Chronic kidney disease - not diabetic - Management
Scenario: Testing for chronic kidney disease

Definition

- Chronic kidney disease is said to be present when there is persistent impairment of kidney function, or evidence of kidney damage (such as proteinuria or haematuria) or structural abnormality of the kidney.
- Worsening renal impairment is associated with a wide range of complications, such as hypertension, anaemia, renal bone disease, malnutrition, neuropathy, and lipid abnormalities. People with chronic kidney disease are roughly twenty times more likely to die of cardiovascular disease than to progress to end-stage renal failure.
- Renal function is assessed by measuring serum creatinine and calculating estimated glomerular filtration rate (eGFR).
- The classification of chronic kidney disease is based on eGFR, the presence of proteinuria or haematuria, and whether the person is known to have a structural renal abnormality (see Classification of CKD).

Who should I test for chronic kidney disease?

- Test people with risk factors for chronic kidney disease:
  - Diabetes (Types 1 and 2).
  - Hypertension.
  - Cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease, cerebrovascular disease).
  - Structural renal tract disease, renal calculi, or benign prostatic hypertrophy.
  - Multi-system diseases with potential kidney involvement, such as systemic lupus erythematosus.
  - Family history of chronic kidney disease stage 5 or hereditary kidney disease.
  - Those taking nephrotoxic drugs such as lithium, ciclosporin, diuretics, and long-term nonsteroidal anti-inflammatory drugs.
- Test people with an incidental finding of:
  - Proteinuria or haematuria on a urinary dipstick.
  - A low estimated glomerular filtration rate. For example, less than 60 mL/min/1.73 m^2.
- Do not use obesity (in the absence of diabetes or hypertension), or age, gender, and ethnicity alone as a risk factor for chronic kidney disease.

How should I test for chronic kidney disease?

- For people at risk of chronic kidney disease, measure serum creatinine (to calculate estimated glomerular filtration rate [eGFR]) and urinary albumin:creatinine ratio, and check urine for haematuria by dipstick.

o If eGFR is less than 60 mL/min/1.73 m^2, repeat within 2 weeks (unless previous values show the eGFR is stable):

o If the eGFR remains less than 60 mL/min/1.73 m^2 with no evidence of acute deterioration, repeat within 3 months to confirm the diagnosis of chronic kidney disease.

o If the eGFR is deteriorating (a decrease of more than 25% of the initial value), consider a diagnosis of acute kidney injury and seek specialist advice.

o If the urinary albumin:creatinine ratio is 30 mg/mmol or more:

o Repeat on an early morning urine sample (if it is 70 mg/mmol or more, there is no need to repeat the test).

o If dipstick test shows 1+ or more of blood:

o Exclude a urinary tract infection (UTI).

o Persistent haematuria is considered to be present if two out of three dipstick tests show 1+ or more of blood (after exclusion of a UTI).

- If the eGFR is 60 mL/min/1.73 m^2 or more, the urinary albumin:creatinine ratio is less than 30 mg/mmol, and there is no haematuria, reassure the person that they do not have chronic kidney disease. However, if the person is in a high risk group continue to monitor eGFR annually.

- If the person has confirmed chronic kidney disease (eGFR is persistently less than 60 mL/min/1.73 m^2, or there is persistent proteinuria or haematuria, or there is a structural kidney abnormality) assess for possible causes, grade severity (based on classification system), and see Management issues.

Chronic kidney disease - not diabetic - Management
Scenario: Management of stage 1 and 2 chronic kidney disease

Definition

- Chronic kidney disease is said to be present when there is persistent impairment of kidney function, or evidence of kidney damage (such as proteinuria or haematuria), or structural abnormality of the kidney.

- Worsening renal impairment is associated with a wide range of complications, such as hypertension, anaemia, renal bone disease, malnutrition, neuropathy, and lipid abnormalities. People with chronic kidney disease are roughly twenty times more likely to die of cardiovascular disease than to progress to end-stage renal failure.

- Renal function is assessed by measuring serum creatinine and calculating estimated glomerular filtration rate (eGFR).

- Chronic kidney disease stages 1 and 2 are diagnosed when the eGFR is 60 mL/min/1.73 m^2 or more *and* there is evidence of proteinuria or haematuria, or a structural abnormality of the kidney (see Classification of CKD).

- People with chronic kidney disease stage 1 and 2 can usually be managed in primary care.

When is referral recommended in stage 1 or 2 CKD?

