Hotter Topics in Feline Medicine - Challenging Cases for Advanced Practitioners Mini Series

Session 2: Acute and chronic kidney disease

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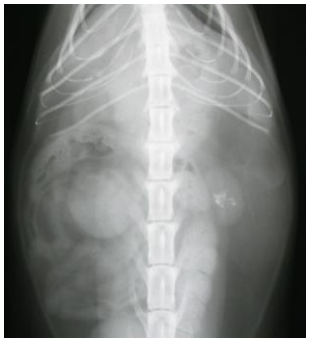

1. INTRODUCTION

Chronic kidney disease (CKD) is a common and important cause of morbidity and mortality in cats. It can be seen in cats of all ages, but occurs most commonly as an acquired disease of middle-aged to older cats. CKD is believed to be two to three times more common in cats than dogs. Increasingly, with the routine use of plasma biochemistry testing, more and more cats are being found to be azotaemic. Azotaemia refers to increased levels of plasma creatinine and urea. These begin to rise when the glomerular filtration rate (GFR) is no longer able to maintain normal excretory function. Unfortunately, the relationship between plasma creatinine and GFR is curvilinear. So the GFR may decrease rapidly in the early stages of CKD without incurring increases in creatinine, then, later on even small reductions in GFR may cause dramatic increases in creatinine. It is generally accepted that more than three-quarters of functioning renal tissue must be lost before azotaemia becomes apparent (Finco et al 1995; Squires 1996).

IRIS – International Renal Interest Society

- **Staging of CKD (modified 2015)**
- **Algorithms for proteinuria & hypertension**
- **Treatment recommendations for cats & dogs**
  http://www.iris-kidney.com/guidelines/staging.html
  http://www.iris-kidney.com/guidelines/recommendations.html

ISFM Consensus Guidelines on the Diagnosis & Management of Feline Chronic Kidney Disease (Sparkes *et al.,* JFMS, 2016, 18:219-239)

- CKD podcast – Andy Sparkes; jfm.sagepub.com/site/Podcast/podcast_dir.xhtml

The classification of CKD into clinical stages can be very helpful. However, it is important to look at all of the abnormal clinical findings, and not concentrate on the urea and creatinine levels alone. That said, cats with CKD can usually be divided into:

- **IRIS Stage 1:** Chronic kidney insufficiency (nonazotaemia renal failure) – ~67% of kidney function lost. Urine concentration ability is reduced, but urea and creatinine levels are still within normal limits. Serum creatinine concentration <140 umol/l (1.6 mg/dl). Indications of renal compromise may include abnormal renal palpation, imaging, and/or proteinuria of renal origin.
- **IRIS Stage 2:** Azotaemia kidney failure – ~75% of kidney function lost. Urea and creatinine levels are raised. Serum creatinine concentration 140-250 umol/l (1.6-28 mg/dl). Phosphate levels are usually raised. However, initially the cat is not necessarily ill.
- **IRIS Stage 3:** Uraemia kidney failure – >90% of kidney function lost. The urea, creatinine and other nitrogenous waste products are raised. Serum creatinine concentration 250-440 umol/l (2.8-5.0 mg/dl). Synthesis of calcitriol and erythropoietin are usually impaired. The cat is systemically ill.
- **IRIS Stage 4:** End-stage kidney failure – >95% of kidney function lost. Serum creatinine concentration >440 umol/l (>5.0 mg/dl). Excessive ammonium generation with kidney. Life is not sustainable without dialysis or renal transplant.
- Further classification can then be made on the basis of presence of proteinuria and/or systemic hypertension (see later).

In 1998, with the support of Novartis Animal Health, the International Renal Interest Society (IRIS) was formed. It was established in recognition of the importance of renal disease in small animal practice, and aims to help veterinary practitioners to better understand, diagnose and treat renal disease in cats and dogs. (For more information on IRIS visit: www.iris-kidney.com).

IDEXX now measure serum symmetric dimethylarginine (SDMA) concentration, which appears to indicate enal insifficience earlier that serum creatinine concentration, and is not affected by lack of muscle mass, as serum creatinine is:

- Serum creatinine concentration normal but SDMA >14 ug/dl → classify as IRIS 1
- IRIS 2 poor body condition SDMA ≥25 ug/dl → classify as IRIS 3
- IRIS 3 poor body condition SDMA ≥45 ug/dl → classify as IRIS 4

This paper will very briefly discuss the aetiology, clinical signs and diagnosis of feline CKD, after which it will focus more deeply on possible long-term management options.

2. AETIOLOGY

While the underlying cause of most cases of feline CKD remains obscure, a number of different aetiologies have been documented (Table 1). The most common histopathological finding is of chronic interstitial nephritis (Lucke 1968), however, the cause of this is uncertain, but in some cases may involve chronic pyelonephritis or glomerulonephritis.

3. CLINICAL SIGNS

The clinical signs of cats with CKD are often non-specific, with dehydration, anorexia, lethargy and depression being seen most commonly (see Table 2) (Lulich et al 1992; Krawiec and Gelberg 1989; DiBartola et al 1987; Elliott and Barber 1998). Polyuria and polydipsia are seen less commonly than in the dog. This may result in part from poor recognition on the part of the owners, but also because cats with CKD often retain some degree of urine-concentrating ability. The presence of small kidneys cannot be relied on as an indicator of CKD as many cats have enlarged kidneys due renal lymphoma, polycystic kidney disease or peri-renal pseudocysts. Other manifestations of uraemia in cats include vomiting (due to uraemic gastritis, hypergastrinaemia, or the central effects of uraemia toxins), pale mucous membranes (due to anaemia – see below), and hypertensive retinopathy (see below).

4. DIAGNOSIS

Diagnosis of CKD is usually based on clinical signs plus the presence of azotaemia and inappropriately concentrated urine. However, because cats often retain some ability to concentrate their urine it is not necessary to document isosthenuria (SG ~ 1.010). In fact, while most cats with CKD fail to concentrate their urine above 1.035, isosthenuria is seen in only ~60% of cases (Barber and Elliott 1998; Lulich et al 1992; DiBartola et al 1987; Elliott and Barber 1998). It is important to know what the cat is eating as normal cats fed on a dry diet typically have a urine SG>1.050; therefore, a SG of 1.040 in a cat fed only on dry food would be abnormal.

