferritin is greater than 800µg/L).

Oral or IV iron can be given, although for replenishing iron stores IV iron achieves more rapid results. Almost all patients will receive IV iron during dialysis, with the dose depending on serum iron levels. The most common IV iron preparations administered are iron sucrose or iron dextran. Newer iron preparations are now available, such as ferric carboxymaltose or iron isomaltoside, which can be given at higher doses less frequently. These newer products are more expensive.

Mineral and bone disorder
In the past, the mineral and bone disorder that is associated with CKD was referred to as renal osteodystrophy or renal bone disease. However, these terms only reflect damage caused to bones (eg, bone pain, deformity or fractures). More recently, evidence has revealed that extraskeletal calcification also occurs in CKD, which substantially increases cardiovascular mortality and morbidity and can reduce a patient’s quality of life. Because of this, Kidney Disease Improving Global Outcomes recommends using the term “CKD mineral and bone disorder” (CKD-MBD), which encompasses the broader syndrome (see Figure 1).6

CKD-MBD begins to appear from CKD stage 3 onwards and can manifest itself as one or a combination of the following:6

- Abnormalities in calcium, phosphate, parathyroid hormone (PTH) and vitamin D metabolism
- Abnormalities of bone turnover, mineralisation, volume, linear growth and strength
- Vascular or soft tissue calcification

In the early stages of CKD, phosphate excretion is reduced. Initially, this triggers a compensatory increase in secretion of PTH, which stimulates the kidney to excrete more phosphate (therefore serum phosphate levels may not be elevated). As CKD progresses, the ability of PTH to do this diminishes and phosphate levels rise.

In addition, renal hydroxylation of inactive calcidiol to the active form of vitamin D (calcitriol) is reduced. Low levels of calcitriol lead to reduced intestinal absorption of calcium resulting in hypocalcaemia.

The net result of this hyperphosphataemia, hypocalcaemia and low levels of calcitriol is the stimulation of PTH synthesis and secretion. This is called secondary hyperparathyroidism and it is treated by correcting the imbalance of calcium, phosphate and...
calcitriol. However, ongoing stimulation of the parathyroid glands causes hyperplasia — the parathyroid tissue continues to secrete PTH despite correcting calcium, phosphate and calcitriol. This is termed refractory hyperparathyroidism.

Acting early to correct imbalances in serum phosphate and calcium, and therefore limit the development of secondary hyperparathyroidism, is central to the prevention of CKD-MBD.

The treatment targets for patients with CKD-MBD are as follows:

- **Phosphate**: pre-dialysis, the aim of therapy is to maintain phosphate of 0.9–1.5mmol/L and for those patients on dialysis 1.1–1.7mmol/L.
- **Calcium**: serum calcium (adjusted for albumin) should be within normal limits for pre-dialysis patients and for dialysis patients calcium should, ideally, be 2.1–2.5mmol/L.
- The recommended level of PTH is two to nine times the normal limit (ie, 10–40pmol/L).

**Phosphate**

Limiting dietary phosphate is essential to control hyperphosphataemia. This can be difficult for CKD patients, who need to remain well nourished (most patients have reduced appetite), because high-protein foods tend also to be high in phosphate. Examples of phosphate-rich food include oily fish and dairy products. Because of difficulties with patient adherence to dietary restrictions, other interventions are usually required. Dialysis removes phosphate, but this is only applicable to patients with stage 5 CKD. Phosphate binders are used routinely and are often initiated pre-dialysis (stage 3–4 CKD) irrespective of serum phosphate levels.

Phosphate binders work by reducing gastrointestinal absorption of phosphate from food and are taken before, with or soon after food for maximum efficacy.

Choosing the most appropriate binder for a patient must take into consideration calcium levels, cost, adverse effects and patient preference (see Box 2). Poor compliance with phosphate binder therapy is well documented — 22–74% of patients report non-adherence. Therefore, patient counselling that includes addressing barriers to adherence is an essential task for the pharmacist.

**Calcium-containing phosphate binders**

Calcium-containing phosphate binders are available as a carbonate or an acetate. Calcium acetate is considerably more expensive than calcium carbonate. However, many patients will opt for calcium acetate preparations because they dislike the chalky taste of calcium carbonate. Both options reduce phosphate effectively and are cheaper than the non-calcium-containing binders.

Patients are usually started on one tablet three times a day with meals and the dose is titrated upward according to biochemical markers. The use of calcium-containing binders is limited by the potential for hypercalcaemia (and thus increased risk of vascular calcification). To keep calcium within range, many patients will require treatment with a combination of calcium- and non-calcium-containing binders or monotherapy with a non-calcium containing binder.

**Non-calcium-containing phosphate binders**

In the UK, the non-calcium-containing phosphate binders that are available are aluminium, sevelamer and lanthanum. In the past, aluminium hydroxide was used commonly due to its high efficacy and low cost. However, in the 1970s it was identified that, with long-term use, aluminium could accumulate and cause toxicity. Because of this the popularity of the drug reduced. Generally, the use of aluminium is now reserved for patients with hyperphosphataemia that is difficult to control and it is only used for six months at a low dose.