- Refer according to local guidelines, where available. The urgency of referral should be based on clinical judgement.

- Referral to a nephrology specialist is usually required for people with:

  - Heavy proteinuria (urinary albumin:creatinine ratio 70 mg/mmol or more), unless this is known to be due to diabetes and already appropriately treated.

  - Proteinuria (urinary albumin:creatinine ratio 30 mg/mmol or more) *with* haematuria.

  - Uncontrolled hypertension (despite four antihypertensive drugs at therapeutic doses — see the CKS topic on Hypertension - not diabetic).

  - A rare or genetic cause of chronic kidney disease, or the suspicion of one (such as polycystic kidney disease).

  - Suspected renal artery stenosis (such as refractory hypertension, recurrent pulmonary oedema with normal left ventricular function, or an increase in serum creatinine of 20% or more when started on an angiotensin-converting enzyme inhibitor).

- If the person has urinary tract obstruction (for example the bladder is palpable), refer to a urologist — unless urgent medical intervention is needed for problems such as hyperkalaemia (potassium greater than 6 mmol/L) or fluid overload.

In depth

What tests should be monitored in CKD stage 1 and 2

- Use clinical judgement; if in doubt, seek specialist advice.

- The following should be measured routinely:

  - Estimated glomerular filtration rate (eGFR) every 12 months.

  - A test for proteinuria every 12 months:

    - If the person is not already known to have proteinuria, measure the urinary albumin:creatinine ratio.

- If the person is known to have proteinuria, monitoring can be with urinary albumin:creatinine or protein:creatinine ratios.

- If there is haematuria (with no urological cause), carry out a dipstick test for haematuria every 12 months or until it is no longer persistent.

In depth

How do I know if the eGFR has deteriorated significantly?

- If a decline in estimated glomerular filtration rate (eGFR) is seen, repeat three times over a period of at least 90 days.

- A significant eGFR decline is indicated if there is more than a:

- 5 mL/min/1.73 m^2 decrease within 1 year, *or*

- 10 mL/min/1.73 m^2 decrease within 5 years.

- If a large decline in eGFR is seen (25% or more), repeat within 2 weeks to exclude acute kidney injury.

In depth

What lifestyle advice is recommended?

- Encourage people with chronic kidney disease to:

- Stop smoking (if appropriate) and drink sensible amounts of alcohol (see the CKS topics on Smoking cessation and Alcohol - problem drinking).

- Take regular exercise, and achieve a healthy body weight (see the CKS topic on Obesity).

- Eat a healthy diet.

- Avoid using over-the-counter nonsteroidal anti-inflammatory drugs (except on medical advice).

- Provide information appropriate to the stage and cause of chronic kidney disease.

In depth

What blood pressure is recommended?

- In people with chronic kidney disease, ideally aim for:

- Systolic blood pressure less than 140 mmHg (target range 120–139 mmHg).

- Diastolic blood pressure less than 90 mmHg.

- In people with chronic kidney disease *and* a urinary albumin:creatinine ratio of 70 mg/mmol or more, ideally aim for:

  - Systolic blood pressure less than 130 mmHg (target range 120–129 mmHg).

  - Diastolic blood pressure less than 80 mmHg.

In depth

When are ACE inhibitors or AIIRAs recommended?

- Offer an angiotensin-converting enzyme (ACE) inhibitor to people with chronic kidney disease if there is:

  - Hypertension *and* proteinuria with a urinary albumin:creatinine ratio of 30 mg/mmol or more, *or*

  - Proteinuria with a urinary albumin:creatinine ratio of 70 mg/mmol or more (irrespective of blood pressure).

- Start with a low dose and titrate up to the maximum tolerated therapeutic dose (within the maximum licensed dose), by doubling the dose every 1–2 weeks. After each upward titration, monitor the person's renal function, serum potassium level, and blood pressure.

- If the person cannot tolerate an ACE inhibitor (due to non-renal adverse effects), offer an angiotensin-II receptor antagonist (AIIRA) as an alternative (see prescribing ACE inhibitors and AIIRAs).

- For people with hypertension *and* no proteinuria (urinary albumin:creatinine ratio less than 30 mg/mmol), treat in line with current guidance on hypertension management (see the CKS topic on Hypertension - not diabetic).

In depth

When are statins or aspirin recommended?

- People with chronic kidney disease should be offered antiplatelet and statin treatment as for the rest of the population.

  - For primary prevention of cardiovascular disease (CVD), calculate the CVD risk based on existing risk tables (see the CKS topic on CVD risk assessment and management).

