

## Diabetes Type 1 and 2 — screening/managing renal disease

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### About this topic

#### Have I got the right topic?

##### Age from 16 years onwards

This guidance covers the screening and early management of diabetic kidney disease in people over 16 years with Type 1 and Type 2 diabetes. We recognize that Type 2 diabetes is now being seen in children, and where they are managed will depend on the expertise available locally in primary care.

This guidance incorporates advice from the National Institute for Health and Clinical Excellence (NICE) guideline on *Diabetic renal disease: prevention and early management*, and the Royal College of General Practitioners (RCGP) *Clinical guideline for Type 2 diabetes: Diabetic renal disease: prevention and early management (February 2002)*.

This guidance does not cover the management of established renal failure, the management of other diabetic complications, or the management of renal disease in people without diabetes.

There are separate CKS topics on [Diabetes Type 1 and 2 — foot disease](#), [Diabetes Type 1 and 2 — hypertension](#), [Diabetes Type 1 and 2 — retinopathy](#), [Diabetes Type 2 — blood glucose management](#) and [Lipids management](#).

The target audience for this guidance is healthcare professionals working within the NHS in England, and providing first contact or primary health care. *Patient information from NHS Direct* is intended to be printed and given to people with this condition, and the *Shared decision making* sections are designed to provide a focus for discussion during the consultation about the treatment options.

### Changes

**Version 1.0.0, revision planned in 2009.**

**Last revised in October 2006**

**April-June 2006** — reviewed. Validated in September 2006 and issued in October 2006.

This guidance has been reviewed and updated following a full literature review. The scope of the guidance has been extended to include management of diabetic kidney disease in people with Type 1 and Type 2 diabetes and a scenario has been added on screening for diabetic kidney disease. The guidance title has changed from *Diabetes Type 2 — renal disease* to *Diabetes Type 1 and 2 — screening/managing renal disease*.

### Previous changes

**April 2006** — minor update to references. Issued in May 2006.

**October 2005** — minor technical update. Issued in November 2005.

**March 2003** — written. Validated in June 2003 and issued in July 2003.

### Update

#### New evidence

##### Evidence-based guidelines

No new evidence-based guidelines since 1 March 2007.

##### HTAs (Health Technology Assessments)

No new HTAs since 1 March 2007.

##### Economic appraisals

No new economic appraisals relevant to England since 1 March 2007.

##### Systematic reviews and meta-analyses

No new systematic review or meta-analysis since 1 March 2007.

##### Primary evidence

No new high quality randomized controlled trials since 1 March 2007.

### New policies

No new national policies or guidelines since 1 March 2007.

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## New safety alerts

No new safety alerts since 1 March 2007.

## Changes in product availability

No changes in product availability since 1 March 2007.

## Concise knowledge for clinical scenarios

### Which scenario?

- *Screening and diagnosis*: advises on the routine screening of people with diabetes who have not been diagnosed with renal disease and how to confirm the diagnosis if a screening test is positive.
- *Manage diabetic kidney disease*: advises on the management of a person with confirmed diabetic kidney disease, to reduce the disease progression and reduce and cardiovascular disease risk. It also provides information on monitoring of renal impairment and when to refer a person with renal impairment for specialist management.

### Which therapy?

- **Screening for albuminuria and renal impairment in people with diabetes should occur at the time of diagnosis. If there is no evidence of renal disease, screening should be repeated annually.**

#### Screen for albuminuria:

- **The albumin:creatinine ratio (ACR) taken first thing in the morning, is the screening test of choice for albuminuria.** A urine dipstick test (preferably taken first thing the morning) is an alternative if access to ACR testing is not readily available.

#### Confirm microalbuminuria or proteinuria:

- **If the ACR is greater than or equal to 2.5 mg/mmol (men) or 3.5 mg/mmol (women),** repeat the test up to three times. The result is confirmed by two positive tests.
- **If the urine dipstick test is positive,** it is recommended that the diagnosis is confirmed and microalbuminuria distinguished from proteinuria by ACR testing.

#### Check estimated glomerular filtration rate (eGFR)

- Stage renal impairment by eGFR. If renal impairment is present see *follow-up advice*.

#### Confirming the diagnosis of diabetic kidney disease

- **If urinary albumin levels are raised and any degree of diabetic retinopathy is present, a diagnosis of diabetic kidney disease is likely.** If retinopathy is not present, the possibility of a non-diabetic, alternative cause of renal disease should be investigated.
- **If eGFR indicates renal impairment is present in the absence of albuminuria and/or microvascular disease** (e.g. diabetic retinopathy), other causes of renal disease are much more likely.

### Should I refer or investigate?

#### Refer?

- **All people with diabetes should be referred at diagnosis** to a specialist diabetes service, or to a dietician, podiatrist, and retinal screening service, as available.
- **Refer to a nephrologist:**
  - o People with stage 3 renal impairment with:
    - A haemoglobin of less than 11 g/dL due to chronic renal impairment
    - An abnormality of calcium or phosphate confirmed by a repeat fasting test taken without a tourniquet
    - A parathyroid hormone level above 70 ng/L
  - o People presenting with stage 4 or above renal impairment as determined by estimated glomerular filtration rate (eGFR)
  - o People with albuminuria or renal impairment of uncertain origin, including:
    - Albuminuria without diabetic retinopathy
    - Reduced eGFR of uncertain cause

#### Investigate?

- Tests for albuminuria and renal function should be undertaken as detailed in *Which therapy?*
- Where other causes of albuminuria or renal impairment are likely, investigations to exclude these causes should be considered, guided by clinical suspicion.

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- Investigation of the complications of people with stage 3 renal impairment include checking parathyroid hormone level when first diagnosed and monitoring haemoglobin, calcium, and phosphate annually.

### Follow-up advice

- If the diagnosis of diabetic kidney disease or renal impairment is confirmed, management and follow up proceeds as detailed in *Manage diabetic kidney disease*.

### Prescriptions

#### Drug rationale

- There are no prescriptions offered.

### Shared decision making

- Diabetic kidney disease is diagnosed when the level of albumin in the urine is raised and there is no other obvious cause for this.
- Urine tests can detect albumin, and show how much is present in the urine.
- A blood test can show how well the kidneys are functioning. This test is called the estimated glomerular filtration rate (eGFR).

### Which therapy?

#### Management of a person with confirmed diabetic kidney disease involves:

- Initiating an angiotensin-converting enzyme (ACE) inhibitor**, regardless of the blood pressure. If an ACE inhibitor is not tolerated, switch to an angiotensin-II receptor antagonist (AIIRA).
- Managing cardiovascular disease risk factors.** For further information see the CKS topic on *Cardiovascular risk – assessment and management*.
  - Initiate further antihypertensive drugs if blood pressure remains above the threshold of 130/80 mmHg on an ACE or AIIRA (for further information see the CKS topic on *Diabetes Type 1 and 2 – hypertension*):
    - For people without proteinuria**, aim for an ideal target of less than 130/80.
    - For people with proteinuria**, the ideal target is less than 125/75.
  - Manage blood glucose.**
    - The ideal target is to maintain HBA<sub>1c</sub> to less than 6.0% but a target HBA<sub>1c</sub> of between 7.0 and 8.0% is more realistic for most people.** For further information see the CKS topic on *Diabetes Type 2 – blood glucose management*.
  - Start lipid-lowering therapy** and treat to target.
  - Start antiplatelet prophylaxis** for most people with diabetes.
- Monitoring albuminuria and renal function:** see *follow-up advice*.
- Refer* if there is significant renal impairment or complications of renal impairment.

### Practical prescribing points

For further information please see the *Medicines Compendium* ([www.medicines.org.uk](http://www.medicines.org.uk)) or the *British National Formulary* ([www.bnf.org](http://www.bnf.org)).

#### ACE inhibitors or angiotensin-II receptor antagonists (AIIRAs)

- Do not use angiotensin-converting enzyme (ACE) inhibitors or an angiotensin-II receptor antagonist (AIIRA) in pregnancy.** These drugs are also best avoided in breastfeeding, although some sources consider enalapril to be safe if the mother is treated with normal therapeutic doses.
- Before starting an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor antagonist (AIIRA)**, check urea, electrolytes, and estimated glomerular filtration rate (eGFR).
- People at high risk of first-dose hypotension, hyperkalaemia, or renal failure to start treatment in hospital** (if in doubt, discuss with a specialist). This includes people with:
  - Renal impairment, with an estimated glomerular filtration rate (eGFR) level of less than 30 ml/min/1.73m<sup>2</sup>
  - A previous fall in eGFR of greater than 15% following use of an ACE or AIIRA
  - A strong clinical suspicion of renal artery stenosis
  - Hyponatraemia (sodium below 130 mmol/l)
  - Hyperkalaemia (potassium above 6.0 mmol/l)
  - Hypovolaemia
  - Unstable heart failure

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- o Who cannot tolerate withdrawal of high dose diuretic treatment (e.g. more than furosemide 80 mg a day) prior to starting an ACE inhibitor or AIIRA
- o High-dose vasodilator treatment
- **Low-dose start doses should be considered for people who are more prone to adverse effects**, such as elderly, frail, or renally impaired people.
- **Advise people starting an ACE inhibitor or AIIRA at home to take the first dose at bedtime**, as it is best that they lie down if they experience any symptoms of first-dose hypotension such as dizziness.
  - o If the drug is well tolerated, subsequent doses should be taken in the morning.
  - o If symptoms do not subside, the drug should be stopped and the person should return to their doctor.
- **Avoid potassium-sparing diuretics or potassium supplements**, because of the risk of hyperkalaemia.
- **If a person develops a persistent troublesome cough with an ACE inhibitor**, consider switching to an AIIRA.
- **Follow-up** by rechecking urea, electrolytes, and estimated glomerular filtration rate (eGFR) within 2 weeks of starting an ACE or AIIRA.

**Concomitant use of drug formulations with a high sodium content**

- Effervescent compound analgesics should be avoided where possible as they can aggravate hypertension. Note: soluble aspirin contains a relatively small sodium content.

**Should I refer or investigate?**

**Refer?**

**All people with diabetes should be referred at diagnosis** to a specialist diabetes service, or to a dietician, podiatrist, and retinal screening service, as available.

- **Refer to a nephrologist:**
  - o People with stage 3 renal impairment with:
    - A haemoglobin of less than 11 g/dL due to chronic renal impairment
    - An abnormality of calcium or phosphate, confirmed by a repeat fasting test taken without a tourniquet
    - A parathyroid hormone level above 70 ng/L
  - o People with stage 4 or above renal impairment as determined by estimated glomerular filtration rate (eGFR)
  - o People with albuminuria or renal impairment of uncertain origin, including:
    - Albuminuria without diabetic retinopathy
    - Reduced eGFR without albuminuria
- **Women who are pregnant, or planning a pregnancy**, will require treatment to be changed, and therefore need a careful assessment of benefits and risks when the most appropriate antihypertensive drug is selected. CKS therefore recommends that women in this category should be managed by an obstetrician, who may in turn refer to physicians for further management recommendations.

