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Agenda item No:	13 – Medicines Management Resource for Chronic Kidney Disease
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1.0 ACTION FOR AWMSG

AWMSG members are requested to consider the *Medicines Management Resource for Chronic Kidney Disease (CKD)* for endorsement.

2.0 PURPOSE

A National CKD Audit has been implemented in England and Wales to provide a comprehensive picture of management and outcomes for people with CKD stages 3–5. Its purpose is to improve the quality of patient care and assess each GP practice against NICE CKD quality guidelines and standards to encourage quality improvement. The results of the audit were intended to enable comparison between practices, and help GPs to identify, and share, best practice.

The Medicines Management Resource for CKD will support primary care teams in undertaking the audits and in the medicines management of relevant patients. By endorsing this resource, AWMSG will help ensure high quality care for patients with CKD in Wales. Audit involvement will allow access to data collected by Audit+ on medicines management issues in patients with CKD that can be used for AWMSG national audits, identification of further educational opportunities and the development of national guidelines. It is also envisaged that this resource will support the new National Prescribing Indicators for 2017–2018, one of which is linked to CKD patients.

2.1 Process

- AWPAG meeting 22 June 2016
- AWPAG meeting September 2016
- Consultation November 2016
- AWMSG Steering Committee January 2017
- AWMSG February 2017

2.2 Stakeholders

- Welsh Renal Clinical Network
- Renal Pharmacists' Group
- Renal Registry
- Primary and Community Care Development and Innovation, PHW
- NHS Wales Informatics Service (NWIS)
- Welsh Government
- Primary care Wales
- GP cluster networks
- AWTTC
- Health boards
- 1000 Lives
- Public Health Wales
- GPC Wales
- GPOne
- Yellow Card Centre Wales
- Medicines and Therapeutics Committees
- Chief Pharmacists
- South West Wales Renal Medicines Service

EXECUTIVE SUMMARY

Early identification and management of chronic kidney disease (CKD) patients is essential in limiting individual disease progression and the development of complications.

The National CKD Audit and Clinical Effectiveness Prescribing Programme National Audit: Medicines Management for CKD are intended to lead to an improvement in the identification of relevant patients, and to improve their medicines management and therapeutic outcomes.

An improvement delivered through the work of the audits can alleviate some of the pressures on dialysis and transplant services within Wales.

CKD is closely linked to other common conditions such as acute kidney injury and cardiovascular disease. Improvement in the care of patients with CKD can also bring benefits in these therapeutic areas.

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1.0 BACKGROUND

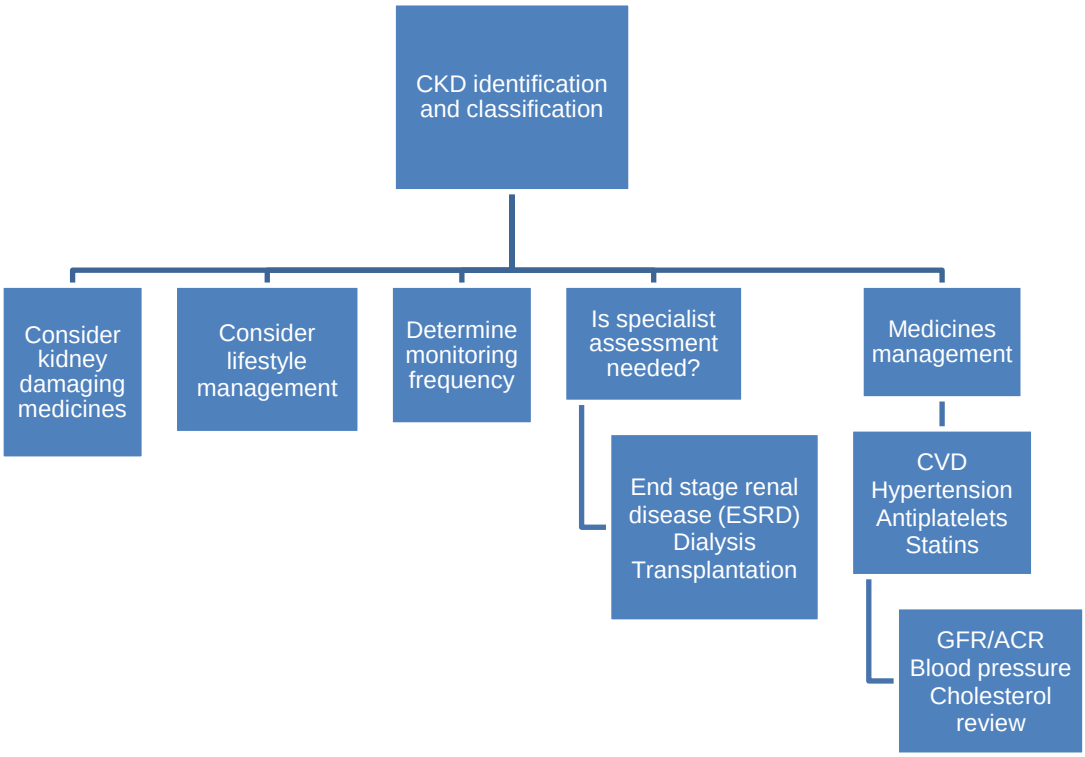
The National Chronic Kidney Disease Audit (NCKDA), commissioned by the Health Quality Improvement Partnership in 2014, is intended to improve the identification, management and care of chronic kidney disease (CKD) patients in primary care within NHS Wales.

To support this audit and to ensure that CKD patients (stage 3–5) receive appropriate medicines management, a Clinical Effectiveness Prescribing Programme (CEPP) National Audit: Medicines Management for CKD has been produced by the All Wales Prescribing Advisory Group (AWPAG), NHS Wales Informatics Service (NWIS) (part of Public Health Wales) and the Welsh Renal Clinical Network for 2017–2018.

The CEPP National Audit: Medicines Management for CKD forms part of an educational resource pack, which also includes supporting information, signposting to useful resources and an educational slide set. The resource pack is intended to raise awareness amongst prescribers and patients of the potential harms associated with CKD and to provide healthcare professionals with information and training to aid in the appropriate medicines management of these patients. The CEPP National Audit: Medicines Management for CKD details are provided within Appendix 1.

CKD is often without any symptoms in the early stages of the disease and a small proportion of CKD patients can progress quite quickly to end stage renal disease (ESRD) requiring dialysis or transplantation. In recent years there have been concerns raised around the number of undiagnosed CKD patients progressing unnoticed to this severe form of the disease. Also, commonly associated with CKD is a high risk of premature cardiovascular disease (CVD). Therefore, a plan for effective identification and management of CKD patients is essential. Figure 1 provides a summary of considerations in the medicines management of CKD patients.

