

NEWSLETTER

Supporting the Derbyshire Health Community

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PACEF update

The current Traffic Lights list can be accessed via the PACEF intranet site
www.nodysis.nhs.uk/guidelines/pacef%20web.htm.

RED drugs are those where prescribing responsibility would normally lie with a hospital consultant or a specialist. AMBER drugs are those that although usually initiated within a hospital setting, could appropriately become the responsibility of the GP. This would normally be under a shared care agreement. GREEN drugs are regarded as routine for primary care prescribing. BROWN drugs are those that PACEF does not recommend for use (or only in restricted circumstances) due to lack of data on safety, effectiveness, or cost-effectiveness.

<u>Drug</u>	<u>Date considered</u>	<u>Decision</u>
Efalizumab	September 2006	RED
Rituximab	September 2006	RED
Clenil Modulite (beclometasone cfc-free MDI)	August 2006	GREEN Prescribe by brand name
Celluvisc eye drops	August 2006	GREEN
Natalizumab	August 2006	RED
Rimonabant	August 2006	BROWN
Desloratidine	July 2006	BROWN
Levocetirizine	July 2006	BROWN
Pegaptanib injection	July 2006	RED
Rotigotine patch	July 2006	BROWN
Zaleplon	July 2006	BROWN
Zolpidem	July 2006	BROWN
Zopiclone	July 2006	BROWN
Formoterol cfc-free MDI (Atimos Modulite)	June 2006	GREEN
Letrozole	June 2006	AMBER

Appropriate use of insulin in type 2 diabetes

The consultant diabetologists at Chesterfield Royal Hospital recently raised concerns with us about increased use of new insulin analogues. A PACT analysis revealed that the expenditure on insulins has risen considerably in North Derbyshire over the last few years and is currently £1.89 million per year (June 06 figures). This may be partly explained by the increasing prevalence of type 2 diabetes but the PACT data shows that there has been a very significant switch from standard insulins to the more expensive newer insulin analogues. If this rate of increase continues then by June 08 the expenditure will be around £2.4 million per year.

Insulin analogue manufacturers are relentlessly promoting the use of insulin analogues and many clinicians seem to be prescribing them as first-line treatments. Is this justifiable? Is it good use of scarce resources? The insulin analogues provide useful alternatives to standard insulin for those who have frequent severe hypoglycaemia or nocturnal hypoglycaemic episodes but this will predominantly be people with type 1 diabetes.