**Investigate?**

- For advice on drug monitoring, see *What do I need to do when starting and monitoring someone on an ACE inhibitor?*

**Follow-up advice**

- **Check urea, electrolytes, and estimated glomerular filtration rate (eGFR) within 2 weeks of starting or increasing an ACE inhibitor or AIIRA and within 2 weeks of subsequent dose increases.**
- **A rise in serum creatinine concentration of more than 20% or fall in eGFR of more than 15%** after initiation or dose increase should be followed by further measurements within 2 weeks.
  - o If deterioration in kidney function is confirmed, seek specialist advice on whether to stop drug treatments or investigate renal artery stenosis.
- **If serum potassium levels rise to above 6.0 mmol/L (hyperkalaemia):**
  - o Nephrotoxic drugs (e.g. NSAIDs) should be stopped
  - o Potassium-retaining diuretics (amiloride, triamterene, spironolactone) should be reduced or stopped
  - o Loop diuretic dosage should be reduced if there is no sign of congestion
- **Consider referring to a dietician:** people not taking any of the aforementioned drugs and those in whom hyperkalaemia persists despite reducing or stopping them. A low-potassium

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diet (such as up to 2 g/day), or dietary advice combined with reducing the ACE inhibitor or AIIRA dose, may help resolve hyperkalaemia in the majority of people [Ahuja et al, 2000].

- **If hyperkalaemia persists, despite appropriate adjustments to other drug treatments, the ACE inhibitor should be stopped.** Note: severe hyperkalaemia (e.g. greater than 8 mmol/L) can cause cardiac arrest and death with very few warning symptoms.
- **Check the blood pressure at each follow-up visit.** Increase the dose of ACE inhibitor or AIIRA up to the standard maintenance dose as long as the drug is tolerated. Recheck urea, electrolytes, and eGFR.

**Also monitor:**

- Albumin:creatinine ratio, annually.
- Estimated glomerular filtration. Frequency of monitoring depends on stage of renal impairment, see [Table 1](#).
- For all people at stage 3 renal impairment, check parathyroid hormone level when first diagnosed and monitor haemoglobin, calcium, and phosphate annually.

**Table 1.** Stages of declining renal function.

Stage of renal function	eGFR ml/min/1.73m <sup>2</sup>	Monitoring
1* – Normal GFR	> 90	Annually
2* – Mild impairment	60 to 89	Annually
3 – Moderate impairment	30 to 59	6-monthly
4 – Severe impairment	15 to 29	3-monthly
5 – Established renal failure	< 15	3-monthly

eGFR, estimated glomerular filtration rate.  
\* The terms stage 1 and 2 are only applied when there is a structural abnormality determined by renal ultrasound or functional abnormality such as persistent proteinuria or haematuria.

## Prescriptions

### Lisinopril tablets: titrate from 2.5mg to 5mg per day

#### Age from 16 years onwards

- Lisinopril 2.5mg 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 28 tablets.
- NHS Cost £1.38
- Licensed use: yes
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

### Enalapril tablets: titrate from 2.5mg to 5mg per day

#### Age from 16 years onwards

- Enalapril 2.5mg 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 28 tablets.
- NHS Cost £1.14
- Licensed use: no
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

### Ramipril capsules: titrate from 1.25mg to 2.5mg per day

#### Age from 16 years onwards

- Ramipril 1.25mg 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 28 capsules.
- NHS Cost £1.96
- Licensed use: no
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

### Irbesartan tablets: titrate from 75mg to 150mg per day

#### Age from 18 years onwards

- Irbesartan 75mg 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 28 tablets.

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- NHS Cost £10.29
- Licensed use: yes
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

**Losartan tablets: titrate from 25mg to 50mg per day**

**Age from 16 years onwards**

- Losartan 25mg 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 28 tablets.
- NHS Cost £18.09
- Licensed use: yes
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

**Lisinopril tablets: titrate from 5mg to 10mg per day**

**Age from 16 years onwards**

- 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 28 tablets.
- NHS Cost £1.64
- Licensed use: yes
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

**Enalapril tablets: titrate from 5mg to 10mg per day**

**Age from 16 years onwards**

- 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 28 tablets.
- NHS Cost £1.56
- Licensed use: no
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

**Ramipril capsules: titrate from 1.25mg to 2.5mg per day**

**Age from 16 years onwards**

- Ramipril 1.25mg 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 28 capsules.
- NHS Cost £1.96
- Licensed use: no
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

**Irbesartan tablets: titrate from 150mg to 300mg per day**

**Age from 18 years onwards**

- 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 28 tablets.
- NHS Cost £12.57
- Licensed use: yes
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

**Losartan tablets: titrate from 50mg to 100mg per day**

**Age from 16 years onwards**

- 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 28 tablets.
- NHS Cost £18.09
- Licensed use: yes
- Patient Information: It is important that you have an appointment with either the doctor or the practice nurse 7 days after starting this prescription.

**Lisinopril tablets: 2.5mg once a day**

**Age from 16 years onwards**

- Lisinopril 2.5mg tablets. Take one tablet once a day. Supply 28 tablets.

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- NHS Cost £1.38
- Licensed use: yes

**Lisinopril tablets: 5mg once a day**

**Age from 16 years onwards**

- Lisinopril 5mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £1.64
- Licensed use: yes

**Lisinopril tablets: 10mg once a day**

**Age from 16 years onwards**

- Lisinopril 10mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £2.10
- Licensed use: yes

**Lisinopril tablets: 20mg once a day**

**Age from 16 years onwards**

- Lisinopril 20mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £2.85
- Licensed use: yes

**Ramipril capsules: 1.25mg once a day**

**Age from 16 years onwards**

- Ramipril 1.25mg capsules. Take one capsule once a day. Supply 28 capsules.
- NHS Cost £1.96
- Licensed use: no

**Ramipril capsules: 2.5mg once a day**

**Age from 16 years onwards**

- Ramipril 2.5mg capsules. Take one capsule once a day. Supply 28 capsules.
- NHS Cost £1.82
- Licensed use: no

**Ramipril capsules: 5mg once a day**

**Age from 16 years onwards**

- Ramipril 5mg capsules. Take one capsule once a day. Supply 28 capsules.
- NHS Cost £2.68
- Licensed use: no

**Enalapril tablets: 2.5mg once a day**

**Age from 16 years onwards**

- Enalapril 2.5mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £1.14
- Licensed use: no

**Enalapril tablets: 5mg once a day**

**Age from 16 years onwards**

- Enalapril 5mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £1.56
- Licensed use: no

**Enalapril tablets: 10mg once a day**

**Age from 16 years onwards**

- Enalapril 10mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £1.69
- Licensed use: no

**Enalapril tablets: 20mg once a day**

**Age from 16 years onwards**

- Enalapril 20mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £1.97

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- Licensed use: no

**Irbesartan tablets: 75mg once a day**

**Age from 18 years onwards**

- Irbesartan 75mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £10.29
- Licensed use: yes

**Irbesartan tablets: 150mg once a day**

**Age from 18 years onwards**

- Irbesartan 150mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £12.57
- Licensed use: yes

**Irbesartan tablets: 300mg once a day**

**Age from 18 years onwards**

- Irbesartan 300mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £16.91
- Licensed use: yes

**Losartan tablets: 25mg once a day**

**Age from 16 years onwards**

- Losartan 25mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £18.09
- Licensed use: yes

**Losartan tablets: 50mg once a day**

**Age from 18 years onwards**

- Losartan 50mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £18.09
- Licensed use: yes

**Losartan tablets: 100mg once a day**

**Age from 18 years onwards**

- Losartan 100mg tablets. Take one tablet once a day. Supply 28 tablets.
- NHS Cost £24.20
- Licensed use: yes

**Drug rationale**

**Drugs not included**

- **Antihypertensive drug classes other than angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (AIIRAs)** are not recommended first-line drugs for people with diabetic kidney disease, as there is a lack of trial data investigating their use in this population.
- **Angiotensin-converting enzyme (ACE) inhibitors other than enalapril, lisinopril, and ramipril** are not included, because there is less trial data concerning their use than for those included. Although there are good trial data to support the effect of captopril, it has a shorter half-life than other ACE inhibitors and needs to be taken in divided doses, and is no longer recommended [[ABPI Medicines Compendium, 2005](#)]. If a person is already taking an ACE inhibitor that is not specifically recommended in this scenario, it seems logical to stay on the ACE prescribed as there is probably a drug class effect.
- **Angiotensin-II receptor antagonists (AIIRAs) other than irbesartan, and losartan** are not included. These are the only two AIIRAs licensed for use in people with diabetic kidney disease and there are trial data to support their use. If a person is already taking an AIIRA that is not specifically recommended in this scenario, it seems logical to stay on the AIIRA prescribed as there is probably a drug class effect.

**Drugs included**

- **Angiotensin-converting enzyme (ACE) inhibitors: enalapril, lisinopril, and ramipril**, are included. Low-dose start prescriptions are preferred for people with renal impairment (as well as elderly or frail people) but standard-dose start options are also offered. There are randomized controlled trial (RCT) data available to support the use of these drugs in people with diabetic kidney disease [[Kshirsagar et al, 2000](#); [ACE Inhibitors in Diabetic](#)

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Nephropathy Trialist Group, 2001; Marre et al, 2004; Newman et al, 2005]. Lisinopril has a licence for the treatment of microalbuminuria in people with Type 2 diabetes, although this only covers people with hypertension [ABPI Medicines Compendium, 2004]. Where possible, titrate an ACE inhibitor to the highest dose tolerated in people with diabetes and microalbuminuria.

- **Angiotensin-II receptor antagonists (AIIRAs) irbesartan, and losartan** are included. They may be used as an alternative to ACE inhibitors in people with a persistent ACE inhibitor-induced cough. Irbesartan and losartan are both licensed for the treatment of diabetic nephropathy and there are trial data to support their use [Brenner et al, 2001; Lewis et al, 2001; Parving et al, 2001]. Where possible, titrate an AIIRA to the highest dose tolerated in people with diabetes and microalbuminuria.
  - o Irbesartan is licensed for the treatment of renal disease (both microalbuminuria and macroalbuminuria) in patients with hypertension and Type 2 diabetes.
  - o Losartan is licensed for the treatment of proteinuria in people with Type 2 diabetes.

**Shared decision making**

- **Treatments for diabetic kidney disease** include the following:
  - o **An angiotensin-converting enzyme (ACE) inhibitor** helps to prevent the progression of the kidney disease. It will also reduce blood pressure.
  - o **An angiotensin-II receptor antagonist (AIIRA)** is an alternative if you have problems with an ACE inhibitor.
  - o **Good control of your blood glucose level** will help to delay the progression of the kidney disease and reduce your risk of developing associated cardiovascular diseases such as heart disease and stroke. Ideally, maintain your HBA<sub>1c</sub> to less than 6.5%.
- **Other treatments to reduce your risk of developing associated cardiovascular diseases** include:
  - o **Drug treatment to lower blood pressure**, if it is not already below 130/80 mmHg.
  - o **Drug treatment to lower your cholesterol level**, whatever the initial level. The aim is whichever of the following gives the greatest reduction:
    - Reducing total cholesterol to less than 4.0 mmol/l *and* low-density lipoprotein (LDL) cholesterol to less than 2.0 mmol/l, OR
    - A 25% reduction in total cholesterol *and* a 30% reduction in LDL cholesterol.
  - o **A daily low dose of aspirin**, depending on your age and other factors. This reduces the risk of blood clots forming.
  - o **Where relevant, encouraging you to tackle lifestyle risk factors**. This means:
    - Stopping smoking if you smoke
    - Eating a healthy diet
    - Keeping your weight and waist in check
    - Taking regular physical activity
    - Cutting back if you drink a lot of alcohol

**Detailed knowledge about this topic**

**Goals and outcome measures**

**Goals**

- To identify at an early point the presence of microalbuminuria or proteinuria
- To prevent or delay progression from microalbuminuria to proteinuria
- To prevent or delay progression of diabetic kidney disease to established renal failure
- To reduce cardiovascular morbidity and mortality

**Quality and outcomes framework indicators**

**Table 2.** Indicators for diabetes in the quality and outcomes framework (QOF) of the General Medical Services (GMS) contract.