Figure 1. A summary of considerations for the medicines management of CKD patients



2.0 AN INTRODUCTION TO CHRONIC KIDNEY DISEASE

CKD is defined as a reduced glomerular filtration rate (GFR), increased urinary albumin excretion, or both[1]. Worldwide there is an estimated CKD prevalence of 8–16%[1]. In the UK, prevalence is increasing due to a number of factors including an ageing population, increasing rates of diabetes, hypertension and obesity, and an ethnically diverse population[2], and some degree of CKD is present in around one in ten people[3]. Although CKD becomes more common with increasing age, the majority of CKD in elderly patients is non-progressive, and is attributed to normal ageing of the kidneys[3,4]. However, potential complications of the condition include premature CVD e.g. strokes or heart attacks, episodes of acute kidney injury (AKI) and long-term progressive loss of kidney function[5]. Therefore early identification and appropriate management of these patients is essential in limiting the impact of CKD[6].

It has been estimated that around one million people in the UK with CKD remain undiagnosed, and efforts to increase early diagnosis are therefore essential[7]. Particular focus should be on those with diabetes, hypertension, AKI and CVD. Early CKD is largely asymptomatic so for these patients testing is the most likely means of identification to limit progression to the more severe forms of the disease[5,6]. The ASSIST-CKD project, which started in the Heart of England Foundation Trust in 2005, surveys patients' kidney function tests alerting GPs to those with deteriorating renal function. Overall the project has seen the number of patients requiring dialysis decrease by 16%, compared to a rise of 8% across England as a whole[7]. In Wales, the ASSIST-CKD project is scheduled to commence in the South West Wales area at the beginning of 2017[8].

Annual testing for CKD should be carried out in diabetic patients[5]. Those with other risk factors for CKD, including hypertension, CVD, kidney stones, prostatic disease, connective tissue disorders, and family history of kidney disease or previous AKI episodes, should be offered a GFR and an albumin to creatinine ratio (ACR) test at repeated intervals agreed between the patient and healthcare professional[5]. This supports the NHS Wales Prudent Healthcare principle of "Achieve health and well being with the public, patients and professionals as equal partners through co-production"[9]. The National Institute for Health and Care Excellence (NICE) does not state a frequency of this testing; however, the NCKDA took an interval of five years to be appropriate[5]. The results of the pilot phase of the NCKDA found that around 50% of patients with CKD identifiable on their blood tests were appropriately coded within the GP computer system as having CKD[5].

Guidance from NICE states that in order to determine the severity classification of CKD, both the GFR and ACR should be measured[6]. GFR and ACR are independently related to mortality, cardiovascular events, progression to ESRD and AKI[10]. Utilising both the estimated GFR (eGFR) and ACR measures allows a more accurate classification of CKD to be made. The classification of CKD using GFR and ACR is shown in Appendix 2.

Referral for specialist assessment should be made for patients with:

- GFR less than 30 ml/min/1.73 m^2 with or without diabetes;
- ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated;
- ACR 30 mg/mmol or more, together with haematuria;
- Sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months;
- hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses;
- Known or suspected rare genetic causes of CKD;
- Suspected renal artery stenosis[6].

3.0 CALCULATING AN ESTIMATED GLOMERULAR FILTRATION RATE

UK Medicines Information (UKMi) suggests that, when calculating eGFR, care is needed to not overestimate renal function, particularly in people with more advanced CKD. This can be achieved using more than one estimate of renal function[11]. The vast majority of medication dosing information for patients with renal impairment is based around the Cockcroft and Gault (C-G) formula to attain the eGFR, as opposed to the modification of diet in renal disease (MDRD) equation. These means of attaining the eGFR are not interchangeable[12]. Both the C-G and MDRD are less accurate in obese individuals, populations with normal or near-normal GFR and populations of different ethnicities, as well as possibly not being similarly accurate in different age groups[13]. The CKD epidemiology collaboration (CKD-EPI) equation is a better estimate when GFR is normal or mildly reduced and is comparable to the MDRD equation when there are lower GFR levels. NICE recommends that the CKD-EPI method rather than the MDRD should be used for calculating eGFR. Although it is recommended that laboratories should move over to this new method, currently its use is not commonplace[6]. The eGFRs reported using the CKD-EPI are not comparable to those using the MDRD or C-G formulae[14]. It is worth noting that all three methods are limited by their reliance on using serum creatinine[13]. The different estimation calculations are detailed in Appendix 3. The frequency for monitoring renal function is provided within Appendix 4.

4.0 RENIN–ANGIOTENSIN SYSTEM ANTAGONISTS

Renin–angiotensin system antagonists (RASAs) are any medicines which block or inhibit the renin–angiotensin system including angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and direct renin inhibitors. They do not include aldosterone antagonists[6].

Hypertension, along with diabetes, is the greatest risk factor for developing CKD and is associated with a decline in renal function. Therefore, in people with CKD, the aim should be to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and diastolic blood pressure below 90 mmHg. In people with CKD and diabetes, hypertension is associated with a more rapid decline in renal function and so tighter blood pressure control is warranted. A similar approach should be used in people with an ACR of 70 mg/mmol or more; aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg[6]. More intensive antihypertensive therapy may need to be considered in people at higher risk of cardiovascular and kidney disease although lowering the blood pressure too much can be harmful due to the impaired perfusion of vital organs. This includes elderly patients who are at a higher risk of falls especially if postural hypotension is also present[4]. The improvement of blood pressure management within the CKD population was a target of the NCKDA[5], and is an objective of the CEPP National Audit: Medicines Management for CKD.

RASAs offer significant renal protection in addition to that gained from lowering the blood pressure of the patient[4]. A RASA should be offered to those with CKD and one or more of the following[6]:

- Diabetes and an ACR of 3 mg/mmol or more;
- Hypertension and an ACR of 30 mg/mmol or more;
- An ACR of 70 mg/mmol or more.

If a second antihypertensive agent is needed, a combination of RASAs should not be offered[6]. Combining ACE inhibitor and ARB therapy is associated with significantly more adverse effects than either as monotherapy. These include hypotension and related symptoms, hyperkalaemia, renal dysfunction and an increased need for

dialysis[15]. Instead a non-dihydropyridine calcium channel antagonist can be used e.g. diltiazem. These have additional antiproteinuric effects unlike the dihydropyridine antagonists e.g. amlodipine, which may increase proteinuria[4]. Diuretics are also beneficial, particularly if there is any oedema. Loop diuretics are preferable to thiazide diuretics as these are unlikely to be of benefit when the GFR is below 30 ml/minute[16]. Referral for specialist assessment should be considered if hypertension remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses[6].