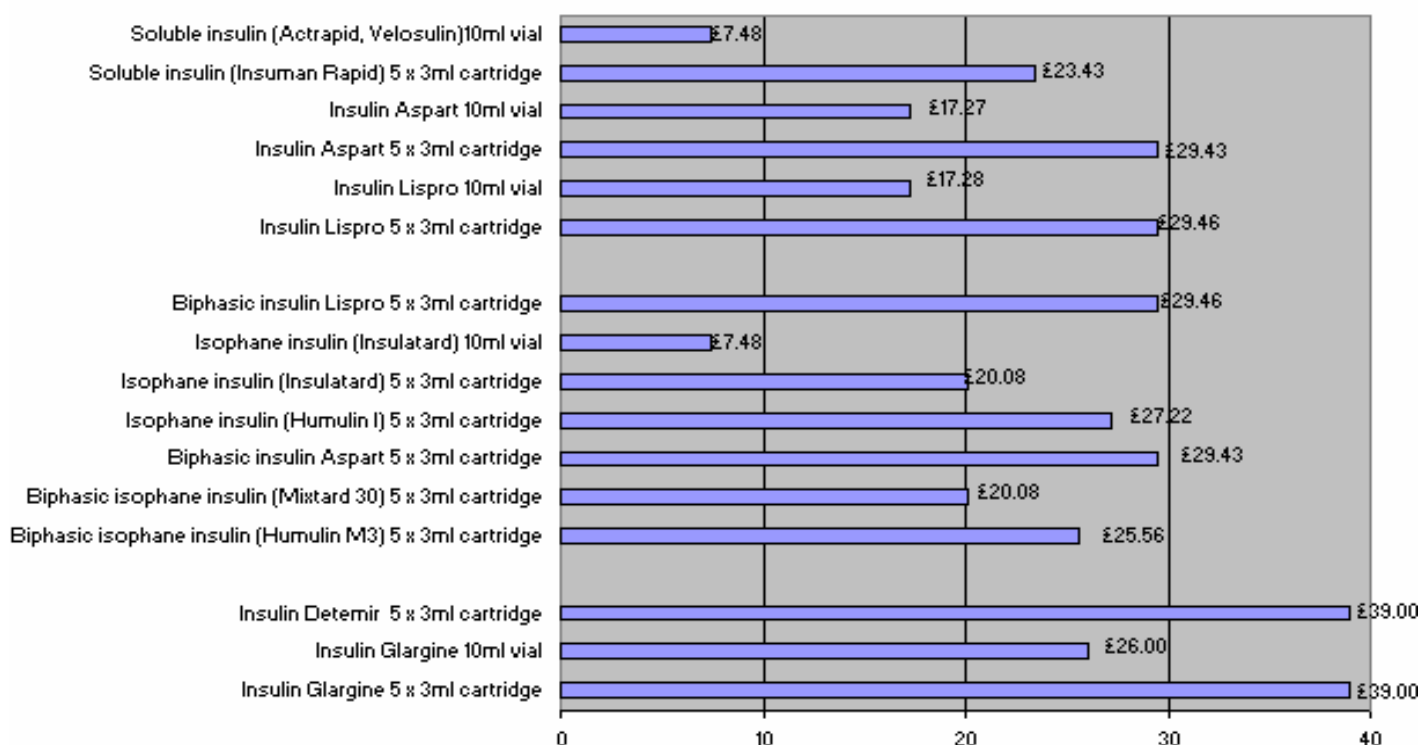
A review of the insulin analogues in DTB¹ concluded that the use of insulin analogues as first-line therapy for patients with diabetes requiring insulin is not justified and the long-term benefits and safety of the analogues still needs to be established. They also advised against routinely switching patients from existing conventional therapy to analogues. The Health Technology Assessment review of insulin glargine² found that for type 2 patients for whom oral antidiabetic agents provide inadequate glycaemic control, there is no evidence that insulin glargine is more effective than NPH (*otherwise known as isophane insulin*) in reducing FBG or HbA_{1c}. They also found no conclusive evidence that glargine is superior to NPH in controlling symptomatic hypoglycaemia and severe hypoglycaemia. The report concludes that there appears to be no improvement in long-term glycaemic control and therefore insulin glargine is unlikely to reduce the incidence of the long-term microvascular and cardiovascular complications of diabetes.

NICE issued guidance on the use of insulin glargine in December 2002. Insulin detemir was not then available but it makes sense to apply this guidance to detemir as well. NICE stated quite clearly that insulin glargine is **not** recommended for routine use for people with type 2 diabetes who require insulin therapy. Their estimates of the cost-effectiveness of insulin glargine in type 2 diabetes were in the range of £32,500 to £72,000 per QALY. NICE's upper limit of cost-effectiveness is between £20,000 and £30,000 per QALY. As NICE states in its 'Social Value Judgements' document, "the resources for the NHS are finite, and the use of cost-ineffective interventions in one area of practice will deny the availability of cost-effective interventions in another". Annex 8 of the revisions to the GMS contract 06/07 states that improving the quality, cost-effectiveness and affordability of prescribing in the context of the overall use of NHS resources is of benefit to patients. Spending too much in one area reduces access to services in other parts of the system. We have to be very sure that health expenditure results in significant health gain, particularly if other interventions that are of proven benefit are not fully provided.

With this in mind, guidance on the appropriate use of insulin in type 2 diabetes is being developed.

1. DTB 2004; 42: 77-80
2. HTA 2004; 8: No. 45

Human Insulin cost chart (August 2006)



Glycated haemoglobin (HbA_{1c}) monitoring

HbA_{1c} has become established as the monitoring test of choice to assess medium term diabetic control and as a key parameter on which to base changes in management of patients. An article in the BMJ provides some useful insight into the appropriate use of HbA_{1c} monitoring¹.