Indicator	Points	Maximum threshold
<b>DM 1</b> The practice can produce a register of all people with diabetes mellitus	6	
<b>DM 2</b> The percentage of people with diabetes whose notes record body mass index (BMI) in the previous 15 months	3	40–90%

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<b>DM 3</b> The percentage of people with diabetes in whom there is a record of smoking status in the previous 15 months, except for those who have never smoked, where smoking status should be recorded once	3	25–90%
<b>DM 4</b> The percentage of diabetic people who smoke and whose notes contain a record that smoking cessation advice or referral to a specialist service, where available, has been offered in the last 15 months	5	25–90%
<b>DM 5</b> The percentage of diabetic people who have a record of HbA <sub>1c</sub> or equivalent in the previous 15 months	3	40–90%
<b>DM 6</b> The percentage of people with diabetes in whom the last HbA <sub>1c</sub> is 7.4 or less (or equivalent reference range depending on the local laboratory) in the last 15 months	16	25–50%
<b>DM 7</b> The percentage of people with diabetes in whom the last HbA <sub>1c</sub> is 10 or less (or equivalent reference range depending on the local laboratory) in the last 15 months	11	40–90%
<b>DM 8</b> The percentage of patients with diabetes who have a record of retinal screening in the previous 15 months	5	25–90%
<b>DM 9</b> The percentage of people with diabetes with a record of presence or absence of peripheral pulses in the previous 15 months	3	40–90%
<b>DM 10</b> The percentage of patients with diabetes with a record of neuropathy testing in the previous 15 months	3	40–90%
<b>DM 11</b> The percentage of diabetic people who have a have a record of their blood pressure in the past 15 months	3	40–90%
<b>DM 12</b> The percentage of people with diabetes in whom the last blood pressure is 145/85 mmHg or less	17	40–60%
<b>DM 13</b> The percentage of people with diabetes who have a record of microalbuminuria testing in the previous 15 months (except people with proteinuria)	3	40–90%
<b>DM 14</b> The percentage of people with diabetes who have a record of serum creatinine testing in the previous 15 months	3	25–90%
<b>DM 15</b> The percentage of people with diabetes with a diagnosis of microalbuminuria or proteinuria who are treated with angiotensin-converting enzyme (ACE) inhibitors (or angiotensin-2 receptor blocker)	3	40–80%
<b>DM 16</b> The percentage of people with diabetes who have a record of total cholesterol in the previous 15 months	3	40–90%
<b>DM 17</b> The percentage of people with diabetes whose last measured total cholesterol within previous 15 months is 5 mmol/l or less	6	40–70%
<b>DM 18</b> The percentage of people with diabetes who have had influenza immunization in the preceeding 1 September to	3	40–85%

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31 March		
<b>DM 19</b>	6	
The practice can produce a register of all patients aged 17 years and over with diabetes mellitus, which specifies whether the patient has Type 1 or Type 2 diabetes		
<b>DM 20</b>	17	40–50%
The percentage of patients with diabetes in whom the last HbA1c is 7.5 or less (or equivalent test/reference range depending on local laboratory) in the previous 15 months		
<b>DM 21</b>	5	40–90%
The percentage of patients with diabetes who have a record of retinal screening in the previous 15 months		
<b>DM 22</b>	3	40–90%
The percentage of patients with diabetes who have a record of estimated glomerular filtration rate (eGFR) or serum creatinine testing in the previous 15 months		
<b>CKD 1</b>	6	
The practice can produce a register of patients aged 18 years and over with chronic kidney disease (CKD) (US National Kidney Foundation: Stage 3 to 5 CKD)		
<b>CKD 2</b>	6	40–90%
The percentage of patients on the CKD register whose notes have a record of blood pressure in the previous 15 months		
<b>CKD 3</b>	11	40–70%
The percentage of patients on the CKD register in whom the last blood pressure reading, measured in the last 15 months, is 140/85 or less		
<b>CKD 4</b>	4	40–80%
The percentage of patients on the CKD register with hypertension who are treated with an ACE inhibitor or angiotensin-2 receptor blocker (unless a contraindication or adverse effect has been recorded)		
Data from [NHS Confederation and BMA, 2005; NHS Employers, 2006]		

## Background information

### Glossary

#### Albumin

**Albumin** is a protein present in blood serum that does not normally pass into the glomerular filtrate and on into the urine in significant quantities in the healthy kidney.

#### Albuminuria

**Albuminuria** is defined as a raised albumin excretion greater than 30 mg/day. Microalbuminuria and proteinuria are sub-types of albuminuria.

#### Chronic kidney disease

- **Chronic kidney disease (CKD)** is defined as a persistent impairment of renal function (glomerular filtration rate of less than 90 ml/min/1.73m<sup>2</sup>) with other evidence of chronic kidney damage.
- Other evidence of chronic kidney disease includes:
  - o Persistent microalbuminuria or proteinuria.
  - o Persistent haematuria (after exclusion of other causes, e.g. urological disease).
  - o Structural abnormalities of the kidneys demonstrated on ultrasound scanning or other radiological tests.
  - o Biopsy-proven chronic glomerulonephritis.

#### Diabetic kidney disease

**Diabetic kidney disease** is defined as raised urinary albumin levels in people with diabetes, in the absence of other renal disease. Diabetic renal disease and diabetic nephropathy are synonymous.

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### Established renal failure

**Established renal failure (ERF)** is defined as persistent impaired renal function in a person with a glomerular filtration rate of less than 15 ml/min/1.73m<sup>2</sup> or a person requiring long-term dialysis. End-stage renal disease (ESRD) and end-stage renal failure (ESRF) are synonymous terms.

### Estimated glomerular filtration rate

**Estimated glomerular filtration rate (eGFR):**

- Estimates the volume of blood filtered by the kidneys over a given period of time.
- Is used to assess renal function.
- Is calculated from an individual's age, sex, and serum creatinine concentration and is adjusted in people with African-Caribbean origin.

### Glomerular filtration rate

**Glomerular filtration rate (GFR):**

- Is the volume of blood that is filtered through the kidney in a given period of time.
- Is used as a measure of renal function.
- Is reduced by pathological processes, such as glomerulosclerosis, that replace healthy renal tissue and reduce the number of glomeruli available for filtration.

### Glomerulosclerosis

**Glomerulosclerosis** describes the pathological change in the kidney that occurs with diabetes and other disease processes. Chronic hyperglycaemia leads to irreversible non-enzymatic glycation of proteins that results in protein cross-linking. Accumulation of cross-linked protein in the extracellular matrix is thought to cause ischaemia resulting in fibrosis.

### Glomerulus

**Glomerulus:** a small knot of blood vessels that forms part of the filtration unit of the kidney. Approximately one million are present in the tissue of each healthy kidney.

### Impaired renal function

**Impaired renal function** refers to the loss of capacity of the kidneys to filter a given volume of blood over a given period of time, and can be quantified by measuring the glomerular filtration rate.

### Microalbuminuria

**Microalbuminuria** is defined as a urinary albumin excretion of between 30 mg/day and 300 mg/day. Incipient nephropathy is a synonymous term.

### Normoalbuminuria

**Normoalbuminuria** is the level of albumin excretion by the healthy kidney that is considered to be normal, and is defined as urinary albumin excretion of less than 30 mg/day.

### Proteinuria

**Proteinuria** is defined as a raised urinary albumin excretion greater than 300 mg/day. Macroalbuminuria, overt nephropathy, and nephropathy are synonymous terms.

### Serum creatinine concentration

**Creatinine** is a breakdown product of skeletal muscle that is excreted by the kidney:

- Its serum concentration varies between individuals with normal renal function, in proportional to their muscle mass, and hence the 'normal' reference range for a population is broad.
- Its concentration in an individual increases with declining renal function.
- The serum creatinine concentration generally does not increase above the normal reference range until renal function has declined by 50%.
- Even a modest rise in creatine concentration above the reference range is indicative of significant renal impairment.

### What is it?

- **Diabetic kidney disease is defined as abnormal quantities of albumin in the urine (albuminuria) in people with diabetes**, in the absence of other renal disease.
- **Diabetic kidney disease is categorized by the quantity of albumin lost in the urine in a 24-hour period:**
  - o **Microalbuminuria** is defined as a urinary albumin loss of between 30 mg/day and 300 mg/day.

- o **Proteinuria** is defined as a urinary albumin loss greater than 300 mg/day.

[Bilous, 2003]

## Pathophysiology

**Hyperglycaemia is the underlying cause of the pathological changes of diabetic kidney disease, characterized by glomerulosclerosis and albuminuria.**

### Glomerulosclerosis

- Chronic hyperglycaemia leads to irreversible non-enzymatic glycation of proteins that results in protein cross-linking. Accumulation of cross-linked protein within the extracellular matrix of the kidney is thought to cause ischaemia, resulting in glomerulosclerosis.
- With progression of disease, glomerulosclerosis progressively replaces healthy renal tissue, which results in reduced capacity of the kidneys to filter the blood and is reflected by a progressive fall in glomerular filtration rate.

### Albuminuria

- Albumin normally remains within the blood passing through the glomerulus of the healthy kidney.
- Hyperglycaemia leads to increased levels of vasoactive substances within the kidney, including angiotensin II.
- These vasoactive substances increase the filtration pressure and permeability of vascular endothelium in the glomerulus, allowing albumin to pass into the glomerular filtrate and be excreted in the urine.
- The development of systemic hypertension causes a further rise in filtration pressure in the glomerulus with a consequent increase in urinary albumin loss.
- **Microalbuminuria** is the earliest indicator of diabetic kidney disease. It may revert to normoalbuminuria, persist, or progress to proteinuria.
- **Proteinuria is irreversible** and marks the beginning of a progressive linear worsening in renal function and albumin excretion, progressing to established renal failure in people who survive long enough.

### What causes hypertension in people with diabetes?

- **In people with Type 1 diabetes**, the development of diabetic kidney disease correlates with a progressive increase in blood pressure. The blood pressure initially remains within normal limits but may eventually increase to levels diagnostic of hypertension years after the diagnosis of diabetes. It is not clear whether observed changes in blood pressure initiate the nephropathic process or occur as a result of it.
- **In people with Type 2 diabetes**, hypertension is a common presenting feature because the underlying mechanism causing diabetes is also thought to increase the risk of hypertension.
  - o People with Type 2 diabetes are resistant to the glucose-lowering effects of insulin. Compensatory high levels of insulin increase sodium retention by the kidney which tends to increase blood pressure.
  - o Compensatory mechanisms resist this effect, but in susceptible individuals these mechanisms fail and hypertension develops.
  - o Glomerulosclerosis may also develop, adding a further cause of development of hypertension.