Azotaemia is not always caused by CKD, and a single blood sample showing an increase in creatinine and/or urea should not be over-interpreted. In general, serum creatinine concentrations reflect renal function more accurately than urea concentrations. However, serum creatinine may also be increased because of dehydration (pre-renal azotaemia), intestinal absorption of exogenous creatinine (e.g. a cooked meat diet), catabolic conditions (e.g. starvation, fever, excessive exercise, infection, necrosis), or a marked increase in body muscle mass (IRIS 2000). Urea may be increased because of dehydration, intestinal absorption of exogenous protein (e.g. a high protein diet or gastrointestinal haemorrhage), certain catabolic states (starvation, hyperthyroidism, or the use of corticosteroids), or post-renal failure/obstruction. Once azotaemia

has been detected its continued presence should be confirmed with further blood samples and a urine sample should be collected for assessment of its concentration.

Occasionally, the degree of azotaemia is not as severe as expected. This is seen most commonly in very thin cats which lack sufficient muscle mass to incur markedly raised creatinine levels, and occasionally in cats with severe liver dysfunction that are unable to produce urea.

In addition to azotaemia, a number of other clinicopathological changes are seen commonly in cats with CKD (Table 3) (Barber and Elliott 1998; Lulich et al 1992; DiBartola et al 1987; Elliott and Barber 1998). These include hyperphosphataemia (due to reduced GFR), acidosis (because the kidneys fail to excrete sufficient acid), hypokalaemia (due to inappropriate kaliuresis) and hypoproliferative anaemia (due to reduced erythropoietin production, reduced red blood cell survival times, uraemic suppression of erythropoiesis, and/or gastrointestinal bleeding). Other changes may relate to stress and/or dehydration (e.g. altered white blood cell numbers, hyperglycaemia, hyperproteinaemia).

In addition, proteinuria has recently been shown to be an independent risk factor for the progression of CKD in cats (Lees et al 2005; Syme et al 2006; Elliott and Syme 2006; Kuwahara et al 2006; Jepson et al 2007; King et al 2007). While only ~10% of cats with CKD have a urinary protein to creatinine ratio (UPC) of >1.0, recent studies have shown that in cats with CKD a UPC >0.4 (0.3-0.6) is in indicator of poor prognosis, and may warrant treatment (Lees et al 2005). One study found that mean survival times were 449 days in cats with a UPC <0.2, 224 days in cats with a UPC 0.2-0.8, and only 117 days in cats with a UPC >0.8 (King et al 2007). A separate study found that mean survival times were ~700 days with a UPC <0.43, but ~270 days with a UPC >0.43 (Syme et al 2006). While the presence of proteinuria typically indicates glomerular damage it is now suggested that proteins in the glomerular filtrate may be directly renotoxic contributing to progression of renal failure. IRIS now recommend that each cat is assessed for proteinuria by UPC and classified into the ranges <0.2 [non-proteinuria], 0.2-0.4 [borderline proteinuric] and >0.4 [proteinuria] (Elliott and Syme 2006; **IRIS Guidelines**).

While CKD is usually progressive, some cats may have long periods of relatively stable renal function in both experimental (Ross et al 1982; Adams et al 1994) and naturally occurring disease (Elliott and Barber 1998). Because of this it can be difficult to give an accurate prognosis for a particular cat with CKD. The plasma creatinine concentration is a weak prognostic indicator. In contrast, the presence of anaemia tends to indicate a poor prognosis. Also, cats in end-stage renal failure are more likely to be hyperkalaemic and/or acidotic, have lower urine specific gravity and more acidic urine (Elliott and Barber 1998). End-stage renal failure is also more likely to be associated with worsening renal secondary hyperparathyroidism (RHPTH), reduced levels of calcitriol and reduced levels of ionised calcium (Barber and Elliott 1998), and increased white blood cell counts (Kuwahara et al 2006; King et al 2007).

While it would be advantageous to detect CKD as soon as it develops, this can only be performed where GFR can be measured. Unfortunately, while a number of suitable techniques have been validated (e.g. measurement of GFR using the clearance of inulin, iohexol, Tc-DTPA, or exogenous creatinine) they are not currently routinely available.

It is essential when making a diagnosis of CKD that a full and thorough diagnostic investigation be made. The initial investigation and follow-up monitoring should include:

- Physical examination (including retinal examination)
- Bodyweight and body condition score (1 being very thin to 9 being obese), plus calculation of the percentage body weight change since the previous consultation
- Systolic and, where possible, diastolic blood pressure
- Haematology (looking for anaemia in particular)
- Serum biochemistry (urea, creatinine, potassium, sodium, calcium, phosphate, proteins, and serum thyroxin concentration)

- Urinalysis, UPC and urine bacterial culture
- Where possible, assessment of acid-base status
- Periodical assessment of iron status is also warranted, especially in anaemic CKD cats
- +/- parathyroid hormone status monitoring (especially in cats receiving calcitriol therapy)

It is important to remember that while young animals usually have only one disorder at a time, this is often not the case with the older patient. In older patients the diagnosis and treatment of CKD may be complicated by the concurrence of multiple interacting disease processes. It is only by detecting and treating the concurrent diseases at the same time as the CKD that the cat can best be managed.

The initial investigation should include a thorough physical examination (including ocular examination, measurement of body weight and systemic blood pressure), plus collection of a blood sample (for routine biochemical and haematological analysis, including serum thyroxin assessment), and a urine sample (for routine urinalysis, assessment of UPC ratio, and bacterial culture).

5. MEDICAL MANAGEMENT

Where an underlying cause for the CKD can be found this should be addressed. For example, bacterial nephritis or pyelonephritis should be treated with appropriate antibiotics, nephrotoxins should be removed (e.g. non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics, exposure to ethylene glycol antifreeze, lilies or grapes), pre-renal complications should be corrected (e.g. dehydration or cardiac disease), and post-renal obstruction should be resolved. The rest of this section will consider the aetiology of some of the more important problems associated with CKD, and then discuss the pros, cons and practical application of possible treatment options. However, it is important to tailor the specific treatment plan to the individual cat, according to their specific needs and situation.

5.1 The importance of maintaining sufficient fluid intake

An inadequate fluid intake can result in dehydration, reduced renal perfusion, pre-renal azotaemia and exacerbation of CKD. Some cats may be presented with acute decompensation of their CKD, while others may experience chronic or recurrent dehydration. Maintaining an adequate fluid intake is therefore of prime importance. Owners should be made aware of the increase in obligate fluid loss that typically accompanies CKD and so ensure that their cat has constant access to fresh water. In addition, they should encourage further fluid consumption by feeding a moist diet, and offering tempting ‘soups’ (e.g. made from cat food diluted with warm water, not salty fish stock, human gravy that may contain sufficient onion powder to induce haemolytic anaemia in cats, or milk which contains high levels of phosphate).