  - For secondary prevention of CVD, see the CKS topics on Antiplatelet treatment and Lipid modification - CVD prevention.

In depth

Prescriptions

Start angiotensin-converting enzyme inhibitor

Age from 18 years onwards

Start enalapril: titrate from 5mg to 10mg once a day

Enalapril 5mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £1.02
Licensed use: yes

Start lisinopril: titrate from 5mg to 10mg once a day

Lisinopril 5mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £0.82
Licensed use: yes

Start ramipril: initial titration from 2.5mg to 5mg

Ramipril 2.5mg capsules
Take one capsule once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two capsules once a day.
Supply 56 capsules.

Age: from 18 years onwards
NHS cost: £2.30
Licensed use: yes

Start angiotensin-II receptor antagonist

Age from 18 years onwards

Start irbesartan: titrate from 150mg to 300mg once a day

Irbesartan 150mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £25.14
Licensed use: yes

Start losartan: titrate from 50mg to 100mg once a day

Losartan 50mg tablets

Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £25.60
Licensed use: yes
Black triangle

Chronic kidney disease - not diabetic - Management

Scenario: Management of stage 3 chronic kidney disease

Definition

- Chronic kidney disease is said to be present when there is persistent impairment of kidney function, or evidence of kidney damage (such as proteinuria or haematuria) or structural abnormality of the kidney.
- Worsening renal impairment is associated with a wide range of complications, such as hypertension, anaemia, renal bone disease, malnutrition, neuropathy, and lipid abnormalities. People with chronic kidney disease are roughly twenty times more likely to die of cardiovascular disease than to progress to end-stage renal failure.
- Renal function is assessed by measuring serum creatinine and calculating estimated glomerular filtration rate (eGFR).
- Chronic kidney disease stage 3 is diagnosed when eGFR is 30–59 mL/min/1.73 m^2, *with or without* evidence of proteinuria or haematuria or a structural abnormality of the kidney (see Classification of CKD).
- Most people with chronic kidney disease stage 3 can be managed in primary care. Treatment of complications such as anaemia and renal bone disease requires specialist input.

When is referral recommended in stage 3 CKD?

- Refer according to local guidelines, where available. The urgency of referral should be based on clinical judgement.
- Referral to a nephrology specialist is usually required for people with:

o Acute renal failure, suggested by a rapid decrease in the estimated glomerular filtration rate (eGFR) of more than 25% of the initial value.

o Heavy proteinuria (urinary albumin:creatinine ratio 70 mg/mmol or more), unless this is known to be due to diabetes and already appropriately treated.

o Proteinuria (urinary albumin:creatinine ratio 30 mg/mmol or more) *with* haematuria.

- Rapidly declining eGFR, defined as more than 5 mL/min/1.73 m^2 in 1 year, or more than 10 mL/min/1.73 m^2 within 5 years.
- Uncontrolled hypertension (despite four antihypertensive drugs at therapeutic doses — see the CKS topic on Hypertension - not diabetic).
- A rare or genetic cause of chronic kidney disease, or the suspicion of one (such as polycystic kidney disease).
- Suspected renal artery stenosis (such as refractory hypertension, recurrent pulmonary oedema with normal left ventricular function, or an increase in serum creatinine of 20% or more when started on an angiotensin-converting enzyme inhibitor).
- Complications of chronic kidney disease, such as anaemia (haemoglobin less than 11 g/dL) and renal bone disease (for example abnormal serum calcium or phosphate).

- If the person has urinary tract obstruction (for example the bladder is palpable), refer to a urologist — unless urgent medical intervention is needed for problems such as hyperkalaemia (potassium greater than 6 mmol/L), uraemia, acidosis, or fluid overload.

In depth

What tests should be monitored in CKD stage 3

- Use clinical judgement; if in doubt, seek specialist advice.
- In chronic kidney disease stage 3A (estimated glomerular filtration rate [eGFR] 45–59 mL/min/1.73 m^2):
- Measure eGFR every 6 months.
- In chronic kidney disease stage 3B (eGFR 30–44 mL/min/1.73 m^2):
- Measure eGFR every 6 months.
- Do a full blood count to exclude anaemia (haemoglobin < 11 g/dL). The frequency of subsequent monitoring depends on whether there is evidence of a downward trend.
- Do not routinely measure serum parathyroid hormone or vitamin D unless this is clinically indicated (such as in the presence of an abnormal calcium level).
- Test for proteinuria every 12 months:
- If the person is not already known to have proteinuria, measure the urinary albumin:creatinine ratio.
- If the person is known to have proteinuria, monitoring can be with urinary albumin:creatinine or protein:creatinine ratios.