In CKD patients, the serum potassium concentration and eGFR should be measured before starting a RASA. These tests should be repeated between one and two weeks after starting and after each dose increase[6,15]. From baseline, a 30% or more rise in serum creatinine or a 25% or more fall in eGFR requires an investigation into alternative causes of deterioration. Such causes could be volume depletion e.g. dehydration, and concurrent medications e.g. non-steroidal anti-inflammatory drugs (NSAIDs). If considered necessary there could be a dose reduction to that previously tolerated or a cessation of this medicine and an alternative antihypertensive commenced[4,6]. Although 'sick day guidance' is only supported by weak evidence, there should be a discussion with patients about what to do if they suffer any condition likely to lead to dehydration e.g. diarrhoea, vomiting[17]. There have been patient information leaflets made available to support patients in self management[18]. However, the suggested actions should be considered on an individual patient basis in a manner of clinical appropriateness and co-production.

Following the introduction or dose increase of a RASA, no dose modification is needed if the decrease in the eGFR from pre-treatment baseline is less than 25% or serum creatinine increase from baseline is less than 30%. However, where appropriate the test should be performed again within one to two weeks[6]. There should also be regular monitoring of renal function, particularly in higher risk groups e.g. the elderly[19].

Hyperkalaemia is a possible adverse effect of RASA therapy. This risk is increased in those patients taking certain other medicines such as potassium-sparing diuretics, aldosterone antagonists or ciclosporin[15]. If prior to commencing a RASA the potassium level is greater than 5.0 mmol/litre, do not offer the treatment. If during treatment the level increases to 6.0 mmol/litre or more, stop the RASA. In both situations, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken with the serum potassium level being rechecked. Concurrent use of medicines known to promote hyperkalaemia is not a contraindication to their use; however, more frequent monitoring of potassium is likely to be required[6].

5.0 STATINS AND ANTIPLATELETS

CKD patients should be considered as being in the highest risk group for CVD[1]. The risks are increased as the eGFR decreases and the ACR increases[6]. However, people with an eGFR less than 60 ml/min/1.73 m^2 with or without albuminuria are at an increased risk of CVD. Lipid-lowering therapies reduce the incidence of cardiovascular events in CKD patients[20]. Statins may have benefits such as reducing oxidative stress and inflammation in addition to their lipid lowering effects[21]. Therefore offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD[22]. Until 2015–2016, an AWMSG National Prescribing Indicator (NPI) measured low acquisition cost statins as a percentage of all statin, ezetimibe and simvastatin/ezetimibe combination prescribing[23,24]. Between 2014–2015 and 2015–2016 across Wales there was a 0.2% increase in low acquisition cost statin prescribing[25].

There is no requirement to use a reduced dose of atorvastatin in renal impairment[26]. If the eGFR is 30 ml/min/1.73 m^2 or more and a greater than 40% reduction in non-HDL cholesterol has not been achieved at three months then increase the atorvastatin dose

up to a maximum of 80 mg daily[22]. If the eGFR is less than 30 ml/min/1.73 m^2, renal specialist agreement should be sought before increasing the atorvastatin dose. Prior to increasing the atorvastatin dose, investigate other factors with the patient if the reduction in non-HDL cholesterol is not being achieved, such as adherence, timing of dose, diet and lifestyle measures. An increased use of statins to reduce CVD risk is a target of the NCKDA[5]. An investigation into the prescribing of statins for CKD patients is one of the objectives of the CEPP National Audit: Medicines Management for CKD.

CVD includes ischaemic heart disease, chronic heart failure, peripheral vascular disease and cerebral vascular disease. Antiplatelet drugs should be offered to CKD patients for the secondary prevention of CVD[6]. The increased risk of bleeding from their use should be considered when prescribing[6]. Investigating the cost effectiveness of low-dose aspirin for the primary prevention of CVD for CKD patients at the highest risk is a current NICE research recommendation[6].

6.0 BISPHOSPHONATES

NICE Clinical Guideline (CG) 182 on CKD in adults makes a recommendation to offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people with a GFR of 30 ml/min/1.73 m^2 or more (GFR category G1, G2 or G3)[6]. Osteoporosis treatment is aimed at increasing bone mass and decreasing fracture risk. If bisphosphonate treatment is to be commenced, the three oral bisphosphonates – alendronate, ibandronate and risedronate – are licensed for use in people with an eGFR as low as 30[27,28] or 35[29] ml/minute. If a patient's bone mineral density continues to decrease following oral bisphosphonate treatment then consideration should be given to if, and how, the patient is taking their medication.

Use of bisphosphonates is not recommended in patients with a CrCl below 30–35 ml/min where use would be outside of the licensed indications within individual SPCs. However, any decision to stop or continue treatment should be made on an individual patient basis. If treatment is to continue, a renal specialist should be consulted about using these agents with an eGFR below 30 ml/minute and, if used, their use should be reviewed regularly in case renal function deteriorates further[30]. Denosumab is not cleared by the kidney and therefore the recommended dosing in renal impairment is the same as in normal renal function[31]. However, in people with an eGFR below 30 ml/min there is a major risk of hypocalcaemia and so calcium and vitamin D supplements should also be given[30,31].

When the eGFR is less than 30 ml/min/1.73 m^2, serum calcium, phosphate and parathyroid hormone concentrations should also be measured. This should identify particular biochemical abnormalities, e.g. hyperphosphataemia or hyperparathyroidism, which are associated with CKD mineral and bone disorder (CKD-MBD)[30]. CKD-MBD can appear as one of, or a combination of, the following[32]:

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

The frequency of tests for CKD-MBD patients should be determined by the measured values and clinical circumstances, and specialist opinion may help to guide further[6].

Cases of bisphosphonate associated adynamic bone disease have been reported in CKD patients, which complicates their management further[11]. For CKD patients at risk of fractures, important lifestyle advice would include improving muscle tone and strength as well as improving balance[30].

7.0 ACUTE KIDNEY INJURY

AKI is a rapid deterioration in renal function over a period of hours to a few days and results in a failure to regulate fluid, electrolyte and acid-base balance[33]. AKI has been said to be "one hundred times more deadly than methicillin-resistant *Staphylococcus aureus* (MRSA)", affecting one in six people admitted to hospital. There is an estimated mortality rate of around 25 to 30%[34]. However, around 20% of AKI cases are thought to be preventable[35].