### Why is diabetic kidney disease associated with diabetic retinopathy and cardiovascular disease?

- Albuminuria is strongly associated with the development of cardiovascular disease and diabetic retinopathy.
- Increases in permeability of the vascular endothelium seen in the glomeruli are also thought to occur in other blood vessels throughout the body. In retinal blood vessels this is thought to play a role in the development of diabetic retinopathy, as well as playing a role in the formation of atheroma in larger blood vessels, causing cardiovascular disease.

[Bilous, 2003; Gilbert and Cooper, 2003]

## How common is it?

### For people with Type 2 diabetes:

- At the time of diagnosis, figures from the UK Prospective Diabetes Study (UKPDS) suggest that about 12% of people have microalbuminuria and 1.9% have proteinuria [Turner et al, 1998].
- In those people who have normoalbuminuria at diagnosis, microalbuminuria develops in approximately 15% and proteinuria in 5% within 5 years.
- Prevalence of microalbuminuria in all people with Type 2 diabetes ranges from 8% to 32%; most estimates are around 25%.
- Prevalence of proteinuria in all people with Type 2 diabetes ranges from 5% to 19%.

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**Clinical Knowledge Summaries: Previous version – Diabetes Type 1 and 2 – screening/managing renal disease**

- The prevalence in Asian and black people (of African or Caribbean ethnicity) with diabetes progressing to established renal failure is approximately six times higher than in a population of white people with diabetes.

[NHS CRD, 2000; SIGN, 2001; McIntosh et al, 2002]

**For people with Type 1 diabetes:**

- Microalbuminuria or proteinuria is rarely present at the time of diagnosis [American Diabetes Association, 2002].
- The prevalence of microalbuminuria 5 years after the diagnosis of Type 1 diabetes is approximately 14%.
- The prevalence of microalbuminuria in all people with Type 1 diabetes is approximately 27%.
- The prevalence of proteinuria in people with Type 1 diabetes at 15–29 years' duration is approximately 18% (95% CI 11 to 24%).

[Harvey et al, 2001]

**How do I know my patient has it?**

**Screening for renal disease in people with diabetes should be done at the time of diagnosis. If there is no evidence of renal disease, screening should be repeated annually.**

- **Diabetic kidney disease is detected by:**
  - o Screening for the *presence of microalbuminuria or proteinuria*.
  - o Assessing *renal function* (by measuring serum creatinine and calculating the estimated glomerular filtration rate).
- **Diabetic kidney disease is diagnosed** when urinary albumin levels are *confirmed* to be raised and there is no other obvious cause for this:
  - o If urinary albumin levels are raised and any degree of diabetic retinopathy is present, a diagnosis of diabetic kidney disease is likely. If retinopathy is not present, the possibility of a non-diabetic cause of renal disease should be investigated.
  - o If renal function is impaired (as assessed by the estimated glomerular filtration rate) and albuminuria and/or microvascular disease is absent (e.g. diabetic retinopathy), other causes of renal disease are much more likely and the cause should be investigated.
- **For information on monitoring of people who are found to have renal disease**, see *How should I monitor someone with diabetic kidney disease?*

[McIntosh et al, 2002; NICE, 2004]

**Screening for and diagnosing albuminuria**

**Screening for albuminuria in people with diabetes**

- **This should be done at the time of diagnosis of diabetes and at least annually afterwards.**
- **The urinary albumin:creatinine ratio (ACR) is the preferred screening and diagnostic test.**
- **A urine dipstick test** is a reasonable alternative as an initial screening test for albuminuria, if the ACR test is not readily available.
- **For both the ACR and urine dipstick test, a first-morning urine sample should be used** because the composition of the urine is least variable first thing in the morning after rising from sleep. This occurs because:
  - o The concentration of albumin in the urine varies with the volume of urine produced.
  - o Albumin excretion is increased following exercise and with upright posture.
- If the urine dipstick test is positive it is recommended that the diagnosis is confirmed and microalbuminuria distinguished from proteinuria by ACR testing.
- If the ACR is greater than or equal to 2.5 mg/mmol (men) or 3.5 mg/mmol (women), repeat the ACR test up to three times.

**Diagnosing microalbuminuria and proteinuria**

- **Persistent microalbuminuria is diagnosed** if at least two ACR tests are:
  - o Between 2.5 mg/mmol and 30 mg/mmol in men.
  - o Between 3.5 mg/mmol and 30 mg/mmol in women.
- **Proteinuria is diagnosed** if at least two ACR tests are above 30 mg/mmol in men or women.
- **For information on monitoring people with albuminuria**, see *How should I monitor someone with diabetic kidney disease?*

[McIntosh et al, 2002; NICE, 2004; Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and The Renal Association, 2006]

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#### Urinary albumin:creatinine ratio

- **The albumin:creatinine ratio (ACR)** measured from a urine sample taken first thing in the morning is a suitable test for screening for, and diagnosing, microalbuminuria and proteinuria.
- It is calculated from the concentration of albumin and creatinine in the urine.
- It closely correlates with the 24-hour albumin excretion rate (AER).
  - It has high sensitivity and specificity using the 24-hour AER as the gold standard.
  - It more accurately correlates with the 24-hour AER than urine dipstick tests (which assess the concentration of urinary albumin alone). This is because the ACR is little affected by urine concentration, unlike urine dipstick tests.
- Analysers to determine the ACR are available for use in a primary care setting, but where these are not available a first-morning urine sample will have to be sent to the local laboratory.

[McIntosh et al, 2002]

#### Urine dipstick test

- A urine dipstick test for microalbuminuria of a sample of urine passed first thing in the morning has acceptable sensitivity and specificity as a screening test for the presence of albumin in the urine, and is cheap and easily carried out.
- It is less favoured than the urinary albumin:creatinine ratio (ACR) because it does not correlate as well with the 24-hour albumin excretion rate (AER).
  - Whereas the 24-hour AER remains relatively constant from day to day, the urinary albumin concentration varies with the volume of urine produced, which alters depending on how much the person has previously drunk.
  - It gives a positive result if either microalbuminuria or proteinuria is present but cannot be used to accurately distinguish between them.
- Regarding the dipstick tests available for detecting albuminuria, there are adequate data to evaluate the Micral-Test II, the Microbumintest and the Albustix test. Of these, only the Micral-Test II performed adequately at detecting microalbuminuria. Using radioimmunoassay with a timed 24 hour sample as a reference standard, the sensitivity of the Micral-Test II is 93% and the specificity is 93% for detecting urinary albumin levels of 20 mg/l (microalbuminuria).

[McIntosh et al, 2002]

#### 24-hour albumin excretion rate

- The 24-hour albumin excretion rate (AER), assessed by radioimmunoassay, is considered to be the gold standard test for albuminuria. However, it is expensive and time-consuming and is not considered suitable as a screening test and is rarely used for diagnosis.
- It accurately measures the quantity of albumin lost in the urine in a 24-hour period (calculated from the volume of urine collected in 24 hours and the urinary albumin concentration).

[McIntosh et al, 2002]

#### Assessing renal function

**The estimated glomerular filtration rate (eGFR) should be used to assess the renal function of all people with diabetes, at the time of diagnosis. If there is no evidence of renal impairment, screening should be repeated annually.**

##### Assessing serum creatinine and eGFR

- **The eGFR is now preferred to measurement of serum creatinine alone for assessment of renal function**, because:
  - It is a more sensitive test for detecting early renal impairment. Serum creatinine increases as renal function declines but only rises above the reference range when the glomerular filtration rate falls by approximately 50% for most people.
  - The rate declines in proportion to the decline in renal function.
  - Comparison can be made between individuals, allowing for staging of declining renal function.
- **The eGFR is calculated from the serum creatinine concentration, the age, and the sex of the individual**, and is adjusted in people of African-Caribbean origin.
- **The eGFR cannot be accurately estimated in people with abnormal muscle mass**, including the following conditions/groups:
  - Muscle-wasting states
  - Amputees
  - Malnutrition
  - Pregnancy

**Clinical Knowledge Summaries: Previous version – Diabetes Type 1 and 2 – screening/managing renal disease**

- o Acute renal failure
- o Oedematous states
- o Children
- **Stages of declining renal function** defined by eGFR are given in [Table 3](#).
- **For information on monitoring people with renal impairment**, see [How should I monitor someone with diabetic kidney disease?](#)

**Table 3.** Stages of declining renal function.

Stage of renal function	eGFR, ml/min/1.73m <sup>2</sup>
1* – Normal GFR	> 90
2* – Mild impairment	60 to 89
3 – Moderate impairment	30 to 59
4 – Severe impairment	15 to 29
5 – Established renal failure	< 15

eGFR, estimated glomerular filtration rate  
\* The terms stage 1 and 2 are only applied when there is a structural abnormality determined by renal ultrasound or functional abnormality such as persistent proteinuria or haematuria.

[[Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and The Renal Association, 2006](#)]

**What are the risk factors for the development and progression of diabetic kidney disease?**

- **Risk factors associated with the onset of microalbuminuria** have been investigated by two well-conducted prospective studies.
  - o Baseline characteristics of people who developed microalbuminuria were compared with the baseline characteristics of those who did not. All people were normoalbuminuric at the time of diagnosis.
    - In the first trial, 4097 people with type 1 diabetes and 6513 people with Type 2 diabetes were studied over a 4.6-year period [[Cederholm et al, 2005](#)].
    - In the second trial, 286 people with Type 1 diabetes were studied over a median of 18 years [[Hovind et al, 2004](#)].
  - o **The most significant factors associated with the development of microalbuminuria** in people with Type 1 and Type 2 diabetes, found by these trials, were:
    - Higher levels of HbA<sub>1c</sub>
    - Increasing duration of diabetes
    - Higher systolic and diastolic blood pressures
    - A raised body mass index
    - Male sex
- **Risk factors associated with the progression of diabetic kidney disease** in people with established disease include [[Vaugh and Robertson, 1997](#); [Ayodele et al, 2004](#); [Newman et al, 2005](#)]:
  - o Higher levels of HbA<sub>1c</sub>
  - o Higher systolic and diastolic blood pressures
  - o Cigarette smoking
  - o High-protein diet in people with Type 1 diabetes
  - o Dyslipidaemia

**What else might it be?**

- A single positive result for albuminuria may also indicate:
  - o Urinary tract infection
  - o Other renal pathology
  - o Severe hyperglycaemia
  - o Intercurrent cardiac failure
  - o Contamination with blood
  - o Vigorous exercise

**Complications and prognosis**

**Complications**

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**Clinical Knowledge Summaries: Previous version – Diabetes Type 1 and 2 – screening/managing renal disease**

- **Established renal failure (ERF):**
  - Once proteinuria develops, renal function progressively declines. Years of declining renal function eventually end in ERF in people who do not die from other causes.
  - People with Type 2 diabetes generally develop diabetes later in life when the risk of cardiovascular disease (CVD) is higher. Compared with people with Type 1 diabetes, people with Type 2 diabetes and proteinuria are more likely to die from other causes, particularly heart disease, before ERF develops.
  - ERF develops in 50% of people with Type 1 diabetes within 10 years of developing proteinuria.
- **Cardiovascular disease:**
  - For people with diabetes, the risk of cardiovascular disease (CVD) is substantially higher than for the general population.
  - For people with diabetes who develop diabetic kidney disease, the risk of CVD is increased even further. Compared with people with diabetes who do not have diabetic kidney disease:
    - People with microalbuminuria have between a twofold to fourfold increased risk of developing cardiovascular disease.
    - People with with proteinuria have between a fivefold to eightfold increased risk of developing CVD.