Glycation of haemoglobin to produce HbA_{1c} occurs throughout the 120-day average lifespan of the red blood cell. Repeat testing in less than 120 days or situations that shorten this lifespan will produce HbA_{1c} results that do not reflect current diabetic control. In a case study presented, a 57-year-old man was started on metformin and 6 weeks later a sulphonylurea was added based on an HbA_{1c} of 8.7%. Two weeks later the patient collapsed at work and had to be revived with a sweet drink. Insufficient time had been allowed for the HbA_{1c} to fall before treatment was intensified, resulting in an avoidable hypoglycaemic episode.

The article discusses the appropriateness of targets set for HbA_{1c} levels. The authors advise that these aspirations for improved diabetes control may be difficult to achieve in some patients, and clinicians should recognise that the change in risk corresponding to a change in HbA_{1c} is non-linear. Thus in a population study in which the mean HbA_{1c} value was reduced from 9% to 7%, approximately 50% of the decrease in events occurred at a mean HbA_{1c} of 8.6%, and 70% at 8.0%; thus small improvements can give rise to large benefits, even if perfection cannot be achieved.

A recent editorial also discussed the issue of HbA_{1c} targets². The author comments that the JBS2 target of a level below 6.5% is unrealistic. He adds that even the GMS target of below 7.4% is too low for most individuals and the pursuit of perfection is leading to progressive weight gain and recurrent hypoglycaemia.

Remember to lend a hand to people with type 2 diabetes (see PACEF guideline on managing type 2 diabetes) and to individualise targets appropriately.

1. BMJ 2006; 333:586-8
2. Pract Diab Int 2006; 23:280-1

Is it a DREAM result?

The results of the recently published DREAM trial¹ received some hype in the national press. Is this something we should get excited about? In the DREAM trial, 5,269 people aged 30 years or more with impaired fasting glucose or impaired glucose tolerance and no previous cardiovascular disease were randomly assigned to receive rosiglitazone 8mg daily or placebo. The primary outcome was a composite of incident diabetes or death.

After a median of 3 years follow-up, 11.6% of individuals given rosiglitazone and 26.0% given placebo developed the composite primary outcome (HR 0.40; p<0.0001). The NNT was 7 but note that there was no difference in death rates. The endpoint of cardiovascular events composite was not significantly different but confirmed heart failure was more common in the rosiglitazone group (p=0.01) with a NNH of 250.

The accompanying editorial² comments that the reduction in progression to diabetes is no different from that expected from the glucose-lowering effect. Previous studies have shown that both metformin and acarbose reduce the risk of developing diabetes in people with impaired glucose tolerance. The NNT of 7 in this study is exactly the same as that achieved for lifestyle change (aimed at weight loss of 7% through low-fat diet and exercising 150 minutes per week) in a study from 2002³.

The long-term benefits and safety of rosiglitazone are still unknown, it is only licensed for the treatment of type 2 diabetes and it is expensive. As the editorial concludes "Given the prolonged benefits and demonstrable cost-effectiveness of intensive lifestyle intervention for people at high risk of diabetes, such interventions should remain the mainstay for the prevention of type 2 diabetes".

Key point: Lifestyle modifications have been shown to be effective and cost-effective in people at risk of progression to diabetes and are the mainstay of management.

1. Lancet 2006; 368:1096-1105
2. Lancet 2006; 368: 1218-19
3. NEJM 2002; 346: 393 – 403

Appropriate use of blood glucose testing strips

As reported in the December 2005 edition, a systematic review assessing the effects of self-monitoring of blood glucose (SMBG) in people with type 2 diabetes who are not using insulin found that there is no strong evidence that SMBG improves HbA_{1c} to a clinically significant degree or improves quality of life.

The Fremantle Diabetes Study¹, published recently, adds to the evidence base. They found that HbA_{1c} was not significantly different between SMBG users and nonusers, either overall or within diabetes treatment groups (diet, oral hypoglycaemic agents, and insulin). The authors concluded that their data do not support a role for SMBG in type 2 diabetic patients in improving glycaemic control, irrespective of treatment. They do add the caveat that SMBG can be valuable in the identification and prevention of hypoglycaemia and in dose adjustment in insulin-treated patients.