Adults with acute illness should be investigated for AKI in the following[34]:

- CKD;
- Heart failure;
- Liver disease;
- Diabetes;
- History of AKI;
- Oliguria;
- Hypovolaemia;
- Signs and symptoms such as a reduction in urine output, yellow or brown urine, feeling unwell without an easily identifiable reason, presence of any dehydration indicators e.g. light headedness, headache, tiredness;
- Neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a carer;
- Use of drugs with nephrotoxic potential;
- Use of iodinated contrast agents within the past week;
- Symptoms or history of urological obstruction, or conditions that may lead to obstruction;
- Sepsis;
- Deteriorating warning signs;
- Age 65 years or over.

Most AKI cases are multifactorial with an estimated three quarters being secondary to a combination of pre-renal failure, e.g. hypoperfusion, and intrinsic acute tubular injury, e.g. nephrotoxins[33]. The management of AKI is dependent upon underlying aetiology; however, initial management should include clinical assessment of volume status, appropriate fluid resuscitation and medication review[33]. A smartphone app is currently being developed within Abertawe Bro Morgannwg University Health Board to support the management of AKI patients[8].

In all people who are at risk of AKI, serum creatinine should be regularly monitored[34]. The pharmacological management of patients with AKI will be largely determined by the individual circumstances of each patient; however, NICE has provided the following specific guidance[34]:

- Do not routinely offer loop diuretics to treat AKI;
- Consider loop diuretics for treating fluid overload or oedema while:
  - An adult, child or young person is awaiting renal replacement therapy, or
  - Renal function is recovering in an adult, child or young person not receiving renal replacement therapy;
- Do not offer low-dose dopamine to treat AKI.

AKI is a risk factor for developing CKD[36]. The presence of AKI in CKD patients necessitates an assessment of GFR[34]. If potentially nephrotoxic medications are being taken, their continued use should be reviewed. However, in CKD patients with no apparent acute signs and symptoms, a rise in creatinine may be due to an AKI rather than a worsening CKD picture[34]. In patients who have suffered an AKI, the serum creatinine should be monitored for at least two to three years irrespective of whether the level has returned to baseline and there is no evidence of CKD[6]. Some studies of

adults who have recovered from AKI have shown a reduced quality of life, potentially associated with higher depression rates[34]. NICE has made ascertaining the long-term outcomes of AKI one of its research recommendations[34].

8.0 KIDNEY DAMAGING MEDICATIONS

Establishing a cause of renal impairment is important, as certain factors, e.g. nephrotoxic drugs, can usually be addressed[6]. Impaired renal function prior to hospital admission has been shown to be a patient related risk factor for medicine-related admissions[37]. The study by Pirmohamed et al which considered adverse drug reactions as a cause of hospital admission found renal failure was the second most common type of adverse drug reaction to cause patient death[38]. Therefore in patients taking medicines that can adversely affect the kidneys, renal function should be tested at least annually via GFR and ACR[6]. Some of the medications with the potential to harm the kidneys are listed in Table 1. Adverse drug reactions such as renal impairment should be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) via the Yellow Card reporting scheme: Yellow Card.

Table 1. Potential kidney damaging medications

Potential kidney damaging medications:[1,6,34,]	
Non-steroidal anti-inflammatory drugs (NSAIDs)	Angiotensin-receptor blockers (ARBs)
Calcineurin inhibitors e.g. ciclosporin, tacrolimus	Diuretics
Lithium	Antibiotics e.g. gentamicin
Angiotensin converting enzyme (ACE) inhibitors	Proton pump inhibitors (PPIs)

8.1 Non-steroidal anti-inflammatory drugs

Regular use of non-steroidal anti-inflammatory drugs (NSAIDs) is a risk factor for the development of CKD[2]. As with other drugs known to be nephrotoxic, regular NSAID use should be accompanied by GFR monitoring at least every year[6]. An objective of the CEPP National Audit: Medicines Management for CKD is to review the prescribing of NSAIDs in CKD patients.

8.2 Proton pump inhibitors

Within Wales, proton pump inhibitor (PPI) usage is a current NPI, with the purpose of encouraging the appropriate use of PPIs[23]. Across Wales between 2014–2015 and 2015–2016 there was an increase of 3.12% for PPI defined daily doses per 1,000 prescribing units[25]. Current recommendations are for PPIs to be co-prescribed with NSAIDs to patients with an increased need for gastro-protection e.g. those patients over 65 years of age[39]. However, concern has recently been expressed that PPIs may increase the risk of kidney damage and may cause CKD in those patients taking PPIs long term[40,41]. Although complete avoidance of PPI therapy is not justified, a regular review of the indication and ongoing need should be made. Therefore it is recommended that all patients receiving a PPI should be offered an annual review and encouraged to step down from treatment doses where appropriate[42,43]. The All Wales Therapeutics and Toxicology Centre (AWTTC) has produced a resource pack to support the appropriate prescribing and 'deprescribing' of PPIs[44].

8.3 Combining kidney damaging medications

Use of an NSAID by a patient taking an ACE inhibitor or an ARB increases the risk of further impairment to renal function. The risk is increased again in those patients who are salt and volume depleted e.g. those taking concurrent diuretics[15]. ACE inhibitors, ARBs, NSAIDs, and diuretics were identified by Pirmohamed et al as amongst the most common drug groups to cause hospital admission[38]. A prominent example of an interaction between these drug groups is renal failure associated with the concomitant use of diuretics and ACE inhibitors[38]. A study of prescribing safety in primary care found an observed prevalence of patients with advanced stage CKD and prescribed an

ACE inhibitor, NSAID and loop diuretic of 2.83%[45]. It is worth being mindful that some NSAIDs i.e. ibuprofen and naproxen, are available on general sale from retail outlets and over the counter from pharmacies. Therefore unintentional use of nephrotoxic medications could be prevalent in the CKD population, particularly in more elderly patients requiring anti-inflammatory analgesics. Hence, use of potential nephrotoxic medications should be discussed with a CKD patient. Currently ibuprofen and naproxen are the preferred NSAID choices and there is also an NPI measuring the percentage of NSAID prescribing made up by these two agents[23]. Between 2014–2015 and 2015–2016 there was a 2.39% increase to 81.5% for ibuprofen and naproxen prescribing as a percentage of all NSAIDs[25].