- If the person has haematuria (with no urological cause), carry out a dipstick test for haematuria every 12 months or until it is no longer persistent.

In depth

How do I know if the eGFR has deteriorated significantly?

- If a decline in estimated glomerular filtration rate (eGFR) is seen, repeat three times over a period of at least 90 days.
  - A significant eGFR decline is indicated if there is more than a:
  - 5 mL/min/1.73 m^2 decrease within 1 year, *or*
  - 10 mL/min/1.73 m^2 decrease within 5 years.
- If a large decline in eGFR is seen (25% or more), repeat within 2 weeks to exclude acute kidney injury.

In depth

What lifestyle advice is recommended?

- Encourage people with chronic kidney disease to:
  - Stop smoking (if appropriate) and drink sensible amounts of alcohol (see the CKS topics on Smoking cessation and Alcohol - problem drinking).
  - Take regular exercise, and achieve a healthy body weight (see the CKS topic on Obesity).
  - Eat a healthy diet.
  - Avoid using over-the-counter nonsteroidal anti-inflammatory drugs (except on medical advice).
- Provide information appropriate to the stage and cause of chronic kidney disease.

In depth

What blood pressure is recommended?

- In people with chronic kidney disease, ideally aim for:
  - Systolic blood pressure less than 140 mmHg (target range 120–139 mmHg).
  - Diastolic blood pressure less than 90 mmHg.
- In people with chronic kidney disease *and* a urinary albumin:creatinine ratio of 70 mg/mmol or more, ideally aim for:
  - Systolic blood pressure less than 130 mmHg (target range 120–129 mmHg).

- Diastolic blood pressure less than 80 mmHg.

In depth

When are ACE inhibitors or AIIRAs recommended?

- Offer an angiotensin-converting enzyme (ACE) inhibitor to people with chronic kidney disease if there is:
  - Hypertension *and* proteinuria with a urinary albumin:creatinine ratio of 30 mg/mmol or more, *or*
  - Proteinuria with a urinary albumin:creatinine ratio of 70 mg/mmol or more (irrespective of blood pressure).
- Start with a low dose and titrate up to the maximum tolerated therapeutic dose (within the maximum licensed dose), by doubling the dose every 1–2 weeks. After each upward titration, monitor the person's renal function, serum potassium level, and blood pressure.
- If the person cannot tolerate an ACE inhibitor (due to non-renal adverse effects), offer an angiotensin-II receptor antagonist (AIIRA) as an alternative (see prescribing ACE inhibitors and AIIRAs).
- For people with hypertension *and* no proteinuria (urinary albumin:creatinine ratio less than 30 mg/mmol), treat in line with current guidance on hypertension management (see the CKS topic on Hypertension - not diabetic).

In depth

When are statins or aspirin recommended?

- People with chronic kidney disease should be offered antiplatelet and statin treatment as for the rest of the population.
  - For primary prevention of cardiovascular disease (CVD), calculate the CVD risk based on existing risk tables (see the CKS topic on CVD risk assessment and management).
  - For secondary prevention of CVD, see the CKS topics on Antiplatelet treatment and Lipid modification - CVD prevention.

In depth

Prescriptions

Start angiotensin-converting enzyme inhibitor

Age from 18 years onwards

Start enalapril: titrate from 5mg to 10mg once a day

Enalapril 5mg tablets

Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £1.02
Licensed use: yes

Start lisinopril: titrate from 5mg to 10mg once a day

Lisinopril 5mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £0.82
Licensed use: yes

Start ramipril: initial titration from 2.5mg to 5mg

Ramipril 2.5mg capsules
Take one capsule once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two capsules once a day.
Supply 56 capsules.