1. Diabetes Care 2006; 29:1764-70

POWERbreathe Medic

This device for inspiratory muscle training has recently been added to the Drug Tariff and hence is prescribable on NHS prescription. Unlike 4Ulcercare (see June 06 edition) there does seem to be some reasonably robust evidence to support its use.

Clinical Evidence classifies inspiratory muscle training (IMT) as 'likely to be beneficial'. A meta-analysis of studies investigating IMT in patients with COPD from 2002¹ concluded that IMT is an important addition to a pulmonary rehabilitation programme directed at COPD patients with inspiratory muscle weakness. A trial published in 2005² concluded that during IMT in patients with significant COPD there is an increase in exercise capacity, improvement in quality of life, and decrease in dyspnoea. In addition, long-term IMT can decrease the use of health services and hospitalisation days.

We have discussed this at PACEF and concluded that it is reasonable to prescribe POWERbreathe but only if recommended after assessment by a respiratory specialist. The device costs £17.90.

1. Eur Respir J 2002; 20:570-76
2. Chest 2005; 128:3177-82

GI bleeding with SSRIs

The potential for SSRIs to cause GI bleeding has been discussed in this newsletter before. This is an article from the Mersey ADR Newsletter (Summer 06) on this subject.

Case reports and observational studies suggest that selective serotonin reuptake inhibitors (SSRIs) can increase the risk of abnormal bleeding. Serotonin is released from platelets in response to vascular injury, promoting vasoconstriction and potentiating platelet aggregation. Since platelets cannot themselves synthesise serotonin, depletion of platelet serotonin stores caused by SSRI therapy could induce bleeding complications.

Studies have shown a positive correlation between the degree of serotonin reuptake inhibition and rates of abnormal bleeding. The antidepressants with the highest degree of serotonin reuptake inhibition are clomipramine, fluoxetine, sertraline and paroxetine.

There is a well-established association between non-steroidal anti-inflammatory drugs (NSAIDs) and gastrointestinal bleeding. Concurrent use of NSAIDs has been shown to potentiate the bleeding effect observed with SSRIs.

The absolute additional risk of an upper gastrointestinal bleed (requiring admission to hospital) with an SSRI prescribed alone is about 1 in 300 patient years, but co-prescription of SSRIs with aspirin increases the risk to 1 in 200 and with NSAIDs to 1 in 80. The risk with a NSAID alone is 1 in 200.

Both the *Summary of Product Characteristics* (SmPC) and the BNF state that SSRIs are to be used with caution in patients with concomitant use of drugs that increase risk of bleeding or in those with a history of bleeding, especially gastro-intestinal.

The SPARCL Study

Therapy with statins reduces the risk of stroke (and other vascular events) in patients with coronary heart disease. The subgroup of patients with cerebrovascular disease but no CHD in the Heart Protection Study¹ (HPS) benefited from a reduction in vascular events to a similar degree to patients with existing CHD. The SPARCL study² was designed to determine whether a daily dose of atorvastatin 80mg would reduce the risk of stroke in patients without CHD who had had a stroke or TIA within the last 6 months.

Method

- Eligible patients were men and women over 18 years of age who had had an ischaemic or haemorrhagic stroke or a TIA (diagnosed by a neurologist within 30 days after the event) 1 to 6 months before randomisation.
- Patients had to be ambulatory, with a modified Rankin score of no more than 3, and to have an LDL-C level of at least 2.6 mmol/L and no more than 4.9 mmol/L.
- Patients with known CHD were excluded from the trial, as were those with atrial fibrillation, other cardiac sources of embolism, and subarachnoid haemorrhage.
- Patients who were taking lipid-altering drugs had to stop these medications 30 days before the screening phase of the study.
- Eligible patients were randomly assigned to double blind therapy with either atorvastatin 80mg or placebo daily.
- All patients were counselled about diet throughout the study.
- The primary outcome was the time from randomisation to a first non-fatal or fatal stroke.
- There were several prespecified secondary composite outcomes including major coronary event (death from cardiac causes, non fatal MI, or resuscitation after cardiac arrest) and major cardiovascular event (stroke plus any major coronary event).
- The analysis was performed on an intention-to-treat basis with the inclusion of all patients who underwent randomisation.
- The study was supported by Pfizer.