In patients who have renal impairment it is likely there will be problems associated with the use of medicines due to possible altered pharmacokinetics, increased sensitivity and increased adverse effects[12]. Thus dosages of relevant medications are often reduced depending upon a patient's GFR. Information concerning the dosing of individual medications in renal impairment is available via the individual summary of product characteristics (SPC) for the medication (Medicines.org). The British National Formulary (BNF) also has information around dosing in renal impairment (Medicines Complete). More specialist practice-based information is available from the Renal Drug Database (subscription required). Local medicines information centres (UKMi Directory) have access to the Renal Drug Database as well as other information to aid in the decision-making process.

9.0 LIFESTYLE MANAGEMENT IN CKD

CKD patients should be informed as much about their disease as possible to support effective self management. This should include informing patients about the modifiable factors in CKD management such as lifestyle changes[6]. Lifestyle management is a key component in the self management of CKD, enabling patients to share in decision making and make informed choices about their care. This follows the prudent healthcare principle of "achieve health and well being with the public, patients and professionals as equal partners through co-production"[9]. In those patients for whom it is appropriate, changes such as smoking cessation, dietary modifications, and exercise and weight loss can be important considerations[2]. Dietary modifications can include changes to potassium, phosphate, calories and salt intake and advice should be appropriate to the severity of CKD[6]. The patient's diet should be assessed in detail with the patient being supported with education and supervision to optimise nutritional benefit and prevent malnutrition[6]. In obese patients, weight loss can ameliorate obesity-induced glomerular hyperfiltration and decrease proteinuria in chronic proteinuric nephropathy patients, as well as improve glycaemic control in people with diabetes mellitus[4]. A low salt diet enhances the benefit of antihypertensive therapy. Low protein diets should not be offered to patients with CKD[6]. Tobacco smoking has an association with an increased incidence of CKD and smoking cessation can reduce the loss of kidney function in progressive CKD[4].

10.0 CYSTATIN-C TO ESTIMATE GFR

Currently creatinine is used as the measure of renal function via the C-G, MDRD or CKD-EPI estimation calculations. Cystatin-C is a more accurate indicator than creatinine, having a higher specificity for significant disease outcomes. Cystatin-C can be used to identify those at higher risk of adverse outcomes, e.g. ESRD, overcoming some of the concerns relating to potential over-diagnosis and disease labelling[10]. This is potentially most beneficial for addressing those people who have a decreased GFR but without albuminuria and have unnecessarily been classed as at increased risk of adverse CKD outcomes where this may not be the case[46]. The use of cystatin-C to confirm CKD is not required if the eGFR is below 45 ml/min/1.73 m^2 or if proteinuria is present. The eGFR calculation using cystatin-C can be inaccurate in certain patient groups such as thyroid disease patients[4,6].

11.0 END STAGE RENAL DISEASE

The proportion of CKD patients progressing to ESRD is estimated at less than 1% per year[5]. Following the progression to ESRD, renal replacement therapies, e.g. dialysis, will be needed which currently have a significant impact upon the lives of patients. Kidney transplants are required by the majority of patients with ESRD; however, there is a shortage of donors and consequently long waiting lists. Across the UK the average time a person spends on the waiting list for a kidney transplant is two to three years, although it can be shorter or longer than this[47]. In 2015, Wales introduced a system of presumed consent for organ donation to increase the availability of suitable donors[48]. However, life-long issues for CKD patients remain around immunosuppression following a kidney transplant, particularly due to the increased risk of infection[49]. Thus meticulous management of patients in the early stages of CKD, with a focused importance on early diagnosis, regular monitoring and appropriate pharmacological therapies, is the most appropriate means to optimise the care of CKD patients and potentially limit their progression to ESRD and the need for dialysis and organ transplantation.

12.0 THE NATIONAL CHRONIC KIDNEY DISEASE AUDIT

The assessment of large groups of people is important in further understanding CKD and improving care. The NCKDA was funded by NHS England and the Welsh Government. The three objectives of the audit were:

- Improve the identification of CKD patients in primary care;
- Improve the management and outcomes of CKD patients;
- Tailor the care of people with CKD to local care pathways[50].

The NCKDA was developed to investigate the performance of GP practices and the variation between practices, against the standards set out in NICE CG182[6]. Service improvement within primary care in NHS Wales can reduce some of the pressure on dialysis and transplant services[51]. A key challenge was to attain active participation by the majority of GP practices in Wales. However, as shown with the National Diabetes Audit (NDA), in which over 97% of Welsh GP practices participated[52], Wales is uniquely placed to achieve a high level of participation facilitating an improvement in the identification of CKD patients in Wales.

13.0 CEPP NATIONAL AUDIT: MEDICINES MANAGEMENT FOR CKD

The suggested CEPP National Audit: Medicines Management for CKD for 2017–2018 will utilise primary care data accessed through Audit+. The aim of this audit will be to ensure patients with CKD (stage 3–5) receive appropriate medicines management. The objectives of the CEPP National Audit are: to ensure the prescribing for patients with CKD (stage 3–5) is in line with NICE recommendations; to review the prescribing of NSAIDs in patients identified as having CKD (stage 3–5); to review blood pressure control in patients with CKD (stage 3–5) and hypertension (with and without diabetes) to ensure optimal therapy; and to investigate if patients with CKD (stage 3–5) are prescribed required statin therapy.

The audit details are provided within Appendix 1.

14.0 PRESENTATION

A slide set of the main medicines management issues from within this resource is available for local adaptation from the AWMSG website. A copy of the slide set is provided in Appendix 5.

15.0 FURTHER INFORMATION

NICE CG182 Chronic kidney disease in adults: assessment and management: www.nice.org.uk/guidance/cg182
NICE CG169 Acute kidney injury: prevention, detection and management: www.nice.org.uk/guidance/cg169
NICE CG181 Cardiovascular disease: risk assessment and reduction, including lipid modification: www.nice.org.uk/guidance/cg181
WeMeReC Bulletin – ACE inhibitors and ARBs (2012): www.wemerec.org/Documents/Bulletins/ARBsBulletin2012.pdf
WeMeReC Bulletin – Medicines-related admissions (2015): www.wemerec.org/Documents/Bulletins/Medicines-related%20admissions-online.pdf
WeMeReC Bulletin – Optimising medicines use in care homes (2016): www.wemerec.org/Documents/Bulletins/optimisingmed2016online.pdf

15.1 Websites

The Renal Association: www.renal.org
British Renal Society: www.britishrenal.org

15.2 Patient resources

The British Kidney Patient Association website: www.britishkidney-pa.co.uk/
Welsh Kidney Patients' Association website: www.wkpa.org.uk/
Think Kidneys – everything you need to know: www.thinkkidneys.nhs.uk/ckd/wp-content/uploads/sites/2/2016/03/Think-Kidneys-Infographic-030316-campaign-final.pdf
Kidney Patient guide – general overview: www.kidneypatientguide.org.uk/contents.php
Kidney Research UK website: www.kidneyresearchuk.org/
National Kidney Federation website: www.kidney.org.uk/

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APPENDIX 1. CEPP NATIONAL AUDIT: MEDICINES MANAGEMENT FOR CKD

1.0 AUDIT

The All Wales Prescribing Advisory Group (AWPAG), NHS Wales Informatics Service (NWIS) (part of Public Health Wales) and the Welsh Renal Clinical Network have developed this audit. The document is for primary care to use to support local prescribing initiatives as part of CEPP.