Age: from 18 years onwards
NHS cost: £2.30
Licensed use: yes

Start angiotensin-II receptor antagonist

Age from 18 years onwards

Start irbesartan: titrate from 150mg to 300mg once a day

Irbesartan 150mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £25.14
Licensed use: yes

Start losartan: titrate from 50mg to 100mg once a day

Losartan 50mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards

NHS cost: £25.60
Licensed use: yes
Black triangle

Chronic kidney disease - not diabetic - Management

Scenario: Management of stage 4 and 5 chronic kidney disease

Definition

- Chronic kidney disease is said to be present when there is persistent impairment of kidney function, or evidence of kidney damage (such as proteinuria or haematuria) or structural abnormality of the kidney.
- Worsening renal impairment is associated with a wide range of complications, such as hypertension, anaemia, renal bone disease, malnutrition, neuropathy, and lipid abnormalities. People with chronic kidney disease are roughly twenty times more likely to die of cardiovascular disease than to progress to end-stage renal failure.
- Renal function is assessed by measuring serum creatinine and calculating estimated glomerular filtration rate (eGFR).
- Chronic kidney disease stages 4 and 5 are diagnosed when eGFR is 15–29 mL/min/1.73 m^2 (stage 4) or less than 15 mL/min/1.73 m^2 (stage 5), *with or without* evidence of proteinuria or haematuria or a structural abnormality of the kidney (see Classification of CKD).
- Specialist referral and shared care is recommended for most people with chronic kidney disease stages 4 and 5. Treatment of complications such as anaemia and renal bone disease require specialist input.

When is referral recommended in stage 4 or 5 CKD?

- Refer according to local guidelines, where available. The urgency of referral should be based on clinical judgement.
- People with chronic kidney disease stage 4 or 5 should usually be referred to a nephrology specialist.
- People with urinary tract obstruction (for example the bladder is palpable) should be referred to a urologist — unless urgent medical intervention is needed for problems such as hyperkalaemia (potassium greater than 6 mmol/L), uraemia, acidosis, or fluid overload.

In depth

What tests should be monitored in CKD stage 4 and 5

- People with chronic kidney disease stage 4 or 5 should usually be under specialist care, but monitoring of blood tests may take place in primary care as part of shared care arrangements.

- Measure estimated glomerular filtration rate (eGFR) every 3 months in stage 4 disease and every 6 weeks in stage 5 disease.
- Check haemoglobin level, as well as serum calcium, phosphate, vitamin D, and parathyroid hormone. Frequency of subsequent monitoring will depend on the results and clinical circumstances.
- Test for proteinuria every 12 months:
- If the person is not already known to have proteinuria, measure the urinary albumin:creatinine ratio.
- If the person is known to have proteinuria, monitoring can be with urinary albumin:creatinine or protein:creatinine ratios.
- If the person has haematuria (with no urological cause), carry out a dipstick test for haematuria every 12 months or until it is no longer persistent.

In depth

How do I know if the eGFR has deteriorated significantly?

- If a decline in estimated glomerular filtration rate (eGFR) is seen, repeat three times over a period of at least 90 days.
- A significant eGFR decline is indicated if there is more than a:
- 5 mL/min/1.73 m^2 decrease within 1 year, *or*
- 10 mL/min/1.73 m^2 decrease within 5 years.
- If a large decline in eGFR is seen (25% or more), repeat within 2 weeks to exclude acute kidney injury.

In depth

What lifestyle advice is recommended?

- Encourage people with chronic kidney disease to:
- Stop smoking (if appropriate) and drink sensible amounts of alcohol (see the CKS topics on Smoking cessation and Alcohol - problem drinking).
- Take regular exercise, and achieve a healthy body weight (see the CKS topic on Obesity).
- Eat a healthy diet.
- Avoid using over-the-counter nonsteroidal anti-inflammatory drugs (except on medical advice).
- Provide information appropriate to the stage and cause of chronic kidney disease.

In depth

What blood pressure is recommended?

- In people with chronic kidney disease, ideally aim for:
  - Systolic blood pressure less than 140 mmHg (target range 120–139 mmHg).
  - Diastolic blood pressure less than 90 mmHg.
- In people with chronic kidney disease *and* a urinary albumin:creatinine ratio of 70 mg/mmol or more, ideally aim for:
  - Systolic blood pressure less than 130 mmHg (target range 120–129 mmHg).
  - Diastolic blood pressure less than 80 mmHg.

In depth

When are ACE inhibitors or AIIRAs recommended?

- Offer an angiotensin-converting enzyme (ACE) inhibitor to people with chronic kidney disease if there is:
  - Hypertension *and* proteinuria with a urinary albumin:creatinine ratio of 30 mg/mmol or more, *or*
  - Proteinuria with a urinary albumin:creatinine ratio of 70 mg/mmol or more (irrespective of blood pressure).
- Start with a low dose and titrate up to the maximum tolerated therapeutic dose (within the maximum licensed dose), by doubling the dose every 1–2 weeks. After each upward titration, monitor the person's renal function, serum potassium level, and blood pressure.
- If the person cannot tolerate an ACE inhibitor (due to non-renal adverse effects), offer an angiotensin-II receptor antagonist (AIIRA) as an alternative (see prescribing ACE inhibitors and AIIRAs).
- For people with hypertension *and* no proteinuria (urinary albumin:creatinine ratio less than 30 mg/mmol), treat in line with current guidance on hypertension management (see the CKS topic on Hypertension - not diabetic).