[Lotufo et al, 2001; Ayodele et al, 2004]

### Prognosis

- The natural history of diabetic kidney disease is progression from microalbuminuria, to proteinuria with a progressive fall in glomerular filtration rate (GFR), leading to established renal failure (ERF).
- In people with microalbuminuria, there is a fivefold increased risk of ERF in people with Type 1 diabetes, and an approximate fourfold increased risk in people with Type 2 diabetes [Newman et al, 2005].
- Microalbuminuria can revert to normoalbuminuria, and this is more likely with treatment. Reversion to normoalbuminuria was associated with younger age, HbA<sub>1c</sub> of less than 8%, and a systolic blood pressure of less than 115 mmHg, in a cohort of 386 people with microalbuminuria followed up for 6 years [Perkins et al, 2003]:
  - Approximately 60% reverted to normoalbuminuria
  - Approximately 10% persisted with microalbuminuria
  - Approximately 20 progressed to proteinuria
- The development of proteinuria is irreversible, and once it has developed there is a steady progressive decline in renal function.
- Mortality and morbidity, particularly from cardiovascular disease (CVD), worsen with disease progression.
  - In people with Type 1 or Type 2 diabetes and microalbuminuria, there is a twofold increased risk of all-cause and cardiovascular mortality compared with those with normoalbuminuria [Newman et al, 2005].
  - People with end-stage renal failure (ESRF) receiving dialysis in the United States have an expected survival of between 4 and 5 years, with most deaths occurring from cardiovascular disease or infection.

[NHS CRD, 2000; Ayodele et al, 2004; Newman et al, 2005]

### Management issues

#### Overview of management

**For a person with diabetes without known kidney disease:**

- *Screen* annually for albuminuria and renal impairment.

**For a person with diabetic kidney disease:**

- Start an *angiotensin-converting enzyme (ACE) inhibitor*, irrespective of baseline blood pressure. If an ACE inhibitor is not tolerated, switch to an angiotensin-II receptor antagonist (AIIRA).
- Manage cardiovascular risk factors.
  - For people *without* proteinuria, add further antihypertensive drugs as required to maintain the blood pressure below 130/80 mmHg.
  - For people *with* proteinuria, add further antihypertensive drugs as required to maintain the blood pressure below 125/75 mmHg.
  - Ensure good glycaemic control, with an HbA<sub>1c</sub> ideally less than 6.0%.
  - Start *lipid-lowering therapy* and treat to target.

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- o Start *antiplatelet prophylaxis*.
- o Advise lifestyle changes, where appropriate (such as smoking cessation, weight control, diet, and exercise). See the CKS topic on *Cardiovascular risk – assessment and management* for further information.
- *Monitor renal function* regularly.
- *Refer* for specialist assessment if renal function is significantly impaired.

### What interventions improve the prognosis of people with diabetic kidney disease?

- **The main goals in managing people with diabetic kidney disease** are to:
  - o **Reduce cardiovascular risk**
  - o **Prevent or delay the development of renal failure**
- Cardiovascular disease accounts for most of the morbidity and mortality associated with diabetic kidney disease.
- Mortality and morbidity, particularly from cardiovascular disease (CVD), worsens with disease progression.
- **Interventions recommended mainly to reduce progression of diabetic kidney disease** are:
  - o *Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists*
- **Interventions recommended to reduce both progression of diabetic kidney disease and cardiovascular disease risk** are:
  - o *Strict control of blood pressure*
  - o *Strict glycaemic control*
- **Additional interventions recommended mainly to reduce the risk of cardiovascular disease** are:
  - o *Lipid-lowering therapy*
  - o *Antiplatelet prophylaxis*
  - o Modification of lifestyle factors that increase cardiovascular disease risk, including smoking, obesity, poor diet, excessive alcohol consumption, and lack of exercise. See the CKS topic on *Cardiovascular risk – assessment and management* for further information.

### When is an ACE inhibitor or angiotensin-II receptor antagonist recommended?

- **Start an angiotensin-converting enzyme (ACE) inhibitor (unless contraindicated) in all people with diabetic kidney disease**, regardless of their blood pressure.
- **An angiotensin-II receptor antagonist (AIIRA) is an alternative if an ACE inhibitor is not tolerated.**
- There is *evidence* that, in people with diabetic kidney disease, ACE inhibitors in particular:
  - o Prevent development of proteinuria
  - o Increase regression to normoalbuminuria
  - o Have possible mortality reduction and additional cardioprotective benefit
- There is limited *evidence* that, in people with diabetic kidney disease, AIIRAs:
  - o Prevent development of proteinuria
  - o Reduce progression to end-stage renal failure
- **Combining an ACE and AIIRA is not recommended** in primary care, although some specialists may initiate this treatment, as there is insufficient *evidence* to support this strategy in people with diabetic kidney disease.

### What is the target blood pressure?

- It is recommended that an angiotensin-converting (ACE) inhibitor or angiotensin-II receptor antagonist is offered to all people with diabetic kidney disease for renal and cardiovascular protection.
- Additional antihypertensive drugs should be considered if blood pressure continues to be greater than or equal to a treatment threshold of 130/80 mmHg. For further information on managing blood pressure see the CKS topic on *Diabetes Type 1 and 2 – hypertension*.

### Optimal treatment targets

- **For people with diabetes without proteinuria: an optimal treatment target of less than 130/80 mmHg** is recommended by the British Hypertension Society and the Joint British Societies following an assessment of the *evidence*.
- **For people with diabetes and proteinuria: an optimal treatment target of less than 125/75 mmHg** is recommended by many experts. This recommendation is supported by an assessment of the *evidence* by the British Hypertensive Society.

#### Audit blood pressure standards

- It is recognized that the optimal blood pressure target may be difficult to achieve in some individuals, particularly elderly people.
  - A blood pressure of less than 140/80 mmHg has been recommended by the Joint British Societies as an audit blood pressure standard.
  - A blood pressure of 145/85 mmHg or less is used as the quality indicator in the Quality and Outcomes Framework.

[Williams et al, 2004; Joint British Societies, 2005; Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and The Renal Association, 2006]

#### What is the HbA1c treatment target?

- **The ideal target for glycaemic control in people with Type 1 and 2 diabetes is normoglycaemia (fasting glucose of less than or equal to 6 mmol/l), with avoidance of hypoglycaemia and decompensated hyperglycaemia. Optimal clinical management targets are normal HbA1c (less than 6%) and fasting or preprandial glucose values of less than 6 mmol/l [Joint British Societies, 2005].**
- These recommendations are based upon *evidence for HbA1c targets* that demonstrates:
  - The risk of developing diabetic kidney disease and diabetic retinopathy is low once average HbA1c is between 7.0% and 8.0%
  - The risk of cardiovascular disease continues to reduce, the closer the HbA1c is to normal.
  - For further information on glucose management, see the CKS topic on *Diabetes Type 2 – blood glucose management*.
- **It is recognized that such a strict HbA1c target is difficult to achieve and increases the risk of potentially serious hypoglycaemic episodes.** A HbA1c target of between 7.0% and 8.0% will be more realistically achievable for most people and less likely to cause hypoglycaemic episodes.

#### When is lipid-lowering therapy recommended?

- **Offer lipid-lowering therapy to all people with diabetic kidney disease**, for the following reasons:
  - The National Institute for Health and Clinical Excellence (NICE) recommends that lipid-lowering therapy should be considered in people with diabetes who have established cardiovascular disease (CVD) or who are at high risk of cardiovascular disease (estimated 10-year CVD risk of 20% or more) [NICE, 2006].
  - Updated Joint British Societies (JBS) risk charts apply only to individuals without diabetes, as most people with diabetes are likely to be at considerably increased risk of CVD [Joint British Societies, 2005].
  - People with diabetic kidney disease are at considerably increased cardiovascular risk, and recommendations from the JBS are that all such people should be offered lipid-lowering therapy.
- **Optimal targets for lipid reduction recommended by the JBS are one of the following (whichever results in the lowest absolute values):**
  - Total cholesterol less than 4.0 mmol/l and low-density lipoprotein (LDL) cholesterol less than 2.0 mmol/l or;
  - A 25% reduction in total cholesterol and a 30% reduction in LDL cholesterol.
- **Audit targets for lipid reduction** are higher than the optimal treatment targets (which are difficult to reach in some people):
  - Total cholesterol less than 5.0 mmol/l.
  - LDL cholesterol less 3.0 mmol/l.
- **For further information on lipid-lowering management**, including the supporting evidence for these recommendations, see the CKS topic on *Lipids management*.

#### When is antiplatelet prophylaxis recommended?

- **Antiplatelet prophylaxis should be offered to all people with diabetic kidney disease**, as they are at high cardiovascular risk [Joint British Societies, 2005].
- In people without established cardiovascular disease, it is recommended that blood pressure first be controlled to at least 150/90 mmHg. From primary prevention trials, there is evidence that antiplatelets provide little cardiovascular protection in individuals with poorly controlled hypertension and therefore risks may outweigh any benefits [Hayden et al, 2002].
- Low-dose aspirin (75 mg once daily) is the usual first-line choice.
- For further information on the use of antiplatelet prophylaxis, including the supporting evidence for these recommendations and advice on what to do if a person is allergic to

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aspirin or is at risk of gastrointestinal adverse effects, see the CKS topic on [Antiplatelet treatment](#).

- If atrial fibrillation is present, warfarin may be a better choice (for further information see the CKS topic on [Atrial fibrillation](#)).

**Should I recommend protein restriction to people with diabetic kidney disease?**

- **Effectiveness of dietary protein restriction to reduce the progression of diabetic kidney disease is controversial** [[Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and The Renal Association, 2006](#)].
- **Present evidence does not support routinely recommending protein restriction to all people with diabetic kidney disease in primary care.** This intervention is probably best reserved for specialist management of people with Type 1 diabetes with renal impairment, under the supervision of a dietician.
- **Limited evidence from a Cochrane review** found that for people with Type 1 diabetes, restriction of dietary protein to between 0.3 and 0.8 g/kg per day, had a statistically significant but small clinical effect in slowing the decline in glomerular filtration rate [[Waugh and Robertson, 1997](#)].
- **For people with Type 2 diabetes**, no studies were identified that examined the effect of this intervention on the progression of diabetic kidney disease. Even if the intervention were shown to be beneficial, the number of people with Type 2 diabetes who might benefit would be small. This is because only a small proportion of people with Type 2 diabetes progress to established renal failure, since they generally develop diabetes later in life compared with people with Type 1 diabetes.

**How should I monitor someone with diabetic kidney disease?**

- **All people with diabetes who are not known to have diabetic kidney disease should have their estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR) assessed annually.**
- **All people with diabetic kidney disease should have their ACR checked at least annually and their eGFR checked annually, or more frequently depending on the severity of the impairment.**

**Monitoring ACR:**

- Microalbuminuria may revert to normoalbuminuria, particularly in people with strict blood pressure and glycaemic control. However, proteinuria is irreversible and marks the onset of a progressive decline in renal function as assessed by eGFR.
- Monitoring of someone with albuminuria allows proteinuria to be identified when it develops and allows the progression of the disease process to be followed. Once proteinuria develops, stricter blood pressure targets of less than 125/75 are recommended.