Where this proves insufficient to meet the cat’s needs many clinicians encourage the regular ‘at home’ administration of subcutaneous fluids by the owners. Lactated Ringer’s solution (LRS) or normal saline are used most frequently, although their long-term use may lead to sodium accumulation which may exacerbate hypertension. This can be prevented by using fluid composed of two parts 5% dextrose to one part LRS, however, dextrose-containing fluids can cause pain and irritation on administration. The amount of fluid given can be adjusted according to need (~50-150 ml, given from daily to once a week with the aim of correcting dehydration *not* of inducing diuresis). In addition, as needed, the fluid can be supplemented with potassium chloride (10 - 20 mmol KCl per litre of fluids) or sodium bicarbonate (0.5 – 8 mmol per litre of fluids - see later for indications). While this can improve the cat’s well being by reducing azotaemia, it should not be done to excess as over-diuresis may actually exacerbate CKD. In all cases, it is sensible to monitor serum electrolyte levels (especially sodium and potassium levels) and monitoring systemic blood pressure so that problems can be detected and corrected quickly. To ease the administration of the fluids an ‘indwelling’ subcutaneous catheter may be considered, as can a nasogastric tube or a percutaneously (PEG) or surgically placed gastrostomy tube.

5.2 The role of diet; including altering the levels of protein and phosphate

Dietary therapy represents the cornerstone of management for patients with CKD. This is because the list of factors within food that may exacerbate or protect against CKD is endless. Most work has concentrated on the roles of protein, phosphate, calcium, potassium, and acidification (see below). However, other studies have suggested that it may be beneficial to restrict sodium chloride (Dworkin et al 1996) although this has since been questioned (Buranakarl et al 2004); to change the lipid content of the diet and alter the balance of free fatty acids from omega-6 unsaturated fatty acids in favour of omega-3 unsaturated fatty acids (Brown et al 1996a and b; Finco et al 2000), where high eicopentaenoic acid content appears beneficial (Plantinga et al (2005); to adding extra water soluble vitamins (e.g. B-complex vitamins); or to adding antioxidants (e.g. Vitamines E and C and □-carotene) (Yu and Paetau-Robinson 2006).

The ideal 'renal diet' should therefore:

- Meet nutrient and energy requirements
- Reduce protein catabolism and alleviate clinical signs of uraemia
- Minimise electrolyte, vitamin and mineral disturbances
- Slow the progression of renal failure

5.2.1 Restriction of dietary protein

The clinical benefits of protein restriction in CKD have been demonstrated in a number of species (Harte et al 1994; Finco et al 1992; Levey et al 1999; Polzin et al 1991). The products of protein catabolism are believed to contribute significantly to the clinical signs associated with uraemia. Reducing the intake of non-essential protein may therefore help to reduce the production of nitrogenous waste and so reduce the severity of the anorexia, vomiting, weight loss, anaemia and lethargy.

Whether or not dietary protein restriction actually helps to reduce the progression of renal failure is more controversial. Experimental studies (mostly in rats and dogs) have shown that in the early stages of CKD a declining number of nephrons is compensated for by an increased GFR for each individual (single) nephron (SNGFR). This increase in SNGFR is achieved by glomerular hyperfiltration, glomerular hypertrophy and glomerular hypertension, and is associated with an increase in proteinuria. Together, these factors may lead to glomerular and tubulointerstitial sclerosis and progression of the CKD. In some experimental models protein restriction has minimised these changes and so retarded the progression of disease (Brown and Brown 1995; Polzin et al 1991). While these findings have been supported by a meta-analysis of several studies in humans (Pedrini et al 1996) there is still considerable debate as to whether or not protein restriction will truly limit the progression of CKD in naturally occurring CKD in most species.

A few studies have investigated the role of protein restriction in cats with CKD. Experimental studies appear to show that significant proteinuria and glomerular morphological injury may occur in cats fed a higher protein diet, however, the presence of increased protein and calorie intake made interpretation difficult (Adams et al 1994; Finco et al 1998). The difficulty of separating out different dietary variables also proved a complicating factor in studies by Harte et al (1994), Elliott et al (2000), Plantinga et al (2005) and Ross et al (2006) where cats with naturally occurring CKD were fed diets restricted in protein and phosphorus (i.e. 'renal diets'). In these studies, the cats fed a 'renal diet' showed marked clinical improvement, less uraemic episodes, reduced levels of plasma urea and phosphate, and fewer renal-related deaths: on average the cats fed 'renal diets' lived about a year longer than those that were fed regular cat food. While the overall benefit of the restricted diets cannot be denied, the individual effects of the protein and phosphorus cannot be determined.

It is generally recommended that cats with CKD be fed a diet with moderate protein restriction; containing protein of ~20% of the caloric intake. Unfortunately, the exact requirements are unknown, and since cats have a naturally high protein requirement it is essential not too over restrict them (Polzin et al 1996), especially if they still have significant muscle mass. It is also important to ensure that the source of protein is of high biological value and contains all of the essential amino acids. A minimum protein content of 3.5 g/kg/day has been recommended.

Unfortunately, while feeding a moderately protein-restricted diet is recommended, the poor palatability of these diets may limit their acceptance. Because of this, it is often recommended that cats with CKD be gradually weaned onto these diets before they start becoming inappetent or anorexic.

5.2.2 Restriction of dietary phosphorus and use of phosphate binders

Hyperphosphataemia occurs in approximately two thirds of cats with CKD (Table 3) (Barber and Elliott 1998; Lulich et al 1992; DiBartola et al 1987; Elliott and Barber 1998), and is believed to contribute to the uraemic complication of CKD. The primary mechanism for hyperphosphataemia is phosphate retention due to reduced GFR. Because the regulation of phosphorus and calcium are intrinsically linked, the phosphorus retention leads to calcium-phosphate deposition in the tissues (metastatic mineralisation), and this, in turn, leads to a reduction in the concentration of plasma ionised calcium. The resultant hypocalcaemia, although subclinical, stimulates the release of parathyroid hormone (PTH). Phosphate retention, when combined with the loss of renal mass, leads to a decreased production and/or activity of renal 1-□-hydroxylase enzyme, and hence a reduction of 1,25 dihydroxyvitamin D (calcitriol). The hypocalcitriolaemia results in a further increase in PTH production and reduced intestinal absorption of calcium. Phosphorus retention is therefore an important factor in the development of renal secondary hyperparathyroidism (RHPTH) (Chew et al 1992).