In depth

When are statins or aspirin recommended?

- People with chronic kidney disease should be offered antiplatelet and statin treatment as for the rest of the population.
  - For primary prevention of cardiovascular disease (CVD), calculate the CVD risk based on existing risk tables (see the CKS topic on CVD risk assessment and management).

- For secondary prevention of CVD, see the CKS topics on Antiplatelet treatment and Lipid modification - CVD prevention.

In depth

Prescriptions

Start angiotensin-converting enzyme inhibitor

Age from 18 years onwards

Start enalapril: titrate from 5mg to 10mg once a day

Enalapril 5mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £1.02
Licensed use: yes

Start lisinopril: titrate from 5mg to 10mg once a day

Lisinopril 5mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £0.82
Licensed use: yes

Start ramipril: initial titration from 2.5mg to 5mg

Ramipril 2.5mg capsules
Take one capsule once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two capsules once a day.
Supply 56 capsules.

Age: from 18 years onwards
NHS cost: £2.30
Licensed use: yes

Start angiotensin-II receptor antagonist

Age from 18 years onwards

Start irbesartan: titrate from 150mg to 300mg once a day

Irbesartan 150mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.

Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £25.14
Licensed use: yes

Start losartan: titrate from 50mg to 100mg once a day

Losartan 50mg tablets
Take one tablet once a day for 7 days (take the FIRST dose at bedtime). Then, if tolerated, take two tablets once a day.
Supply 56 tablets.

Age: from 18 years onwards
NHS cost: £25.60
Licensed use: yes
Black triangle

CKS safe practical clinical answers - *fast*

Important aspects of prescribing information relevant to primary healthcare are covered in this section specifically for the drugs recommended in this CKS topic. For further information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists

Which ACE inhibitor/AIIRA is recommended?

- CKS recommends enalapril, lisinopril, or ramipril (ACE inhibitors) first line.
- CKS recommends irbesartan or losartan (AIIRAs) if an ACE inhibitor is not tolerated because of non-renal adverse effects (for example persistent, troublesome cough).

Basis for recommendation

- There is no evidence to suggest that any particular angiotensin-converting enzyme (ACE) inhibitor is more effective than another in the management of chronic kidney disease [NICE, 2008].
- However, there is evidence from randomized controlled trials to support the use of enalapril, lisinopril, ramipril, irbesartan, and losartan in people with diabetic nephropathy. For supporting evidence, see the CKS topic on Diabetes type 2.
- There is no evidence to suggest any advantage of an ACE inhibitor over an angiotensin-II receptor antagonist (AIIRA); however, economic evidence suggests increased cost-effectiveness for ACE inhibitors compared with AIIRAs [NICE, 2008].

Who should avoid taking ACE inhibitors or AIIRAs?

- Contraindications to angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II antagonists (AIIRAs) include:
  - History of angioedema associated with previous exposure to an ACE inhibitor, or hereditary or idiopathic angioedema.
  - Severe bilateral renal artery stenosis (or severe unilateral renal artery stenosis in people with only one functioning kidney).
  - Severe hepatic impairment.
  - Pregnancy:

- ACE inhibitors are contraindicated during the second and third trimesters of pregnancy. Exposure to an ACE inhibitor during the second and third trimester is known to induce human fetal toxicity (decreased renal function, oligohydramnios, delay in skull ossification, and neonatal toxicity) [MHRA, 2007; Schaefer et al, 2007; ABPI Medicines Compendium, 2008; ABPI Medicines Compendium, 2009a; ABPI Medicines Compendium, 2009b; ABPI Medicines Compendium, 2009c].

- ACE inhibitors are not recommended during the first trimester of pregnancy. Evidence on the risk of teratogenicity after exposure to ACE inhibitors during the first trimester of pregnancy is conflicting, and an increase in the risk of congenital malformation (particularly of the cardiovascular system and central nervous system) cannot be excluded [MHRA, 2007; NTIS, 2007].