**Monitoring eGFR and serum creatinine:**

- The eGFR calculated from the serum creatinine concentration is now recommended for staging the impairment in renal function. This is preferred to the measurement of serum creatinine alone for assessing renal function because it is more sensitive at detecting early renal impairment.
- If the eGFR is reduced, stage the decline of renal function and monitor function depending on the stage – see [Table 4](#).
- For all people at stage 3:
  - o Monitor haemoglobin, calcium, and phosphate annually.
  - o Check parathyroid hormone level when stage 3 renal impairment is first diagnosed.
- For people at stage 4 renal impairment see [When should I refer to a nephrologist?](#)

**Table 4.** Stages of declining renal function.

Stage of renal function	eGFR ml/min/1.73m <sup>2</sup>	Monitoring
1* – Normal GFR	> 90	Annually
2* – Mild impairment	60 to 89	Annually
3 – Moderate impairment	30 to 59	6-monthly
4 – Severe impairment	15 to 29	3-monthly
5 – Established renal failure	< 15	3-monthly

eGFR, estimated glomerular filtration rate.  
\* The terms stage 1 and 2 are only applied when there is a structural abnormality determined by renal ultrasound or functional abnormality such as persistent proteinuria or haematuria.

[[Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and The Renal Association, 2006](#)]

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### When should I refer to a nephrologist?

- **It is recommended that people with significant renal impairment are managed by a nephrologist.** Whether there is direct referral or referral via local specialist diabetic services will depend on local availability.
- **Refer all people with:**
  - Stage 4 and above renal impairment
  - People with a haemoglobin of less than 11 g/dL due to chronic renal impairment
  - People with an abnormality of calcium or phosphate confirmed by a repeat fasting test taken without a tourniquet
  - People with a parathyroid hormone level above 70 ng/l

[Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and The Renal Association, 2006]

### How should I manage women of childbearing age?

- **Women who are pregnant, or planning a pregnancy,** will require a change in treatment, and therefore need a careful assessment of benefits and risks when selecting the most appropriate antihypertensive drug. It is recommended that these women should be referred to both an obstetrician and physician for further management.

### Medicines management

Important aspects of medicines management relevant to primary health care are covered in this section for the drugs that are recommended in this guidance. For more comprehensive information on contraindications, cautions, drug interactions, and adverse effects, see the Medicines Compendium ([www.medicines.org.uk](http://www.medicines.org.uk)), or the British National Formulary ([www.bnf.org](http://www.bnf.org)).

### ACE inhibitors

#### *Which ACE inhibitors are recommended?*

- **CKS recommends enalapril, lisinopril, or ramipril** for people with diabetic kidney disease, as there are data from randomized controlled trials to support the use of these angiotensin-converting enzyme (ACE) inhibitors in people with diabetic kidney disease [Kshirsagar et al, 2000; ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001; Marre et al, 2004; Newman et al, 2005]. Lisinopril has a licence for the treatment of microalbuminuria in people with Type 2 diabetes, although this only covers people with hypertension [ABPI Medicines Compendium, 2004].
- **All ACE inhibitors** are likely to be equally effective in the treatment of diabetic kidney disease, as they probably exhibit a class effect.
- **Captopril is no longer recommended:** although it is licensed for use in people with diabetic kidney disease and there is good evidence available to prove its effect, it has a shorter half-life than other ACE inhibitors and needs to be taken in divided doses [ABPI Medicines Compendium, 2005].
- If a person is already taking an ACE inhibitor that is not specifically recommended, it seems logical to stay on the ACE prescribed as there is probably a class effect of these drugs.

#### *Who should avoid taking ACE inhibitors?*

#### **Angiotensin-converting enzyme (ACE) inhibitors should be avoided in:**

- People with a history of anuria or angioedema with previous exposure to the drug.
- Pregnant women — ACE inhibitors should be avoided throughout pregnancy as they may cause fetal or neonatal injury or death.
- Breastfeeding women — there is a lack of safety data, and manufacturers recommend avoidance. Note: some sources consider enalapril to be safe if the mother is treated with normal therapeutic doses [UKMiCentral, 2003].
- People with bilateral renal stenosis — ACE inhibitors may cause renal failure.
- People with cardiogenic shock.

#### *What do I need to do when starting and monitoring someone on an ACE inhibitor?*

- **Before starting an angiotensin-converting enzyme (ACE) inhibitor:**
  - Stop diuretics, if possible, 1–2 days before starting treatment.
  - Check urea and electrolytes, and estimated glomerular filtration rate (eGFR).
- **People at high risk of first-dose hypotension, hyperkalaemia, or renal failure should start ACE inhibitor treatment in hospital** (if in doubt, discuss with a specialist). This includes people with:
  - Renal impairment, with an eGFR level of less than 30 ml/min/1.73m<sup>2</sup>
  - A previous fall in eGFR of greater than 15% following use of an ACE inhibitor

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- o A strong clinical suspicion of renal artery stenosis
- o Hyponatraemia (sodium below 130 mmol/l)
- o Hyperkalaemia (potassium above 6.0 mmol/l)
- o Hypovolaemia
- o Unstable heart failure
- o Who cannot tolerate withdrawal of high dose diuretic treatment (e.g. more than furosemide 80 mg a day) prior to starting an ACE inhibitor
- o High-dose vasodilator treatment
- **A low starting dose of ACE inhibitor** should be used in people who are more prone to adverse effects (such as elderly, frail, or renally impaired people).
- **Advise people starting an ACE inhibitor at home to take the first dose in the evening:**
  - o If the drug is well tolerated, subsequent doses should be taken in the morning.
  - o If symptoms of hypotension occur, advise them to go to bed and take no further doses until they have been reviewed by their doctor.
- **Recheck the urea, electrolytes, and the eGFR within 2 weeks of starting or increasing the dose of an ACE inhibitor:**
  - o **A rise in serum creatinine concentration of more than 20% or a fall in the eGFR of more than 15%** after initiation or dose increase should be followed by further measurements within 2 weeks. If deterioration in kidney function is confirmed, seek specialist advice on whether to stop drug treatments or investigate renal artery stenosis.
  - o **If serum potassium levels rise to above 6.0 mmol/l (hyperkalaemia):**
    - Stop nephrotoxic drugs (e.g. nonsteroidal anti-inflammatory drugs).
    - Stop or reduce dose of potassium-retaining diuretics (amiloride, triamterene, spironolactone).
    - Stop or reduce the dose of loop diuretics if there are no signs of congestion.
  - o **Consider referring to a dietician:** people not taking any of the aforementioned drugs and those in whom hyperkalaemia persists despite reducing or stopping them. A low-potassium diet (such as up to 2 g/day), or dietary advice combined with reducing the ACE inhibitor dose, may help resolve hyperkalaemia in the majority of people [[Ahuja et al, 2000](#)].
  - o **If hyperkalaemia persists, despite appropriate adjustments to other drug treatments, the ACE inhibitor should be stopped.** Note: severe hyperkalaemia (e.g. greater than 8 mmol/L) can cause cardiac arrest and death with very few warning symptoms.
- **Check the blood pressure at each follow-up visit.** Increase the dose of ACE inhibitor up to the standard maintenance dose as long as the drug is tolerated. Recheck urea, electrolytes, and eGFR.
  - o Within 2 weeks after subsequent increases.
  - o During severe intercurrent illness, particularly if there is a risk of hypovolaemia.
  - o Annually thereafter (unless required more frequently because of impaired renal function).

[[Joint Specialty Committee on Renal Medicine of the Royal College of Physicians and The Renal Association, 2006](#)]

**What are the adverse effects of ACE inhibitors?**

- **Dizziness, headaches, and hypotension** are the most common adverse effects of angiotensin-converting enzyme (ACE) inhibitors. Note: if hypotension is symptomatic, consider seeking expert advice and monitor closely.
- **First-dose hypotension** (causing dizziness, light-headedness, or confusion).
- **Deterioration in renal function** may occur, and requires careful monitoring.
- **Cough** can develop in a small number of people. In some people this is tolerated and in others it may be painful or disruptive enough to require a change in treatment:
  - o Pooled trial data suggests a 4% incidence of cough with ACE inhibitors, although the incidence may be higher in routine clinical practice [[Law et al, 2003](#)].
  - o Consider other causes of cough (e.g. smoking-related lung disease, the development of heart failure).
  - o If a person develops a dry cough that disturbs sleep, and other causes have been ruled out, consider switching to an angiotensin-II receptor antagonist (AIIRA).
- **Hyperkalaemia** can occur, for more information see [What do I need to do when starting and monitoring someone on an ACE inhibitor?](#)

**What drug interactions can occur with ACE inhibitors?**

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- Table 5 lists drug interactions to consider when prescribing an angiotensin-converting enzyme (ACE) inhibitor.

**Table 5.** Managing key drug interactions of angiotensin-converting enzyme (ACE) inhibitors.

Interacting drugs	Outcome effect	Action to take
Alcohol, alprostadil, antipsychotics, antidepressants (possibly), anxiolytics, hypnotics, levodopa, baclofen, nitrates	Increased hypotensive effect	Monitor blood pressure (BP)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Increased risk of renal impairment	Do not prescribe NSAIDs and ACE inhibitors together
Potassium-sparing diuretics Potassium salts	Increased risk of hyperkalaemia	Stop potassium-sparing diuretics and potassium salts Monitor serum potassium levels
Lithium	Increased plasma concentration of lithium with possible toxicity	Monitor lithium levels and adjust lithium dose if necessary

Information detailed in the table comes from relevant Summary of Product Characteristics literature and other sources [Baxter, 2006; BNF 51, 2006].

### Angiotensin-II receptor antagonists

#### Which AIIRAs are recommended?

- **CKS recommends irbesartan and losartan** for people with diabetic kidney disease. Irbesartan and losartan are both licensed for the treatment of diabetic nephropathy and there are trial data to support their use [Brenner et al, 2001; Lewis et al, 2001; Parving et al, 2001].
  - o Irbesartan is indicated for the treatment of renal disease (both microalbuminuria and macroalbuminuria) in patients with hypertension and Type 2 diabetes mellitus.
  - o Losartan is indicated to delay the progression of renal disease in Type 2 diabetic people with macroalbuminuria.
- All angiotensin-II receptor antagonists (AIIRAs) are likely to be equally effective in the treatment of diabetic kidney disease, as they probably exhibit a class effect.
- **In normotensive people with diabetic kidney disease**, doses should be titrated up to the maximum tolerated dose (but not beyond that licensed for any cardiovascular morbidity).
- **The licensed use of irbesartan and losartan in people with diabetic kidney disease covers people with hypertension only**; therefore in normotensive people, the dose should be titrated up to the maximum tolerated dose (but not beyond that licensed for any cardiovascular morbidity).
- If a person is already taking a different angiotensin-II receptor antagonist (AIIRA) from irbesartan or losartan, it seems logical to stay on the AIIRA prescribed as it is likely that there is a class effect of these drugs.

#### Who should avoid taking AIIRAs?

- Angiotensin-II receptor antagonists (AIIRAs) should not be used during pregnancy or breastfeeding.
- Other circumstances where AIIRAs should be avoided are similar to those for *angiotensin-converting enzyme (ACE) inhibitors*.