Results

- 4,731 patients fulfilled the inclusion criteria and were randomised. Mean age was 63 years and 60% were men. 69% had had a stroke (2% haemorrhagic). Only 2.5% had any prior statin therapy. 87% were taking aspirin or another antiplatelet drug.
- The median duration of follow-up was 4.9 years (range 4.0 to 6.6).
- More patients in the placebo group than in the atorvastatin group started non-study statin therapy (7.5% vs 1.0%). The net difference in statin use between groups was 78.1%.
- The mean LDL-C values during the course of the trial were 1.9 mmol/L in the atorvastatin group and 3.3 mmol/L in the placebo group.
- The primary endpoint occurred in 11.2% receiving atorvastatin and 13.1% receiving placebo (unadjusted $p=0.05$). The absolute difference in Kaplan-Meier rates at 5 years was 2.2%. This is an NNT of 46 (95% CI 24 to 500). After prespecified adjustment for baseline factors, atorvastatin was associated with a 16.0% relative reduction in the risk of fatal or non-fatal stroke (HR 0.84; CI 0.71 to 0.99; $p=0.03$).
- The 5-year absolute reduction in the risk of major cardiovascular events was 3.5% (HR 0.80; CI 0.69 to 0.92; $p=0.002$). This is an NNT of 29.
- The effect of atorvastatin on stroke depended on the type of stroke. For ischaemic strokes the hazard ratio was 0.78 (0.66 to 0.94), but for haemorrhagic stroke the HR was 1.66 (1.08 to 2.55). Thus the risk reduction in ischaemic strokes (the more common type) comes with an increased risk of haemorrhagic stroke.
- There was no significant difference in overall mortality (atorvastatin 9.1% vs placebo 8.9%, $p=0.98$).
- There was no significant difference between the groups in the incidence of serious adverse events (41.8% vs 41.2%) but adverse events resulting in discontinuation of study treatment appeared to be more frequent in the atorvastatin group (17.5% vs 14.5%; no p -value quoted; NNH = 33). Persistent elevation of alanine or aspartate aminotransferase was more frequent in the atorvastatin group (2.2% vs 0.5%; $p<0.001$; NNH=59).

Discussion/implications

- The SPARCL investigators conclude that their results support the concept that from the standpoint of statin treatment, stroke or TIA should be considered a coronary heart disease risk equivalent. We reached that conclusion after HPS and this study confirms that patients with cerebrovascular disease benefit from a reduction in CHD risk with statin therapy.
- But should that be treatment with simvastatin 40mg or atorvastatin 80mg daily? The reduction in stroke risk in SPARCL was only just statistically significant, the absolute risk reduction was small, and there was no reduction in overall mortality.
- There are wide confidence intervals around the NNT and an increased incidence in dropouts due to adverse events. The acquisition cost of atorvastatin 80mg is high compared to simvastatin and the cost-effectiveness needs to be ascertained.
- Assuming the NNT of 46 and using current drug prices (DT September 06), the cost to prevent one stroke in this patient population over 5 years would be £84,580.
- Currently, on the evidence from HPS, guidelines will be recommending that patients with an ischaemic stroke or TIA should receive simvastatin 40mg daily. This study provides inadequate evidence on which to base a change in practice.

1. Lancet 2002; 360: 7-22
2. N Engl J Med 2006; 355:549-59

Key point: Patients who have had an ischaemic stroke or TIA should receive simvastatin 40mg daily.

PPIs and the risk of *C. difficile*-associated disease

The new *C. difficile* policy was highlighted in last month's edition of this newsletter. One of the risk factors listed is prolonged use of proton pump inhibitors. A recently published study adds to the evidence base¹.

Classic risk factors for *C. difficile*-associated disease (CDAD) include broad-spectrum antibiotic use, increasing age and prolonged hospital stay. These factors are universally agreed to be important. The role of PPI use is debated.

The authors report a case-control study looking at the use of PPIs and the risk of community-acquired CDAD using the well-validated UK General Practice Research Database¹. The authors used the novel approach of considering oral vancomycin therapy as a proxy for CDAD, which is reasonable as CDAD is the only indication for oral vancomycin.