Sevelamer hydrochloride reduces phosphate without affecting calcium. It also improves lipid profiles, but the mechanism for this is unknown. Furthermore, there is some evidence to suggest that sevelamer attenuates the progression of cardiovascular calcification when compared with calcium binders. The use of sevelamer is limited by the fact that it is only licensed for patients receiving dialysis. Another disadvantage is the high pill burden that may be required to control hyperphosphataemia.

Recently sevelamer carbonate has been licensed in the UK for the control of hyperphosphataemia in all patients with CKD, irrespective of whether or not they are on dialysis. Sevelamer carbonate may have an improved gastrointestinal side effect profile when compared with sevelamer hydrochloride.

For most patients, lanthanum carbonate has a reduced pill burden (compared with sevelamer), but it must be taken with or after food to reduce gastric side effects. Lanthanum is a rare earth element with a density approaching that of a metal. It dissociates in the stomach to the lanthanum ion, which binds to phosphate before excretion into faeces. There are some concerns that lanthanum may accumulate in bone with long-term use although, to date, there is no evidence to support this.

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**Box 2: Comparison of different phosphate binders**

<table>
<thead>
<tr>
<th>PHOSPHATE BINDER</th>
<th>AVERAGE DOSE</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>1–3 tablets with meals</td>
<td>Corrects hypocalcaemia</td>
<td>Hypercalcaemia, constipation</td>
</tr>
<tr>
<td>Aluminium</td>
<td>1–2 capsules with meals</td>
<td>Less hypercalcaemia</td>
<td>Osteomalacia, encephalopathy</td>
</tr>
<tr>
<td>Lanthanum</td>
<td>500–1,500mg with meals</td>
<td>Less hypercalcaemia</td>
<td>Abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea, vomiting, hypercalcaemia</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>3 x 800mg tablets with meals</td>
<td>Lowers plasma cholesterol</td>
<td>Abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea, vomiting</td>
</tr>
</tbody>
</table>

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**Vitamin D**

The replacement of vitamin D, either with calcitriol (1,25-dihydroxycholecalciferol) or alfacalcidol (1α-hydroxycholecalciferol), in patients with CKD-MBD promotes normal physiology and mineral metabolism. Furthermore, vitamin D supplementation can help to correct hypocalcaemia (which has resulted from reduced calcitriol and raised phosphate levels) and correct secondary hyperparathyroidism.10

However, a disadvantage of vitamin D analogues is their risk of hypercalcaemia, hyperphosphataemia and oversuppression of the parathyroid glands. This has the potential to cause suppression of bone turnover and adynamic bone disease (characterised by low bone resorption and formation and normal or low amounts of osteoid tissue, increasing the risk of fracture). The dose of vitamin D analogue that is prescribed will therefore depend on these biochemical markers. Additionally, patients with hyperparathyroidism who are taking a calcium-based phosphate binder can be switched to an alternative binder or the activated vitamin D can be switched to paricalcitol.

Paricalcitol is a synthetic vitamin D-receptor activator. It is tissue-selective — paricalcitol upregulates, and restores the activation of, the vitamin D receptor in the parathyroid gland, but has less effect on bone, calcium and phosphate retention in the intestine.

Compared with calcitriol, paricalcitol has three times greater selectivity for PTH suppression. The dosing schedule outlined by the manufacturer is complex, but most specialist renal centres start treatment with paricalcitol at a dose of 2µg three times a week and titrate according to response. It is licensed for use in patients with hyperparathyroidism who are taking a calcium-based phosphate binder can be switched to an alternative binder or the activated vitamin D can be switched to paricalcitol. Patients are initiated on cinacalcet 30mg once daily and titrated up to a dose of 180mg daily, although the dose may be limited by hypocalcaemia or nausea and vomiting. Often, dividing the dose over the day can alleviate the gastrointestinal side effects.

**Parathyroidectomy** For patients whose PTH cannot be controlled with medicines, a parathyroidectomy may be the best option to prevent further complications of CKD-MBD. Sub-total parathyroidectomy (removing seven-eighths of the total parathyroid tissue) carries the risk of the remaining parathyroid tissue redeveloping hyperplasia, after which the disease can recur.

Alternatively, patients can undergo a total parathyroidectomy, which carries little risk of recurrence of the disease. These patients require lifelong calcium supplementation.

### Other treatments

**Cinacalcet** Cinacalcet is a calcimimetic, which works by increasing the sensitivity of the calcium-sensing receptor in the parathyroid glands to extracellular calcium. This then inhibits the release of PTH and therefore reduces calcium and phosphate concentrations. Cinacalcet has been shown to be highly effective in reducing PTH levels. A study conducted by Cunningham et al showed that treatment with cinacalcet can reduce the incidence of fracture, cardiovascular hospital admissions and parathyroidectomy (see below), but not overall hospital admissions or all-cause mortality.11 Renal clinicians are awaiting the results of the EVOLVE study (“Evaluation of cinacalcet therapy to lower cardiovascular events”) in the hope that it will define more clearly the role of cinacalcet in stage 5 CKD.

NICE recommends that cinacalcet be used for patients with ESRD, refractory secondary hyperparathyroidism and both:

- Uncontrolled plasma levels of PTH (>85pmol/L) refractory to standard therapy and a normal or high adjusted serum calcium
- A contraindication to surgical parathyroidectomy

### References


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