#### What do I need to know when starting and monitoring someone on an AIIRA?

- Renal function and blood pressure should be *monitored* in people taking angiotensin-II receptor antagonists (AIIRAs) in a similar way to the monitoring required for *angiotensin-converting enzyme (ACE) inhibitors*.

#### What are the adverse effects of AIIRAs?

- Adverse effects with angiotensin-II receptor antagonists (AIIRAs) are similar to those seen with *angiotensin-converting enzyme (ACE) inhibitors* although they tend to be milder. These include:
  - o Hypotension
  - o Hyperkalaemia

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- o Angioedema (requires immediate cessation of the drug)
- AIIRAs do not cause cough to the same extent as ACE inhibitors.

### What drug interactions can occur with AIIRAs?

- Drug interactions with angiotensin-II receptor antagonists (AIIRAs) are similar to those listed for *angiotensin-converting enzyme (ACE) inhibitors*.

## Supporting evidence

### Evidence for ACE inhibitor use in normotensive people with diabetic kidney disease

- UK and international guidelines recommend the use of angiotensin-converting enzyme (ACE) inhibitors in people with diabetic kidney disease, even if they do not have hypertension.
  - o In people with diabetic kidney disease, ACE inhibitors improve a range of renal outcome measures regardless of baseline blood pressure (see the CKS topic on *Diabetes Type 1 and 2 – hypertension* for more information on people with diabetes and hypertension).
  - o In addition, there is some evidence that ACE inhibitors may also improve cardiovascular outcomes in people with diabetes who are normotensive.
  - o However, most of this evidence is from placebo-controlled trials; few studies have directly compared ACE inhibitors with other antihypertensive drugs, and most are of poor quality with small sample sizes. Therefore, there is uncertainty about whether the observed benefits are due to a specific effect of ACE inhibitors or are simply due to their blood pressure-lowering effect.

### Preventing development of proteinuria

- A systematic review evaluated the effects of angiotensin-converting enzyme (ACE) inhibitors with follow-up over at least 1 year in people with Type 1 and Type 2 diabetes [[Kshirsagar et al, 2000](#)]:
  - o Microalbuminuria: in nine randomized controlled trials (RCTs) (n = 642), compared with placebo, ACE inhibitors significantly reduced progression to proteinuria, with a relative risk (RR) of 0.35 (95% CI 0.24 to 0.53).
  - o Proteinuria: in seven RCTs (n = 1389, although less than a third had diabetes), compared with placebo, ACE inhibitors significantly reduced progression to further deterioration in renal disease (RR 0.60, 95% CI 0.49 to 0.73).
- A systematic review identified 12 studies (n = 698) that evaluated the effect of ACE inhibitors on urinary albumin excretion rate over at least 1 year in normotensive people with Type 1 diabetes and microalbuminuria [[ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001](#)]. The review found that compared with controlled groups, ACE inhibitors significantly reduced progression to proteinuria, with an odds ratio (OR) of 0.38 (95% CI 0.25 to 0.57, P < 0.001).
- A systematic review identified 11 trials (n = 671) that evaluated the effect of ACE inhibitors on the development of proteinuria over at least 1 year in normotensive people with Type 1 diabetes and microalbuminuria [[Newman et al, 2005](#)]. The review found that, compared with control groups:
  - o ACE inhibitors significantly reduced the relative risk of developing proteinuria (RR 0.36, 95% CI 0.22 to 0.58).
  - o Treating 24 people with Type 1 diabetes and microalbuminuria with an ACE inhibitor for 1 year would prevent one person from developing proteinuria.
- A systematic review identified three trials (n = 253) that evaluated the effect of ACE inhibitors on the development of proteinuria over at least 4 years in normotensive people with Type 2 diabetes and microalbuminuria [[Newman et al, 2005](#)]. The review found that compared with controlled groups:
  - o ACE inhibitors significantly reduced the relative risk of developing proteinuria (RR 0.28, 95% CI 0.15 to 0.53).
  - o Treating 22 people with Type 2 diabetes and microalbuminuria with an ACE inhibitor for 1 year would prevent one person from developing proteinuria.

### Increasing the regression to normoalbuminuria

- A systematic review identified 12 studies (n = 698) that evaluated the effect of angiotensin-converting enzyme (ACE) inhibitors on urinary albumin excretion rate over at least 1 year in normotensive people with Type 1 diabetes and microalbuminuria [[ACE Inhibitors in Diabetic Nephropathy Trialist Group, 2001](#)]. The review found that compared with control groups, ACE inhibitors significantly increased regression to normoalbuminuria with an odds ratio (OR) of 3.07 (95% CI 2.15 to 4.44, P < 0.001).
- A systematic review identified 11 trials (n = 671) that evaluated the effect of ACE inhibitors on the development of proteinuria over at least 1 year in normotensive people with Type 1 diabetes and microalbuminuria [[Newman et al, 2005](#)]. The review found that compared with

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control groups, ACE inhibitors increased the relative risk (RR) of regression to normoalbuminuria (RR 5.3, 95% CI 2.5 to 11.5).

**Inconclusive effect on glomerular filtration rate**

- A systematic review identified 8 trials (n = 549 people) that evaluated the effect of ACE inhibitors on glomerular filtration rate (GFR) decline in normotensive people with Type 1 diabetes and microalbuminuria [[Newman et al, 2005](#)]. The review found that there was no significant difference in annual fall in GFR between ACE inhibitor and control groups in this population.
- In normotensive people with Type 2 diabetes and microalbuminuria, data from three trials was found to be inconclusive as to whether treatment with enalapril was associated with better preservation of GFR [[Newman et al, 2005](#)].

**Possible mortality reduction and additional cardioprotective benefit**

- Angiotensin-converting enzyme (ACE) inhibitors were found to be cardioprotective in a mixed population of hypertensive and normotensive people with diabetic kidney disease [[Heart Outcomes Prevention Evaluation Study Investigators, 2000](#)].
  - o Subgroup analysis of people with diabetes in the Heart Outcomes Prevention Evaluation (HOPE) study found that mortality was lower in the group treated with ramipril 10 mg daily (11%) compared with those receiving placebo (14%; P = 0.004).
  - o In 1140 people with Type 2 diabetes and microalbuminuria, ramipril 10 mg/day reduced the number of cardiovascular events by 25% over 4.5 years.
  - o There is uncertainty about how much of this benefit was due to lower attained blood pressures in the ACE inhibitor group.
- In contrast, a more recent randomized controlled trial in a mixed population of hypertensive and normotensive people with Type 2 diabetes and microalbuminuria or proteinuria (n = 4912) found that low-dose ramipril 1.25 mg/day over 4 years did not differ from placebo with respect to primary outcome measures that consisted of a range of cardiovascular outcomes as well as established renal failure [[Marre et al, 2004](#)].
- Trials that have investigated the effects of ACE inhibitors in other high-risk, normotensive populations have reported conflicting results. In trials of people with chronic stable angina, benefit was seen mainly in those trials with higher baseline blood pressure levels. This suggests that any observed reduction in cardiovascular outcomes is due to blood pressure lowering rather than a specific effect of ACE inhibition. For further information, see the CKS topic on [Angina](#).

**Evidence for AIIRAs in people with diabetic kidney disease**

- **There is increasing evidence to support the use of angiotensin-II receptor antagonists (AIIRAs) as an alternative to angiotensin-converting enzyme (ACE) inhibitors in people with diabetic kidney disease.**
  - o **However, as with ACE inhibitors, interpretation of the literature is difficult:**
    - Does benefit stem from a general blood pressure-lowering effect or an additional cardiorenal protective role beyond this?
    - There is a lack of trial data available in normotensive people with diabetic kidney disease.
  - o As there is no reason to think that similar findings would not be achieved in normotensive people with renal disease, discussion of AIIRAs therefore includes reference to trial data from their use in hypertensive diabetic populations.
  - o As with ACE inhibitors, there is a lack of hard outcome data. Better quality, large-scale trials are needed to investigate antihypertensive drug use in normotensive people with diabetic kidney disease of long enough duration for measurement of definitive end points.
- A recent systematic review investigated the combined benefits of ACE inhibitors and AIIRAs on progression of renal disease [[Casas et al, 2005](#)]. The analyses did not differentiate between people with Type 1 and Type 2 diabetes, and trials included in the analyses were of both hypertensive and normotensive populations.
  - o Overall, compared with placebo, ACE inhibitors and AIIRAs reduced the risk of established renal failure or doubling of serum creatinine, and resulted in lower serum creatinine concentrations and urinary albumin excretion. The degree of benefit was strongly correlated with the achieved reduction in blood pressure.
  - o For information on the discussion of the meta-analyses results in this systematic review, see the CKS topic on [Diabetes Type 1 and 2 – hypertension](#).

**Possible prevention of development of proteinuria**

- **No systematic reviews were found, so evidence suggesting that angiotensin-II receptor antagonists (AIIRAs) prevent development of proteinuria is from randomized controlled trial (RCT) data only.**

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- An RCT in hypertensive people with Type 2 diabetes and microalbuminuria (n = 590) evaluated the effect of irbesartan 150 mg daily or 300 mg daily [Parving et al, 2001]. Over 3 years' follow-up, compared with the placebo group where 30/201 (15%) developed proteinuria:
  - o Irbesartan 300 mg was found to significantly reduce the urinary albumin excretion (UAE) rate and 10/194 (5.2%) reached the end point, with a hazard ratio (HR) of 0.30 (95% CI 0.14 to 0.61, P < 0.001).
  - o Irbesartan 150 mg also reduced the UAE rate and 19/195 (9.7%) reached the end point but this was not significant (HR 0.61, 95% CI 0.34 to 1.08, P = 0.08).

**Possible reduction in progression to established renal disease**

- **No systematic reviews were found, so evidence suggesting that angiotensin-II receptor antagonists (AIIRAs) reduce progression to established renal failure is from randomized controlled trial (RCT) data only.**
- An RCT in mainly hypertensive people with Type 2 diabetes, and proteinuria (n = 1513), compared the effect of losartan (50 to 100 mg daily) with placebo [Brenner et al, 2001]. Over 3.4 years, losartan was found to:
  - o Significantly reduce the incidence of doubling of serum creatinine: 327/751 (44%) with losartan versus 359/762 (47%) with placebo, a relative risk (RR) of 0.84 (95% CI 0.72 to 0.98, P = 0.006)
  - o Significantly reduce progression to established renal failure: 147/751 (20%) with losartan versus 194/762 (26%) with placebo (RR 0.72, 95% CI: 0.58 to 0.89, P = 0.002).
- Another RCT (n = 1715) in mainly hypertensive people with Type 2 diabetes, and proteinuria, and hypertension, compared the effect of irbesartan (300 mg daily) with amlodipine (10 mg daily), and placebo [Lewis et al, 2001]. Over 2.6 years, irbesartan was found to:
  - o Significantly reduce the risk of doubling of serum creatinine: 98/579 (17%) with irbesartan versus 135/569 (24%) with placebo (RR 0.67, 95% CI 0.52 to 0.87, P = 0.003).
  - o Not quite significantly reduce progression to established renal failure: 82/579 (14%) with irbesartan versus 101/569 (18%) with placebo, (RR 0.77, 95% CI 0.57 to 1.03, P = 0.07).