Secondary hyperparathyroidism occurs commonly in cats with CKD. In one study, 84% of cats with naturally occurring CKD were found to have RHPTH; with the severity and prevalence being highest in cats with end-stage renal failure (Barber and Elliott 1998).

Parathyroid hormone may be considered as a uraemic toxin. In excess, it has been associated with a variety of clinical abnormalities, including anaemia, neurotoxicity, osteodystrophy (resulting in low-grade bone pain), arthritis, glucose intolerance, hyperlipidaemia, pancreatitis, immunosuppression and soft tissue mineralisation. While it is clear that when soft tissue mineralisation involves the kidneys it can lead to progressive renal dysfunction, a more general role for PTH in the progression of CKD is still under debate (Chew and Nagode 1992).

Limiting phosphorus consumption appears to slow the progression of CKD. Experimentally, when cats with CKD were fed a diet restricted in phosphate, they developed less renal mineralisation, mononuclear cell infiltration and fibrosis than cats fed a normal diet (Ross et al 1982). Studies in dogs have also shown a beneficial effect to restricting dietary phosphorus once azotaemia develops (Finco et al 1992). As discussed above, (under ‘Restriction of dietary protein’), feeding cats with naturally occurring CKD a diet restricted in both phosphate and protein resulted in a marked clinical improvement, plus reduction of plasma phosphorus and PTH (Barber et al 1999; Elliott et al 2000). Since PTH is believed to be a uraemic toxin reducing its concentration is likely to be beneficial (Barber et al 1999). Interestingly, RHPTH can occur prior to the development of overt hyperphosphataemia. However, the importance of starting phosphate restriction prior to the detection of increased circulating phosphate remains unclear (Barber et al 1999).

Restriction of dietary phosphate is an important part of CKD management. The aim is to normalise the serum phosphate concentration. This can initially be achieved by feeding a phosphate-restricted diet (most commercial ‘renal diets’ are low in protein and therefore also low in phosphorus). However, when that is no longer sufficient, intestinal phosphate binders will need to be added. Monitoring plasma phosphate is an efficient, if not very sensitive, method for the

detection of RHPTH (Barber and Elliott 1998). That said, blood samples should be collected after a 12 hour fast and should be non-haemolysed. A more sensitive method is to directly assess PTH concentration (Barber and Elliott 1998), however, this requires a fasted blood sample, 'frozen shipment' of serum and access to a species-validated test, which is usually expensive.

Intestinal phosphate binders are usually added once the fasting serum phosphorous is >2 mmol/l. Aluminium containing salts, such as aluminium hydroxide, aluminium carbonate or aluminium oxide have been commonly used (30-150 mg/kg/day, divided between meals, and adjusted according to response). Unfortunately, aluminium salt phosphate binders are often poorly palatable, messy to administer, and may lead to nausea, anorexia, or constipation. Of the many products available Alu-Caps™ (capsules containing 475mg of dried aluminium hydroxide; 3M Health care) are perhaps the most palatable, and can be given by mixing a proportion of the contents of a capsule into the cat's food. In humans, it has been shown that the aluminium may become deposited in bone, resulting in worsening renal osteopathy. While this has not been shown to occur in dogs (Finco et al 2000), the situation in cats is unknown. Because of this, some clinicians recommend the use of calcium salts e.g. calcium carbonate (20-100 mg/kg/day, divided between meals), or calcium acetate. However, they are less effective than aluminium salts, and they have the potential to induce hypercalcaemia. Because of this it is essential to normalise the calcium level before starting the medication, and to monitor it closely throughout therapy. A number of companies offer combined products e.g. Ipakitine™ from Vetoquinol; which combines calcium carbonate with chitosan (to reduce phosphate absorption from the intestines), and report significant plasma phosphate reduction in cats with CKD (Wagner et al 2004) (although the product also contains lactulose, which may cause diarrhoea in some cats). A number of newer products are now available; e.g. Renalzin™ from Bayer, which uses lanthanum carbonate, and so circumvents the potential risk of hypercalcaemia. Some clinicians have also used sevelamer hydrochloride, but anecdotally this appears less effective than lanthanum (Arnell and Ross 2009). Since hypophosphataemia can result in weakness and anaemia, it is important to monitor phosphate levels whichever type of phosphate binder is chosen.

5.2.3 Calcitriol therapy

Plasma calcitriol concentrations are reduced in cats with CKD (see above) (Barber and Elliott 1998). Since calcitriol therapy effectively reduces PTH levels it should, in theory, make a useful adjunct to the treatment of cats with CKD (Chew and Nagode 1992). Some clinicians, including the author, use calcitriol therapy extensively, and find that it improves their patients' appetite and general well being (1.5-3.5 ng/kg/day po, given separately from meals; remove the oil from a capsule, dilute in corn oil, then give the appropriate volume, and store for up to two weeks) (Nagode et al 1996). However, there are few controlled studies showing beneficial long-term use and one study using this dosage showed no beneficial response (Hostutler et al 2006). Also, the difficulties associated with its administration and monitoring deter many clinicians from using it. Careful monitoring is essential because calcitriol administration can result in hypercalcaemia and resultant hypercalcaemic nephropathy. Calcium and phosphorous levels must be in the low-normal range before beginning treatment, and they should then be monitored every 2-4 weeks.

5.3 Control of hypokalaemia

Hypokalaemia, probably resulting from inappropriate kaliuresis, is a common finding in cats with CKD (Table 3) (Barber and Elliott 1998; Lulich et al 1992; DiBartola et al 1987; Elliott and Barber 1998). It is currently unclear whether hypokalaemia is usually a cause of CKD, a consequence of CKD, or both. However, there is good evidence to show that hypokalaemia can cause or exacerbate feline CKD (DiBartola et al 1993; Dow et al 1990), and potassium supplementation of hypokalaemic cats with CKD often results in improved renal function (Dow et al 1987).