NICE guidance, quality standards and broader information used to derive the audit standards are:

- NICE QS5: Chronic kidney disease in adults
- NICE Chronic kidney disease pathway
- NICE CG182: Chronic kidney disease in adults: assessment and management
- NICE CG181: Cardiovascular disease: risk assessment and reduction, including lipid modification

A 100% target has been stated within the audit standards detailed below. However, it is recognised that in a small number of patients, achievement of the stated target may not be possible due to specific patient factors. In such patients, clear documentation of these decisions should be made in their medical records.

1.1 Aim and objectives

Aim:
The aim of the audit is to ensure that patients with CKD (stage 3–5) receive appropriate medicines management.

Objectives:

- To ensure the prescribing for patients with CKD (stage 3–5) is in line with the NICE recommendations;
- To review the prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in patients identified as having CKD (stage 3–5);
- To review blood pressure control in patients with CKD (stage 3–5) and hypertension (with and without diabetes) to ensure optimal therapy;
- To investigate if patients with CKD (stage 3–5) are prescribed required statin therapy.

1.2 Audit standards

- 100% of patients with CKD (stage 3–5) who have been prescribed an NSAID have this medication reviewed and stopped if appropriate.
- 100% of CKD (stage 3–5) patients without diabetes and a measured ACR < 30 (PCR < 50) have blood pressure below 140/90 mmHg.
- 100% of CKD (stage 3–5) patients with diabetes or a measured ACR ≥ 30 (PCR ≥ 50) have blood pressure below 130/80 mmHg.
- 100% of CKD (stage 3–5) patients with diabetes and hypertension are treated with a renin-angiotensin system antagonist (RASA).
- 100%[1] of CKD (stage 3–5) patients are offered treatment with a statin.

1.3 Method

The National CKD Audit (NCKDA) aims to measure the management and outcomes for patients with CKD by collecting Primary Care data from NHS practices in regions throughout Wales using Audit+. In order for individual practices to participate in this audit access to the practice data will be enabled through Audit+. These data will be for adult patients only.

[1] 100% standard target in line with NICE clinical audit standards in accordance with Prudent Health Care principles of informed patient choice

Using Audit+ practices can identify the following groups:

Sample 1. Number of patients with CKD (stage 3–5) who have been prescribed an NSAID within the last 12 months
Sample 2. Number of patients with CKD (stage 3–5) and uncontrolled hypertension
Sample 3. Number of patients with CKD (stage 3–5), hypertension and diabetes not on a renin-angiotensin system antagonist (RASA)
Sample 4. Number of patients with CKD (stage 3–5) not on a statin

2. Complete Data Summary Sheets 1–4.

3. Complete Practice Review Sheet (use the Data Summary Sheets to inform discussion).

4. Return Data Summary Sheets and the Practice Review Sheet to (localities to insert contact).

DATA SUMMARY SHEET 1

Sample 1. Number of patients with CKD (stage 3–5) who have been prescribed an NSAID within the last 12 months.

Practice:_____ Date of audit:_____

	Number	Percentage of practice population
Practice list size		100%
(A) Number of patients with CKD (stage 3–5)		
	Number	Percentage of (A)
(B) Number of patients with CKD (stage 3–5) issued with a prescription for an NSAID within the last 12 months		

	Number	Percentage of the audit sample
(C) Sample size i.e. number of CKD (stage 3–5) patients issued with a prescription for an NSAID within the last 12 months		100%
(D) Number of CKD (stage 3–5) patients with a clear indication for NSAID use documented and recorded in their patient notes		
(E) Number of CKD (stage 3–5) patients with assessment of prescribing risk/benefit of NSAID use documented in patient notes		
(F) Number of CKD (stage 3–5) patients in whom the NSAID has been stopped		

DATA SUMMARY SHEET 2

Sample 2. Number of patients with CKD (stage 3–5) and uncontrolled hypertension.

Practice:_____ Date of audit:_____

	Number	Percentage of practice population
Practice list size		100%
(A) Number of patients with CKD (stage 3–5) and hypertension		
	Number	**Percentage of (A)**
(B) Number of patients with CKD (stage 3–5) and hypertension, with their blood pressure outside of recommended targets on the two most recent readings		

	Number	Percentage of the audit sample
(C) Sample size i.e. the number of CKD (stage 3–5) patients with uncontrolled hypertension		100%
(D) Number of CKD (stage 3–5) patients with uncontrolled hypertension despite the use of maximum tolerated therapy of antihypertensive drugs at therapeutic doses		
(E) Number of CKD (stage 3–5) patients with uncontrolled hypertension, with assessment of prescribing risk/benefit documented in patient notes		
(F) Number of CKD (stage 3–5) patients with uncontrolled hypertension despite the use of maximum tolerated therapy reviewed by secondary care renal specialists		

DATA SUMMARY SHEET 3

Sample 3. Number of patients with CKD (stage 3–5), hypertension and diabetes not on a RASA.

Practice:_____ Date of audit:_____

	Number	Percentage of practice population
Practice list size		100%
(A) Number of patients with CKD (stage 3–5), type 2 diabetes and hypertension		
	Number	**Percentage of (A)**
(B) Number of patients with CKD (stage 3–5), type 2 diabetes and hypertension, and not issued a repeat RASA prescription within the last 12 months		

	Number	Percentage of the audit sample
(C) Sample size i.e. the number of CKD (stage 3–5) patients with type 2 diabetes and hypertension not on a RASA		100%
(D) Number of CKD (stage 3–5) patients with type 2 diabetes and hypertension with assessment of risk/benefit of RASA prescribing documented in notes		

DATA SUMMARY SHEET 4

Sample 4. Number of patients with CKD (stage 3–5) not on a statin.