**No apparent mortality reduction or additional cardioprotective benefit**

- **No systematic reviews were found, so evidence suggesting that angiotensin-II receptor antagonists (AIIRAs) have no effect on mortality, or demonstrate additional cardioprotective benefit, is from randomized controlled trial (RCT) data only.**
- A randomized controlled trial (RCT) in mainly hypertensive people with Type 2 diabetes, and proteinuria (n = 1513), compared the effect of losartan (50 to 100 mg daily) with placebo [Brenner et al, 2001]. Over 3.4 years, losartan was found to be associated with:
  - o No significant difference regarding fatal or non-fatal cardiovascular events: 247/751 (33%) with losartan versus 268/762 (35%) with placebo, with a relative risk (RR) of 0.94 (95% CI) 0.81 to 1.08.
  - o No significant difference in death from any cause: 158/751 (21%) with losartan versus 155/762 (20%) with placebo (RR 1.03, 95% CI 0.85 to 1.26).
- Another RCT (n = 1715) in mainly hypertensive people with Type 2 diabetes, and proteinuria, compared the effect of irbesartan (300 mg daily) with amlodipine (10 mg daily), and placebo [Lewis et al, 2001]. Over 2.6 years, irbesartan was found to be associated with:
  - o No significant difference for a composite cardiovascular outcome compared with placebo (RR 0.91, 95% CI 0.72 to 1.14, P = 0.40).
  - o No significant difference in death from any cause (RR 0.92, 95% CI 0.69 to 1.23).

**Evidence for not recommending combined ACE and AIIRA in people with diabetic kidney disease**

- **No trials have compared the combined use of both an angiotensin-converting enzyme (ACE) inhibitor and angiotensin-II receptor antagonist (AIIRA) in normotensive people with diabetic kidney disease.**
- **One trial has been performed in people with hypertension, diabetes, and microalbuminuria and reported a beneficial effect of the combination.**
  - o The Candesartan and Lisinopril Microalbuminuria (CALM) study is the largest trial (n = 197 people) of dual blockade in people with hypertension, Type 2 diabetes, and microalbuminuria [Mogensen et al, 2000]. This 12-week trial showed a significant reduction in blood pressure with dual blockade compared with either lisinopril (20 mg) or candesartan (16 mg) alone, and greater reductions in the urinary albumin:creatinine ratio with combination treatment (50%) compared with lisinopril (39%) or candesartan

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(24%). However, it was unclear whether positive benefits of the combined approach were due to more complete blockade of the renin-angiotensin-aldosterone system or as a result of blood pressure reduction.

### Evidence for other antihypertensives in people with diabetic kidney disease

- One systematic review investigated the effect of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (AIIRAs) in people with renal disease (a subgroup of whom had diabetes), and compared these drugs directly with other antihypertensives. However, few studies directly compared one antihypertensive drug with another. Of these, most were of poor quality and with small sample sizes (only two greater than 100 people), and were unable to adequately determine the relative efficacies.
- A systematic review and meta-analysis investigated the benefits of ACE inhibitors and AIIRAs on progression of renal disease [Casas et al, 2005].
  - In diabetic populations, compared with other antihypertensive drugs, a positive trend of beneficial effect was found for doubling of creatinine, established renal failure, and other markers of renal outcomes. However, the only outcome that significantly improved was a lower daily urinary albumin excretion, although this may have been because of the smaller numbers included in the analysis.
  - The authors concluded that in people with diabetes, additional renoprotective actions of ACE inhibitors and AIIRAs, beyond lowering blood pressure, remain unproven.
- The largest randomized controlled trial (RCT) in people with Type 2 diabetes, proteinuria, and hypertension (n = 1715) compared the effect of irbesartan (300 mg daily) with amlodipine (10 mg daily), and placebo [Lewis et al, 2001]. Over 2.6 years, irbesartan was found to:
  - Significantly reduce the difference (P <= 0.001) in doubling of serum creatinine: 98/579 (17%) with irbesartan versus 144/567 (24%) with amlodipine, with a relative risk (RR) of 0.63 (95% CI 0.48 to 0.81).
  - Not quite reach significance (P = 0.07) with regard to progression to established renal failure: 82/579 (14%) with irbesartan versus 104/567 (18%) with amlodipine (RR 0.77, 95% CI 0.57 to 1.03).
  - Have no significant difference (P = 0.75) regarding death from any cause: 87/579 (15%) with irbesartan versus 83/567 (15%) with amlodipine (RR 1.04, 95% CI 0.77 to 1.40).
- An RCT (n = 250 people) in people with Type 2 diabetes, microalbuminuria, and hypertension, compared the renoprotective effects of telmisartan 80 mg daily and enalapril 20 mg daily, with 5 years of follow up [Barnett et al, 2004].
  - The findings supported the clinical equivalence of AIIRAs and ACE inhibitors as no significant differences were found in glomerular filtration rate change, mortality, and cardiovascular end points.

### Evidence for benefit of dietary protein restriction in Type 1 diabetes

A Cochrane review identified five randomized controlled trials (n = 60) examining the effect of restricting dietary protein intake on the progression of diabetic kidney disease [Waugh and Robertson, 1997].

- **Population:** people with Type 1 diabetes with renal disease.
- **Intervention:** advice to restrict dietary protein to between 0.3 to 0.8 g/kg per day. Interventions were assessed after durations between 6 months and 4.5 years.
- **Comparison:** rate of decline in renal function for an individual on usual diet compared with rate of decline in renal function after advice to restrict dietary protein. Patients acted as their own controls.
- **Outcomes:**
  - Across all the studies there was a modest decline in the rate of fall in glomerular filtration rate with protein restriction.
  - Compliance with the prescribed restriction of dietary protein in the trials was found to be a problem, with worse compliance associated with the most restrictive regimes.
- **Limitations of the evidence:**
  - The small number of people included in the studies.
  - The small clinical effect.
  - Methodological flaws in all the studies.
  - The lack of studies for people with Type 2 diabetes.
  - Studies did not identify the level of protein restriction most effective at reducing the decline in renal function.

### Evidence for an optimal target blood pressure

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**Clinical Knowledge Summaries: Previous version – Diabetes Type 1 and 2 – screening/managing renal disease**

- **An optimal treatment target of less than or equal to 130/80 mmHg** is recommended by the British Hypertension Society [[Williams et al, 2004](#)] and the Joint British Societies [[Joint British Societies, 2005](#)]. This target is recommended on the basis of the following considerations:
  - o Trial data show that the greater the reduction in blood pressure, the greater the benefit in terms of reduced risk of cardiovascular events, and from observational data there seems to be no blood pressure threshold below which cardiovascular risk no longer declines.
  - o Strict blood pressure control is the most important factor preventing the development of diabetic kidney disease and renal failure.
  - o In the Hypertension Optimal Treatment (HOT) trial [[Hansson et al, 1998](#)], among people with hypertension and diabetes there seemed to be a significant advantage of aiming for a diastolic pressure of less than 80 mmHg, which halved the incidence of major cardiovascular events compared with treatment aiming for a diastolic pressure of less than or equal to 90 mmHg.
- **An optimal target of less than or equal to 125/75 mmHg is recommended for people with diabetes and proteinuria by many experts to reduce the rate of deterioration in renal function.** It is recognized that achieving this target may be unrealistic for many individuals.
  - o An assessment of the evidence by the British Hypertensive Society concluded that "reducing blood pressure to less than or equal to 125/75 mmHg may produce additional benefits in patients with chronic renal disease of any aetiology associated with a protein excretion of equal to or greater than one gram in 24-hours" [[Williams et al, 2004](#)].
  - o This recommendation is derived by extrapolating the evidence from a study examining the benefits of strict blood pressure control in non-diabetic subjects with proteinuria [[Peterson et al, 1995](#)]:
    - **Population:** 840 patients with proteinuria and impaired renal function of diverse cause.
    - **Intervention:** Patients were randomly allocated to either group A, with a strict blood pressure target or group B with a usual blood pressure target.
    - **Comparisons:** The decline in renal function and protein excretion was compared between the groups to determine the effect of the blood pressure level on the rate of decline of renal function. The rate of decline in renal function was also compared within each blood pressure group comparing people with a higher initial protein excretion to people with a lower initial protein excretion.
    - **Outcomes:** The rate of decline in renal function was lower in people with the lower blood pressure target. The greatest reno-protective benefit from the lower blood pressure target was seen in people with an initial proteinuria of greater than one gram in 24-hours.

#### Evidence for HbA1c targets

Evidence that strict glucose control in people with Type 1 and 2 diabetes reduces the risk of onset and progression of diabetic kidney disease, as well as retinopathy and cardiovascular disease, comes from two landmark trials [[The Diabetes Control and Complications Trial Research Group, 1993](#), [Laakso, 1999](#)].

##### The UK Prospective Diabetes Study:

- **Population:** people with Type 2 diabetes (n = 3867), newly diagnosed with diabetes.
- **Intervention:** random allocation to intensive treatment with a sulfonylurea.
- **Comparison:** random allocation to conventional treatment with diet alone.
- **Outcomes:** compared over a 10-year period with the conventionally treated group, the intensively treated group showed:
  - o HbA<sub>1c</sub> of 7.0% compared with 7.9% in the comparison group
  - o Microvascular disease reduction of 25%
  - o Myocardial infarcts reduction of 16%
  - o Death related to diabetes reduction of 10%

##### The Diabetes Control and Complications Trial:

- **Population:** people with Type 1 diabetes and retinopathy (n = 1441) and people with Type 1 diabetes with no retinopathy at baseline (n = 726).
- **Intervention:** random allocation to intensive insulin therapy with external insulin pumps or three or more insulin injections daily, guided by frequent blood glucose monitoring.
- **Comparison:** random allocation to conventional insulin therapy with one or two insulin injections daily.
- **Outcomes:** compared with the conventionally treated group over a 6.5-year period, the intensively treated group showed:

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- o HbA<sub>1c</sub> of approximately 7% compared with approximately 9% in the comparison group
- o Reduction in microalbuminuria by 39% (95% CI 21 to 54%)
- o Reduction in proteinuria by 54% (95% CI 19 to 74%)
- Harms: twofold to threefold increase in severe hypoglycaemia episodes.

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**NHS staff in England can link, free of charge, from references to the full text journal articles by clicking on [NHS Athens Full-text].** You will need an NHS Athens password to access these resources. Click here for Athens registration.

**All references with links to [Free Full-text] are freely available online to users in England and Wales.** This includes the full text of Department of Health papers and Cochrane Library reviews.

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**Clinical Knowledge Summaries: Previous version – Diabetes Type 1 and 2 – screening/managing renal disease**

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### Evidence grading

Evidence grading is from the National Institute for Health and Clinical Excellence guideline, *Management of Type 2 diabetes: renal disease, prevention and early management* [NICE, 2002]. The definitions of grades of recommendation used in this guideline are as follows:

- |   |   |
|---|---|
| A | Directly based on category I evidence (systematic review of randomized controlled trials or at least one randomized controlled trial)   |
| B | Directly based on category II evidence (at least one controlled study without randomization or one other type of quasi-experimental study) or extrapolated recommendation from category I evidence    |
| C | Directly based on category III evidence (non-experimental descriptive studies) or extrapolated recommendation from category I or II evidence  |
| D | Directly based on category IV evidence (expert committee reports or opinions and/or clinical experience of respected authorities) or extrapolated recommendation from category I, II, or III evidence |

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