While the most obvious sign of severe hypokalaemia is polymyopathy, with generalised muscle weakness and ventroflexion of the neck, this does not develop until there is severe potassium depletion. Other clinical signs of hypokalaemia can include anorexia, vomiting, weight loss,

lethary and cardiac arrhythmias (Arnell and Ross 2009). Routine assessment of serum potassium is therefore recommended, with supplementation where necessary. Since feeding acidifying, magnesium restricted, and/or high protein diets appears to increase the risk of hypokalaemia these should not be fed to cats with CKD. Instead, it is advisable to feed non-acidifying, protein-restricted diets, and supplementation is recommended if the serum potassium levels fall below 4 mmol/l. Potassium gluconate is used most frequently (initially at 1-4 mmol q12h po, reducing as required). However, potassium citrate may be preferable when the patient is also acidotic (75 mg/kg q12h po). Potassium chloride is used infrequently as it is unpalatable and may cause gastrointestinal irritation. Daily potassium supplementation of non-hypokalaemic cats with CKD does not appear to be beneficial (Theisen et al 1997). It is important to remember that all intravenous (and even subcutaneous) fluids need to be supplemented with potassium to prevent inducing hypokalaemia. Ideally, the amount of potassium added to the fluids is based on the serum potassium levels (Table 4).

5.4 Correction of acidosis

Reduced renal function leads to a decline in the renal capacity for acid excretion. Because of this, acidosis occurs fairly commonly in cats with CKD, particularly those with severe disease (Table 3) (Barber and Elliott 1998; Lulich et al 1992; DiBartola et al 1987; Elliott and Barber 1998). While acidosis is believed to contribute to anorexia, nausea, vomiting, weight loss, lethargy, and hypokalaemia, its role in the progression of renal failure remains unclear (Polzin et al 2000). That said, in other species it is associated with increased protein catabolism, anorexia, and precipitation of uraemic crisis (Fettman et al 1992). In addition, enhanced renal ammoniagenesis can cause activation of the complement cascade and tubulointerstitial injury (Nath et al 1985).

It is advisable to monitor cats with CKD at regular intervals for their acid-base status (assess TCO_2 or plasma bicarbonate). Specific treatment should be considered when TCO_2 is < 15 mmol/l, and should aim to maintain the TCO_2 between 18-23 mmol/l (Finco et al 2000). Treatment most frequently consists of sodium bicarbonate (5-10 mg/kg q8-12h po) or potassium citrate (30 mg/kg q12h po). However, sodium bicarbonate should be used cautiously in hypertensive patients, and potassium citrate may be a better choice when hypokalaemia is also present.

5.5 Correction of hypoproliferative anaemia

Many cats with CKD develop progressive anaemia that results in a variety of clinical signs including lethargy, inappetence, weakness and weight loss (Barber and Elliott 1998; Lulich et al 1992; DiBartola et al 1987; Elliott and Barber 1998). The cause of the anaemia is multifactorial, and includes reduced erythropoietin production related to reduced renal mass, reduced red blood cell survival times, uraemic suppression of erythropoiesis, gastrointestinal bleeding and/or iron or folic acid deficiencies. The most commonly used treatment options include recombinant human erythropoietin (r-HuEPO) (or recombinant feline erythropoietin, if available), iron supplementation (if needed), and anabolic steroids.

A number of studies have shown that r-HuEPO can cause a dramatic reversal of anaemia in cats with CKD, along with a general improvement in well being (Cowgill 1994; Polzin et al 1992; Cowgill et al 1998). Treatment with r-HuEPO is usually started once the PCV has fallen below ~20%: 100 units/kg is given subcutaneously three times a week until the PCV reaches ~30%, after which the dosage interval can be extended. Longer-acting EPO is now available (darbepoietin 6.25ug/cat [0.45ug/kg] sq q7days) (Arnell and Ross 2009, Chalhoub et al 2011). Initially, the PCV and other red cell parameters should be monitored weekly, then once the cat is more stable this can be extended to perhaps once every three to four weeks. If further adjustments are needed the dose can be altered by 25-50 units/cat (Cowgill 1994). Complications to r-HuEPO therapy include poor response due to iron deficiency, hypertension, polycythaemia, induction of anti-r-HuEPO antibodies, and systemic or local allergic reactions. To reduce the risk of iron deficiency it is sensible to assess serum iron levels and total iron binding capacity prior to

starting treatment, and to continue to monitor these parameters while the cat is receiving r-HuEPO. (Serum iron concentration, % iron saturation and total iron binding capacity can be performed by Capital Diagnostics, Edinburgh, UK; while ferritin levels can be assessed by Kansas State University, USA). If iron supplementation is required ferrous sulphate (50-100 mg/cat q24h po) or ferrous fumarate (30-60 mg/cat q24h po) can be given. About 30% of cats treated with r-HuEPO eventually develop antibodies that prevent the r-HuEPO from inducing erythropoiesis and can, occasionally, result in transfusion dependent aplastic anaemia. Its relatively high cost, the risk of side effects, and the cost of the necessary monitoring often limit the use of r-HuEPO.

While some clinicians advocate the use of anabolic steroids (e.g. nandrolone decanoate 1-1.5 mg/kg weekly by intramuscular injection) experimental support for their use is generally poor (Polzin et al 1992), and some anabolic steroids have been shown to induce liver failure.

5.6 Support of adequate food intake: Control of nausea and vomiting, use of gut protectants, appetite stimulants, and intake supplementation

Cats with CKD often have a reduced food intake. Their lack of appetite may be caused by:
i) uraemic gastritis (due to the effects of circulating uraemic toxins or hypergastrinaemia)
ii) gastrointestinal haemorrhage
iii) the central effects of uraemic toxins causing nausea and vomiting
iv) offering rather unpalatable 'renal diets',
v) the presence of constipation (resulting from chronic dehydration and exacerbated by some of the treatments e.g. sucralfate),
vi) anaemia
vii) metabolic acidosis and/or
viii) renal secondary hyperparathyroidism
Cats that do not maintain their food intake may incur protein malnutrition, endogenous protein catabolism, and metabolic acidosis.

Treatment options include the use of H_2-antagonists to reduce gastric acidity (e.g. famotidine 0.5-1.0 mg/kg q24-48h po [not iv], ranitidine 2-4 mg/kg q12h, iv or po [which also has a GI prokinetic effect], or cimetidine 2.5-5.0 mg/kg q8-12h, po, iv), sucralfate to help heal gastric ulceration (250-500 mg/cat q8-12h po), centrally acting anti-emetics to help block the effects of uraemic toxins on the chemoreceptor trigger zone (e.g. metoclopramide 0.2-0.5 mg/kg q6-8h po, or 1-2 mg/kg q24h as a constant iv infusion) or maropitant (0.5-1.0 mg/kg q24h, po or sq), and lactulose (dosed to effect as a laxative, and it has the additional benefit of trapping urea in the bowel and reducing the azotaemia).