- Unless continued treatment with an ACE inhibitor is considered essential, women who are planning a pregnancy should be switched to an alternative treatment with an established safety profile for use in pregnancy. The balance of risks and benefits of continued treatment with an ACE inhibitor versus the potential risk of congenital anomaly should be discussed with the woman. When pregnancy is confirmed, treatment with an ACE inhibitor should be stopped as soon as possible and, if appropriate, alternative treatment should be started [MHRA, 2007].

- Breastfeeding:

- ACE inhibitors are not recommended for use by women who are breastfeeding [MHRA, 2009b].

- During the first few weeks after delivery ACE inhibitors can cause profound neonatal hypotension; preterm babies may be at particular risk [MHRA, 2009a].

- In women who are breastfeeding older infants, the use of captopril, enalapril, or quinapril may be considered if the use of an ACE inhibitor is necessary [MHRA, 2009a]. If used, the infant should be carefully followed up for possible signs of hypotension [MHRA, 2009b].

Who should start an ACE inhibitor or AIIRA under outpatient supervision?

- **People at high risk of first-dose hypotension, hyperkalaemia, or renal failure should start treatment under close supervision** (if in doubt, discuss this with a specialist). This includes people with the following features:

- Renal impairment, with an estimated glomerular filtration rate (eGFR) of less than 30 mL/minute/1.73 m^2.

- A previous decrease in eGFR of more than than 15% after taking an angiotensin-converting enzyme (ACE) inhibitor.

- A strong clinical suspicion of renal artery stenosis.

- Baseline serum potassium of 5.0 mmol/L or greater.

- Hyponatraemia (sodium less than 130 mmol/L).
- Hypovolaemia.
- Unstable heart failure.
- Receiving high-dose diuretic treatment (for example more than furosemide 80 mg per day) who cannot tolerate withdrawal of this prior to starting an ACE inhibitor.
- Receiving high-dose vasodilator treatment.

[NICE, 2003; NICE, 2008; BNF 57, 2009]

What dose of an ACE inhibitor or AIIRA should I prescribe and how should the dose be titrated?

- Consider whether the ACE inhibitor or angiotensin-II receptor antagonist (AIIRA) should be started under specialist supervision.
- Start with a low dose and titrate up to the maximum tolerated therapeutic dose (within the maximum licensed dose), by doubling the dose every 1–2 weeks. After each upward titration, monitor the person's renal function, serum potassium level, and blood pressure.
- Do not increase the dose further if there is worsening renal function or hyperkalaemia.
- The following tables show the recommended doses of ACE inhibitors and AIIRAs for hypertension and diabetic nephropathy.

Table 1. Recommended doses of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (AIIRAs) for hypertension.

Drug	ual starting	wer starting	Maximum licensed dose (p day)
CE inhibitors			
alapril	-10 mg daily	mg daily	) mg
sinopril	) mg daily	5–5 mg daily	) mg
rindopril erbu	mg daily	mg daily	mg
rindopril argin	mg daily	5 mg daily	) mg
mipril	25 mg daily		) mg
andolapril	5 mg daily		mg
IIRAs			

ındesartan	mg daily	·4 mg	! mg
ɔesartan	0 mg daily	mg daily	)0 mg
sartan	) mg daily	mg daily	)0 mg
ılsartan	) mg daily	) mg daily	:0 mg

ata from: BNF, Summaries of Product Characteristics

Table 2. Recommended doses of ACE inhibitors and AIIRAs for diabetic nephropathy.

Dr	sual starting d	wer starting d	aximum recommended dose (per d
CE inhibitors			
ıalap	-10 mg daily	mg daily	) mg
sino	) mg daily	mg daily	) mg
ımip	5 mg daily		) mg
I IRAs			
ɔesa	0 mg daily	mg daily	)0 mg
sart	) mg daily	mg daily	)0 mg

Products not specifically licensed for the management of diabetic nephropa
ata from: BNF, Summaries of Product Characteristics

[NICE, 2003; NICE, 2008; BNF 57, 2009]

How should I monitor someone taking ACE inhibitors or angiotensin-II receptor antagonists?

- Measure serum creatinine and electrolytes, and estimated glomerular filtration rate (eGFR):
  - Before starting therapy.
  - 1–2 weeks after starting treatment.
  - 1–2 weeks after subsequent dose increases.
- Once the target blood pressure has been achieved and is stable, it is usual to monitor:
  - Blood pressure every 3–6 months.

- Urea and electrolytes, and eGFR, every 12 months (unless required more frequently because of impaired renal function).

[Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and Renal Association, 2006; NICE, 2008; BNF 57, 2009]

How should I manage abnormal potassium or eGFR results?

- Some increase in serum creatinine and potassium is expected after starting or increasing the dose of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-II receptor antagonist (AIIRA).
- **If estimated glomerular filtration rate (eGFR) decreases by 24%, or serum creatinine increases by up to 29%:**
  - Do not modify the ACE inhibitor/AIIRA dose and recheck levels in a further 1–2 weeks.
- **If eGFR decreases by 25% or more, or serum creatinine increases by 30% or more:**
  - Investigate other causes of deteriorating renal function, such as volume depletion.
  - Stop or reduce the dose of the following drugs (where appropriate) if the person is taking them:
  - Nephrotoxic drugs (such as nonsteroidal anti-inflammatory drugs).
  - Vasodilators (such as calcium-channel blockers, nitrates).
  - Potassium supplements or potassium-sparing diuretics.
  - Diuretics (consider dose reduction if the person is hypovolaemic).
  - If the decrease in eGFR or the increase in serum creatinine persists despite these measures:
  - Stop the ACE inhibitor or AIIRA therapy, *or*
  - Reduce the dose to a previously tolerated lower dose and recheck levels in 5–7 days (add an alternative antihypertensive medication if required).
- **If serum potassium is 5.0 mmol/L or above:**
  - Investigate other causes of hyperkalaemia and treat accordingly.
  - Stop or reduce the dose of potassium-sparing diuretics (amiloride, triamterene, spironolactone) or nephrotoxic drugs (such as nonsteroidal anti-inflammatory drugs).
- **If serum potassium persists between 5.0 and 5.9 mmol/L despite these measures,** reduce the dose of ACE inhibitors or AIIRA to a previously tolerated lower dose and recheck levels in 5–7 days.

- **Stop ACE inhibitors or AIIRAs if serum potassium persists above 6 mmol/L despite these measures.**

o Consider referral to a dietician: a low-potassium diet (up to 2 g/day), or dietary advice may help resolve hyperkalaemia.

[NICE, 2008]

What adverse effects of ACE inhibitors or angiotensin-II receptor antagonists should I be aware of?

- Angiotensin-converting enzyme (ACE) inhibitors are generally well tolerated, but occasionally adverse effects can occur. Adverse effects with angiotensin-II antagonists (AIIRAs) are similar, although they tend to be milder.

- **Deterioration in renal function**

o Monitor renal function after starting an ACE inhibitor or an AIIRA, after each increase in dose, and regularly throughout treatment.

- **Hyperkalaemia**

o Monitor serum electrolytes after starting an ACE inhibitor or an AIIRA, after each increase in dose, and regularly throughout treatment.

- **Orthostatic hypotension** is a common adverse effect of ACE inhibitors or AIIRAs and may cause dizziness, light-headedness, and confusion.

o If hypotension is asymptomatic, there is no need to change treatment.

o If hypotension is symptomatic:

o If there are no signs or symptoms of congestion, consider reducing the dose of any concomitant diuretic.

o Consider seeking specialist advice.

- **Cough** occurs in 0–15% of people taking an ACE inhibitor, although it rarely necessitates stopping treatment (less than 5% of people) [Micromedex, 2009].

o Cough is common in people with heart failure, or it can be due to smoking-related lung disease or pulmonary oedema.

o If the cough is troublesome (for example it prevents the person from sleeping) and other causes have been ruled out, consider switching to an AIIRA.

o AIIRAs do not cause cough.

[McMurray et al, 2005; European Society of Cardiology, 2008]

What advice should I give to someone taking an ACE inhibitor or an AIIRA?

- Explain the importance of:
  - Achieving the maximum tolerated dose of ACE inhibitor or angiotensin-II receptor antagonist.
  - Regular monitoring of eGFR and serum potassium to achieve this safely.
- Advise the person:
  - That they may experience adverse effects, but that these rarely necessitate stopping treatment.
  - To report symptoms of hypotension to their healthcare professional.
  - To avoid nonsteroidal anti-inflammatory drugs (these may be present in over-the-counter products) and salt substitutes that are high in potassium.
  - The initial dose should be taken late at night or at bedtime to mitigate the hypotensive effects that can occur.
  - If the drug is well tolerated, subsequent doses should be taken in the morning.
  - If symptoms of hypotension occur, advise the person to go to bed and take no further doses until they have been reviewed.

[NICE, 2008]