Practice:_____ Date of audit:_____

	Number	Percentage of practice population
Practice list size		100%
(A) Number of patients with CKD (stage 3–5) not on a statin		

	Number	Percentage of the audit sample
(B) Sample size i.e. the number of CKD (stage 3–5) patients not on a statin		100%
(C) Number of CKD (stage 3–5) patients with assessment of risk/benefit for statin prescribing documented in notes		
(D) Number of CKD (stage 3–5) patients in whom statin therapy has been stopped and reasons are clearly documented in notes		
(E) Number of patients in whom statin use has been discussed and declined by the patient.		

PRACTICE REVIEW SHEET

A. What lessons did the practice learn from carrying out this audit?

B. What discussion/activities did the practice undertake as a result of the audit?

C. What changes has the practice agreed to implement as a result of this audit?

This audit was completed by:

Name(s):_____

Signature(s):_____

Practice (name and address):

_____
_____
_____
_____
_____

APPENDIX 2. CLASSIFICATION OF CKD[6]

Classification of CKD using GFR and ACR categories [From NICE CG182 which is adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013)][53]

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range			
			< 3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased	
			A1	A2	A3	
GFR categories (ml/min/1.73 m^2), description and range	≥ 90 Normal and high	G1	No CKD in the absence of markers of kidney damage			Increasing risk →
	60–89 Mild reduction related to normal range for a young adult	G2				
	45–59 Mild-moderate reduction	G3a				
	30–44 Moderate-severe reduction	G3b				
	15–29 Severe reduction	G4				
	< 15 Kidney failure	G5				
	Increasing risk →					

APPENDIX 3. EQUATIONS FOR ESTIMATING GFR[2,54].

Cockcroft and Gault equation

$$\text{Creatinine clearance, CrCl (ml/min)} = \frac{F \times (140 - \text{age [years]}) \times \text{weight (kg)}}{\text{SrCr (µmol/L)}}$$

F = 1.23 in males and 1.04 in females
SrCr = serum creatinine GFR = glomerular filtration rate (estimated)

Modification of diet in renal disease (MDRD) equation

$$\text{GFR (ml/min/1.73 m}^2) = 175 \times (\text{SrCr [µmol/L]}/88.4)^{-1.154} \times \text{age (years)}^{-0.203}$$

X 0.742 if female, and x 1.21 if African or African Caribbean

Normal GFR is roughly 100 ml/min/1.73 m^2

CKD-EPI Creatinine equation (2009) (National Kidney Foundation, 2016)

$$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

eGFR (estimated glomerular filtration rate) = ml/min/1.73 m^2
S_{Cr} (standardised serum creatinine) = mg/dL
κ = 0.7 (females) or 0.9 (males)
α = −0.329 (females) or −0.411 (males)
min = indicates the minimum of S_{Cr}/κ or 1
max = indicates the maximum of S_{Cr}/κ or 1
age = years

APPENDIX 4. FREQUENCY OF GFR MONITORING

Frequency of GFR monitoring as number of times per year by GFR and ACR category for people with, or at risk of, CKD[6].

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range			
			< 3 Normal to mildly increased	3–30 Moderately increased	> 30 Severely increased	
			A1	A2	A3	
GFR categories (ml/min/1.73 m^2), description and range	≥ 90 Normal and high	G1	≤1	1	≥1	Increasing risk →
	60–89 Mild reduction related to normal range for a young adult	G2	≤1	1	≥1	
	45–59 Mild-moderate reduction	G3a	1	1	2	
	30–44 Moderate-severe reduction	G3b	≤2	2	≥2	
	15–29 Severe reduction	G4	2	2	3	
	< 15 Kidney failure	G5	4	≥4	≥4	
	Increasing risk →					

Frequency of monitoring by classification of CKD using GFR and ACR categories [From NICE CG182 which is adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013)][53]

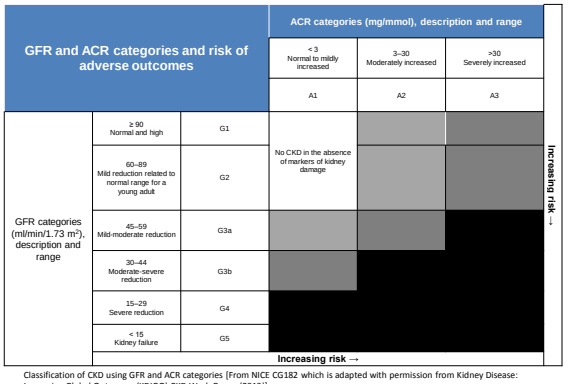
Chronic Kidney Disease (CKD)

Educational slide set

CKD – An introduction

- Estimated "missing million" CKD patients
- Early identification is essential
- NICE – classify severity using: -
  - GFR (glomerular filtration rate), &
  - ACR (albumin to creatinine ratio)
- Increased classification accuracy

Classification of CKD



Classification of CKD using GFR and ACR categories [From NICE CG182 which is adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013)]

Referral for specialist assessment

- Specialist assessment referral should be made for patients with:-
  - A GFR less than 30 ml/min/1.73 m^2 with or without diabetes;
  - Sustained decrease in GFR of 25% or more, and a change in GFR category, or, sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months;
  - ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated;
  - ACR 30 mg/mmol or more together with haematuria;
  - Known or suspected rare genetic causes of CKD;
  - Suspected renal artery stenosis.

Kidney damaging medicines

- Test GFR and ACR at least annually
- ADR of renal failure

Potential kidney damaging medications	
NSAIDs	Calcineurin inhibitors
Lithium	ACE inhibitors
Diuretics	ARBs
Antibiotics	PPIs

- ADRs should be reported to MHRA via Yellow Card Making medicines safer www.mhra.gov.uk/yellowcard
- Combining kidney damaging medicines

Lifestyle management

- General lifestyle advice
- Dietary modifications to optimise nutritional benefit and prevent malnutrition
- Obese patient benefits
- Smoking

Hypertension in CKD

- Aim to keep systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and diastolic blood pressure below 90 mmHg.
- Tighter control if diabetes and/or ACR 70mg/mmol or more; keep systolic below 130mmHg (120–129) and diastolic below 80mmHg.
- First line agent consider RASAs