There are a number of different ways of encouraging cats to eat. These include the use of warmed or aromatic foods, and any intervention that improves the cat's sense of well being. Unfortunately, the use of chemical appetite stimulants is not without risk as diazepam can cause fatal hepatic necrosis (Center et al 1996), mirtazepine has been associated with excitation and even collapse so a lower dose is suggested (1/4-1/8 of a 15mg tablet every three days) (Feline Expert Panel observations), and cyproheptadine has very occasionally been associated with haemolytic anaemia (DGM personal observation). While anabolic steroids (e.g. nandrolone – see above) may appear to help in some case, few clinicians use them routinely. Where cats fail to maintain an adequate calorie (and/or fluid) intake, some clinicians will consider the long-term use of nasogastric or PEG tubes.

5.7 Systemic hypertension, antihypertensive drugs, and ACE inhibitors

It is essential that all cats with CKD be assessed for **hypertension** as it is found in ~ 25% of them in first opinion practice, increasing to 60-65% in referral practice: untreated hypertension can exacerbate CKD (Kobayaski et al 1990; Ross 1992; Littman 1994; Henik 1997; Mishina et al 1998; Brown et al 2000; Elliott et al 2001; Syme et al 2002; Jepson et al 2007). In a small survey

of our own referral CKD cases 14/26 (56%) were found to be hypertensive (systolic blood pressure by Doppler > 175 mmHg – at that time this was considered the definition of hypertension) (Henik 1997; Sparkes et al 1999; Brown et al 2000; Elliott et al 2001); six were diagnosed at initial presentation, and a further eight developed hypertension within five years of being diagnosed with CKD. There is no correlation between the degree of azotaemia and the presence or severity of systemic hypertension (Kobayaski et al 1990; Elliott et al 2001).

The aetiology of hypertension in CKD is complex and multifactorial: activation of the renin-angiotensin-aldosterone system (RAAS) leads to the production of angiotensin II (which produces vasoconstriction) and aldosterone (which promotes sodium retention), and diseased kidneys may be unable to efficiently excrete sodium and water (resulting in extracellular expansion) (Kobayashi et al 1990; Ross 1992; Henik 1997). Diseased kidneys may also be unable to produce adequate amounts of vasodilator substances (e.g. prostaglandins and components of the kallilrein-kinin system), and autonomic dysfunction may result in increased circulating levels of catecholamines and an increased vascular responsiveness. While different types of renal disease may produce hypertension by different mechanisms, the presence of hypertension results in continually high glomerular filtration pressures that may worsen existing renal disease and contribute to further hypertensive injury and disease progression (Kobrin and Aradye 1997).

Persistent hypertension commonly causes damage in the kidneys, eyes, heart and brain (Henik 1997; Elliott et al 2001). Unfortunately, hypertension is usually only suspected very late in the course of disease, once end-organ damage has already occurred. This is typically seen as exacerbation of renal failure, intraocular haemorrhage and/or blindness, left ventricular hypertrophy, and/or cerebral vascular accidents. In our own small series ocular signs were present in 38%, and cardiac changes in 29% of the cases. Of the hypertensive cats, 71% had ocular evidence of hypertensive damage. Findings included anterior chamber, vitreal or retinal haemorrhage, retinal oedema or detachment, arterial tortuosity, alternating constriction and dilation of retinal primary venules, and/or glaucoma.

Blood pressure should be evaluated as a routine part of all clinic visits for cats with CKD, and anti-hypertensive therapy should be prescribed to those where the mean systolic blood pressure readings (taken with the cat in a calm state) are persistently above 160 mmHg and/or where there is evidence of hypertensive retinopathy (Stepien 2004). **IRIS Guidelines:** <150 mmHg [minimal risk], 150-160 mmHg [low risk], 160-180 mmHg [moderate risk], >180 mmHg [high risk]. As we have become more experienced at reliably ascertaining cat blood pressures, the accepted level for hypertension has fallen.

Various methods exist for the indirect measurement of blood pressure. However, in cats, the Doppler method is believed to be most accurate; oscillometric methods tend to underestimate blood pressure (Brown et al 2000; Bartges et al 1996). The only problem with using a Doppler blood pressure machine is that it is not always able to measure the diastolic pressure, especially when operated by inexperienced hands. The diastolic blood pressure of normal cats should be less than 95 mmHg (Mishna et al 1998); **IRIS Guidelines:** <95 mmHg [minimal risk], 95-99 mmHg [low risk], 100-119 mmHg [moderate risk], >120 mmHg [high risk].

Proteinuria is an independent risk factor for the progression of CKD in cats (Lees et al 2005; Syme et al 2006; Elliott and Syme 2006; Kuwahara et al 2006; Jepson et al 2007; King et al 2007). While only ~10% of cats with CKD have a urinary protein to creatinine ratio (UPC) of >1.0, studies have shown that in cats with CKD a UPC >0.4 (0.3-0.6) is in indicator of poor prognosis, and warrants treatment (Lees et al 2005). One study found that mean survival times were 449 days in cats with a UPC <0.2, 224 days in cats with a UPC 0.2-0.8, and only 117 days in cats with a UPC >0.8 (King et al 2007). A separate study found that mean survival times were ~700 days with a UPC <0.43, but ~270 days with a UPC >0.43 (Syme et al 2006). IRIS recommend that every cat is with CKD be assessed for proteinuria by UPC, and classified into <0.2 [non-proteinuria], 0.2-0.4 [borderline proteinuric] and >0.4 [proteinuria] (Elliott and Syme 2006; **IRIS Guidelines**).

Treatment of systemic hypertension and proteinuria:
Treatment of feline systemic hypertension involve treating any underlying conditions, and considering the use of calcium channel blockers (e.g. amlodipine besylate; 0.625-1.25 mg/cat po q24h), and/or angiotensin converting enzyme inhibitors (e.g. benazepril; 0.25-0.5 mg/kg po q12-24h) or angiotensin receptor blockers (e.g. telmisartan 1 mg/kg po q24h). While other therapies have been suggested, including the use of beta adrenergic receptor antagonists (e.g. propranolol), alpha adrenergic receptor antagonists (e.g. prazosin), arteriolar vasodilators (e.g. hydralazine), diuretics (e.g. frusemide), or a low salt diet, they are less reliable and/or ineffective (Bartges et al 1996).

Calcium channel blockers (CCBs) (e.g. amlodipine besylate) are the single agent of choice for the treatment of severe systemic hypertension in cats as they most reliably reduce hypertension (Bartges et al 1996; Henik 1997; Elliott et al 2001, Jepson et al 2007). CCBs may be of particular benefit in cats with CKD as they not only decrease systemic hypertension, they dilate glomerular afferent arterioles, attenuate mitogenic effects of various growth factors, and attenuate mesangial entrapment of macromolecules (Epstein 1992). However, because of preferential afferent arteriolar dilation, elevated systemic blood pressure may be transmitted to the glomerulus, resulting in glomerular hypertension (Tolins and Raji 1991).

In human patients with CKD ± hypertension, first-line therapies are agents that target the activated RAAS, such as **ACE inhibitors and ARB**s (Figure 1). They not only lower systemic hypertension, they also have renoprotective effects, largely attributed to their ability to reduce proteinuria and glomerular hypertension – there are significant long-term benefits in both renal and cardiovascular outcomes when proteinuria is decreased (NKF 2002). It is important to reduce proteinuria as proteins in the glomerular filtrate can be directly renotoxic and contribute to progression of renal failure. ACE inhibitors and ARBs can reduce proteinuria by a number of different mechanisms, including reducing glomerular hypertension, reduced glomerular hyper-permeability due to reduced angiotensin II formation, anti-inflammatory effects, and anti-platelet effects. However, as study in this area continues, it is clear that our simple understanding of the RAAS and roles that ACE inhibitors and ARBs play is far from complete (Rüster and Wolf 2006).

ACE inhibitors can be used to treat hypertension and/or proteinuria in CKD because, by inhibiting the conversion of angiotensin I to angiotensin II, ACE inhibitors decrease aldosterone secretion, decrease plasma and urine angiotensin II, increase urine concentration of prostaglandin E and bradykinin, reduce intra-glomerular capillary blood pressure (due to efferent arteriolar dilation), reduce glomerular hyperfiltration and proteinuria, and reduce glomerulosclerosis and tubulointerstitial kesions (Allen et al 1987; Tolins and Raji 1991, Lefebvre and Toutain 2004). Bradykinin is normally degraded by ACE, so by preventing its degradation ACE-inhibitors can restore these concentrations resulting in vasodilation; however, excessive bradykinin can lead to side effects such as coughing and angioedema (Hanif et al 2010). ACE inhibitors may also lead to reduced renal perfusion and so cause tubular necrosis, resulting in progression of the renal failure (Amadio et al 1990). This may be more of a significant problem for those ACE inhibitors that are exclusively excreted though the kidney and their doses need to be

adjusted in cases of CKD (Allen et al 1987). This is the advantage of using benazepril, as most of its excretion is through the liver.

In cats, the beneficial effects of benazepril have been shown in a number of studies of experimental and naturally occurring CKD. Significant reductions in systemic blood pressure, glomerular capillary pressure, angiotensin II, aldosterone, and proteinuria have been documented (Brown et al 2001; Watanabe et al 1999; Watanabe and Mishina 2007), along with delayed progression of disease and extended survival times (Mizutani et al 2006). Results from the BENRIC study support these findings, with the most significant effects being seen in proteinuric patients, and Persian cats (Gunn-Moore et al 2003; King et al 2007).

ARBs are the fastest-growing class of anti-hypertensive drug in humans, where they are effective and virtually free of side effects. They block angiotensin-II AT1-receptors. By selectively blocking AT1-receptors, aldosterone synthesis and secretion is reduced (adrenal AT1 receptors), causing vasodilation (vascular AT1 receptors), decreased potassium and increased sodium excretion, plus renal inflammation and fibrosis (renal AT1 receptors) (Romero et al 2015). Plasma concentrations of potassium do increase significantly, and although plasma concentrations of renin and angiotensin-II increase, this does not counteract the anti-hypertensive effects of ARBs. They do not interfere with substance P or bradykinin responses. ARBs have the advantage over ACE inhibitors as by selectively binding to the AT1-receptors the AT2-receptors are preserved. AT2 is part of the protective arm of the RAAS, with vasodilatory, natriuretic, anti-fibrotic and anti-inflammatory activities (Burnier and Brunner 2000; Romero et al 2015). In addition, ARBs circumvent the non-ACE-dependent pathways (e.g. those using alternative enzymatic pathways such as chymase) which are responsible for continuing angiotensin II and aldosterone production that may lead to persistent hypertension and proteinuria in spite of ACE therapy ('ACE-escape') (Zaman et al 2002).

Of the ARBs evaluated in cats and dogs telmisartan has been found to be the most effective at reducing blood pressure, and in cats, was more effective than benazepril at achieving this (Coleman et al 2013). In a study of 224 cats with CKD, telmisartan was compared with benazepril, and was found to be as effective in reducing proteinuria, and increasing appetite and survival, with it being most effective it cats with an initial UPC ≥0.4 (Sent et al 2013). Evidence of 'ACE-escape' was seen in that benazepril only reduced proteinuria for 30 days, while telmisartan was significantly more effective at doing this, right to the end point of the study at 180 days (Sent et al 2013).

Is it better to treat cats with CKD with CCBs, ACE inhibitors or ARBs?

i) Where systemic blood pressure is significantly raised (>180 mmHg) amlodipine is required because it is more predictable at reducing severe hypertension (Brown and Henik 2000). Reduced hypertension is associated with reduced proteinuria and increased survival (Jepson et al 2007). However, these cases may also benefit from the addition of an ACE inhibitor or ARB, particularly if their UPC ratio is ≥0.4, if the hypertension is severe and/or refractory to CCB, and/or the cat also has CKD (Kaplan 2001).

ii) There is growing evidence to support the use of ACE inhibitors and ARBs, not only in hypertensive cats, but also more widely in normotensive individuals with CKD, especially if they are proteinuric (Lefebvre and Toutain 2004, King et al 2006, Mizutani et al 2006). While ACE inhibitors and ARBs are most effective in the treatment of CKD associated with mild to severe proteinuria (King et al 2006, Sent et al 2013), their beneficial effect in non-proteinuric cases has led to the suggestion that they may have a positive effect beyond decreasing blood pressure and reducing proteinuria (Jafar et al 2001; King et al 2006).

iii) ACE inhibitors and ARBs should not be given to cases of unstable or acute RF (where significant dehydration is present), and care should be taken when considering starting them in cases of severe CKD (e.g. IRIS Stage 4; place the cat on iv fluids first and monitor the cat for

deterioration or an increase in the plasma creatinine of >30% - if this occurs, stop the ACE inhibitor/ARB). The concurrent use of concurrent ARBs and ACE inhibitors is controversial; some studies in humans have shown benifical effects, while others have resulted in significant hyperkalaemia and hypotension, with worsen renal function (Sharma et al 2011); the author has seen hyperkalaemia develop in a single cat given an ACI inhibitor and ARB concurrently.