RASAs

- E.g. ACE-inhibitors, angiotension-receptor blockers (ARB), renin inhibitors
- Offer a RASA to CKD patients with one or more of the following:
  - Diabetes and an ACR of 3 mg/mmol or more;
  - Hypertension and an ACR of 30 mg/mmol or more;
  - An ACR of 70 mg/mmol or more.
- Measure potassium and GFR: -
  - Before starting RASA and one or two weeks after starting
  - After each dose increase
  - Investigate further if: -
    - 30%+ rise in creatinine or 25%+ fall in GFR
  - Do not use a RASA if: -
    - If potassium prior to commencing >5.0 mmol/litre, do not use RASA
    - If during treatment potassium increases to 6.0 mmol/litre or more stop RASA

Uncontrolled hypertension in CKD

- If a second agent needed consider non-dihydropyridine calcium channel antagonist e.g. diltiazem:
  - If oedema consider loop diuretic.
- Do not offer RASA combination e.g. ACE-inhibitor and ARB
  - Increased risk of ADRs e.g. hyperkalaemia, renal dysfunction
- Refer for specialist assessment if hypertension remains uncontrolled and at least four antihypertensive agents

Antiplatelets

- CKD patients should be considered as being in the highest risk group for cardiovascular disease (CVD)
  - Increased risk if eGFR <60ml/min/1.73m^2 with/without albuminuria
  - Increasing risks as eGFR decreases/ACR increases
- Antiplatelet drugs should be offered for secondary prevention of CVD
  - NB consider increased risk of bleeding when prescribing

Statins

- Lipid-lowering therapies reduce the incidence of CVD events in CKD patients
  - Offer atorvastatin 20mg daily
- Increase dose
  - <40% reduction in non-HDL at 3 months
  - If eGFR <30ml/min/1.73m^2 seek renal specialist agreement
  - Consider other factors also e.g. adherence, diet

Bisphosphonates

- If indicated offer bisphosphonates for the prevention and treatment of osteoporosis in people with a GFR > 30 ml/min/1.73m^2
- Three oral bisphosphonates are alendronate, ibandronate and risedronate
- Renal specialist to advise if treatment continuing when GFR <30ml/min/1.73m^2

Acute Kidney Injury (AKI)

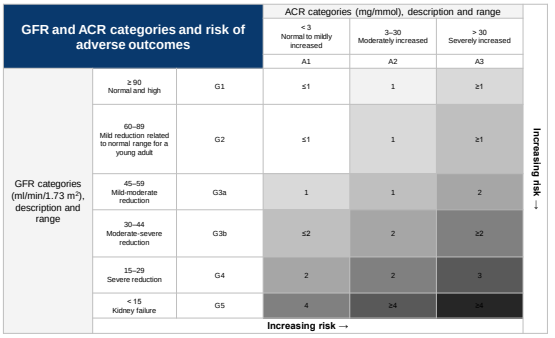
- Adults with acute illness should be investigated for AKI in the following:-

Oliguria	History of acute kidney injury
Hypovolaemia	Use of nephrotoxic drugs
Symptoms or history of urological obstruction, or conditions that may lead to obstruction	Signs and symptoms such as a reduction in urine output, dehydration; neurological or cognitive impairment or disability
CKD	Liver disease
Heart failure	Diabetes
Deteriorating warning signs	Use of iodinated contrast agents within the past week
Sepsis	Age 65+

Acute Kidney Injury (AKI)

- AKI: -
  - Affects up to 1 in 6 patients admitted to hospital
  - Mortality rate approximately 25–30%
  - Around 20% AKI cases possibly preventable
- AKI is a risk factor for developing CKD
  - If AKI suspected attain eGFR
  - Review any nephrotoxic medications prescribed
  - If CKD history consider if worsening CKD
  - If no evidence of CKD monitor creatinine for at least 2–3 years
- AKI management dependent upon underlying aetiology; however, initial management should include: -
  - Clinical assessment of volume status
  - Appropriate fluid resuscitation
  - Medication review

Monitoring in CKD



Frequency of monitoring by classification of CKD using GFR and ACR categories
[From NICE CG182 which is adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013)]

End Stage Renal Disease (ESRD)

- Less than 1% of CKD patients progress to ESRD
  - Renal replacement therapies e.g. dialysis
  - Kidney transplant
    - Lifelong issues e.g. immunosuppression
- Limit ESRD progression
  - Early diagnosis
  - Regular monitoring
  - Appropriate pharmacological management

NCKDA

- To improve identification, management and care of CKD patients
- Pilot study: 50% appropriately coded
- Improvement can avoid some of the pressure on dialysis and transplant services
- Key challenge to attain majority of GP practices to participate

CKD CEPP Audit

- Aim:
  - The aim of the audit is to ensure that patients with CKD (stage 3–5) receive appropriate medicines management.
- Objectives:
  - To ensure the prescribing for patients with CKD (stage 3–5) is in line with the NICE recommendations;
  - To review the prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in patients identified as having CKD (stage 3–5);
  - To review blood pressure control in patients with CKD (stage 3–5) and hypertension (with and without diabetes) to ensure optimal therapy;
  - To investigate if patients with CKD (stage 3–5) are prescribed required statin therapy.

CKD CEPP Audit

Sample 1. Number of patients with CKD (stage 3–5) who have been prescribed a non-steroidal anti-inflammatory drug (NSAID) within the last 12 months
Sample 2. Number of patients with CKD (stage 3–5) and uncontrolled hypertension
Sample 3. Number of patients with CKD (stage 3–5), hypertension and diabetes not on a renin-angiotensin system antagonist (RASA)
Sample 4. Number of patients with CKD (stage 3–5) not on a statin

Further information

NICE guidance

NICE CG182 Chronic Kidney Disease: www.nice.org.uk/guidance/cg182

NICE CG169 Acute kidney injury: prevention, detection and management: www.nice.org.uk/guidance/cg169

NICE CG181 Cardiovascular disease: risk assessment and reduction, including lipid modification: www.nice.org.uk/guidance/cg181

Websites

The Renal Association: www.renal.org/#sthash.MB1bV38T.dpbs

British Renal Society: www.britishrenal.org

Patient resources

The British Kidney Patient Association website: www.britishkidney-pa.co.uk/

Welsh Kidney Patients' Association website: www.wkpa.org.uk/

Think Kidneys – everything you need to know: www.thinkkidneys.nhs.uk/ckd/wp-content/uploads/sites/2/2016/03/Think-Kidneys-Infographic-030316-campaign-final.pdf

Kidney patient guide – general overview: www.kidneypatientguide.org.uk/contents.php

Kidney Research UK: www.kidneyresearchuk.org/