5.8 Urinary tract infections

Urinary tract infections (UTIs) occur commonly in cats with CKD, probably relating to the presence of dilute urine, but also because uraemia has inhibitory effects on neutrophil function. In a number of studies 25-35% of cases were found to have a UTI at some point during their illness (Demetriou et al, 1997; Barber person communication 2001; Mayer-Ronne et al, 2006). Interestingly, 75% of the UTIs occurred in female cats, and many of these cats had recurrent episodes of infection (Barber, personal communication, 2001). Unfortunately, while the presence of a UTI rarely results in specific clinical signs (e.g. typically of pollakiuria, renal pain and/or dysuria) it is highly likely to exacerbate the renal damage. It is therefore essential that cats with CKD be regularly assessed for the presence of a UTI. Unfortunately, pyuria and/or an active urine sediment is not always present in cases of UTI associated with CKD in cats (or diabetes mellitus or hyperthyroidism) (Mayer-Ronne et al, 2006). This may be because uraemic toxins (and hyperglycaemia) can reduce neutrophil function. Since diagnosis can only be confirmed by performing urinalysis *and* bacterial culture, urine samples need to be collected by cystocentesis.

Once a UTI has been confirmed, the chose of antibiotics is best made according to culture and sensitivity, and a prolonged course is required (4-8 weeks). Ideally, culture and sensitivity should be repeated after one week of treatment (to ensure the choice of antibiotic has been correct), and then again one week after completing the course (to confirm the treatment has been effective).

5.9 Long-term monitoring

Long-term monitoring is essential. Each examination should be as extensive as the initial examination (see above), and it should be repeated every one to six months, depending on the severity and extent of the clinical signs.

Further information for owners of cats with CKD a very useful book designed to help owners of cats with CKD is available from www.catprofessional.com and the following site was designed by an owner of a cat with CKD: http://www.felineCKD.com/ which contains particularly useful information on administration of subcutaneous fluids and links to a variety of other useful web sites.

Table 1. Potential aetiologies of feline chronic renal failure

Chronic tubulointerstitial nephritis
Glomerulonephritis
Pyelonephritis
Polycystic renal disease – congenital or acquired
Amyloidosis – familial or acquired
Nephrotoxins – e.g. ethylene glycol, aminoglycoside antibiotics, lilies, grapes (raisons, currents), melamine/cyanuric acid
Hypercalcaemia
Hydronephrosis
Renal lymphoma
Eventual result of untreated pre-renal or post-renal failure

Table 2. Common clinical signs in 412 cases of CKD [a]

Clinical sign	%
Dehydration	62
Anorexia	62
Lethargy / depression	47
Weight loss	46
Polydipsia / polyuria	38
Vomiting	29
Large kidneys (1 or both)	25[b]
Small kidneys (1 or both)	19
Pale mucous membranes	10
Oral ulceration / discomfort	10
Also Retinal detachment Poor coat Thin Halitosis Diarrhoea or constipation Haematuria / dysuria Bone pain / osteodystrophy	

[a] Based on four studies (Lulich et al 1992; Krawiec and Gelberg 1989; DiBartola et al 1987; Elliott and Barber 1998). [b] Based on 337 cats from three studies (Lulich et al 1992; Krawiec and Gelberg 1989; DiBartola et al 1987).

Table 3. Common clinicopathological findings in 286 cases of CKD [a]

Finding	%
↑ plasma urea	98
↑ plasma creatinine	98
↑ plasma PTH	84[b]
Urine specific gravity < 1.030	75[c]
↑ plasma phosphate	63
↓ plasma TCO_2	55
Anaemia	37
↓ plasma calcitriol	36[b]
↓ plasma ionised calcium	25[b]
↓ plasma potassium	21
↑ plasma cholesterol	72
Urine protein:creatinine > 1.0	< 10[c]
Also ↑ plasma amylase ↓ lymphocytes ↑ plasma glucose ↑ white blood cells ↑ plasma ionised calcium	

[a] Based on four studies (Barber and Elliott 1998; Lulich et al 1992; DiBartola et al 1987; Elliott and Barber 1998). [b] Based on 80 cats (Elliott and Barber 1998). [c] Based on 52 cats (Elliott and Barber 1998).

Table 4. Amount of potassium that should be added to iv fluids

Serum potassium levels	Amount of potassium to be added to 500ml fluids
< 2 mmol/l	40 mmol
2.0 – 2.5 mmol/l	30 mmol
2.5 – 3.0 mmol/l	20 mmol
3.0 – 3.5 mmol/l	14 mmol
> 3.5 mmol/l	10 mmol ('maintenance' levels)

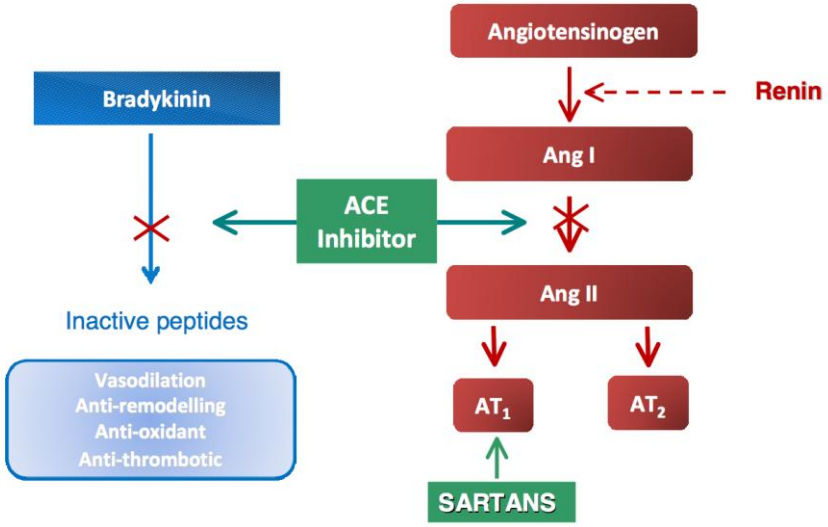

Figure 1: Simplified cartoon for where ACE-inhibitors and ARBs block RAAS. *Courtesy of Boehringer Ingelheim*

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