Exposure to a PPI in the 90 days before the index date was associated with an increased risk of CDAD (OR 3.5; CI 2.3 to 5.2). Antibiotic exposure was also a significant risk factor (OR 8.2; CI 6.1 to 11.0), even though 45% of the case subjects had not received a prescription for an antibiotic during that 90 day period. The authors conclude that the results of this study add additional weight to the evidence that PPI use is associated with an increased risk of CDAD.

In the accompanying editorial², the author comments that PPIs are widely overused in the UK, and a pilot study in Plymouth found that a significant proportion of patients admitted to hospital were taking PPIs with no clear indication for their use. He adds that careful antibiotic prescribing and good hygiene are essential, but recent experience suggests that they may not be enough to turn the tide of increasing CDAD.

1. CMAJ 2006; 175:745-8
2. CMAJ 2006; 175:757-8

Guidelines update

PACEF has recently ratified the following guidelines. These and all the other guidelines/policies are available on the PACEF intranet site.

- Asthma guideline – update
- COPD guideline – update
- Ovarian cancer screening – update

- Cancer referral guidelines – new
- Oxygen guideline – new
- PSA testing guideline – new
- Modafinil shared care - update

More on eGFR and CKD

Further to the article on eGFR in the June 06 edition, I have come across several papers on this subject and thought it worth including the key points.

Data suggests that around 5% of adults have chronic kidney disease (CKD) stage 3, 4, or 5. These people have a markedly increased risk of cardiovascular morbidity and mortality and identification of them should enable earlier initiation of measures to reduce CV risk and also the rate of progression of renal failure¹.

There is a big reserve of kidney function – you only start to feel unwell if the amount filtered per day falls below one-third of its normal amount. It is only at stage 4 or later that you are likely to notice any symptoms². As a normal GFR is approximately 100ml/min/1.73m², the eGFR can be explained to patients as a percentage of normal kidney function³. While this is easy to understand, patients are often shocked and frightened when told their kidney function is, for instance, 52% of normal. Explaining that only 1.3% or less of patients with stage 3 CKD will end up on dialysis can relieve one major fear³. Describing CKD as a risk factor for CV disease, just like hypertension or dyslipidaemia, can also be useful.

It is usual for GFR to fall slowly with age². It makes sense to take the eGFR result in the context of age. If 90 is the lower limit of normal and you lose 1ml/min a year after age 40 normally, then by the time you are 80 an eGFR of 50 would be 'normal'. An eGFR of 60-89 in the absence of other evidence of kidney disease does not signify CKD and does not indicate that further testing is required¹. A recent BMJ article offers the following tips for non-specialists¹.

If the estimated glomerular filtration rate is <60 ml/min then:

- review previous results or repeat the measurement to assess if renal function is stable or declining
- measure blood pressure and test urine for protein and blood
- review drugs for potentially nephrotoxic agents, such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers, diuretics, non-steroidal anti-inflammatory drugs, and antibiotics
- check for urinary symptoms, signs of fluid retention or hypovolaemia, and palpable bladder
- enter into a chronic disease management programme and decide whether referral to a renal clinic is appropriate, using local guidelines or those from the Renal Association

Just a reminder that we are working to the Renal Guidelines from the East Midlands Renal Network for the management of CKD, including referral. These can be found on the PACEF intranet site.

Drugs such as trimethoprim and cimetidine block tubular secretion of creatinine, thus leading to an apparent fall in eGFR. Eating stewed meat causes a substantial rise in serum creatinine (the so-called goulash effect), resulting in an apparent decline in eGFR³.

CKD guidelines define the measure of renal function as a glomerular filtration rate that has been normalised to a body surface area of 1.73m² (the normal mean value for adults). Drug dosing should not be based on eGFR values because it is the individual's actual, non-normalised GFR that determines how quickly any drug will be cleared by his or her kidneys. In contrast, the eGFR tells us what an individual's kidneys would be capable of clearing if he/she had a body surface area of 1.73m². Cockcroft and Gault should remain the gold standard to estimate GFR when adjusting drug doses to an individual's renal function⁴. This will be of greatest significance in those patients whose size differs substantially from the average (1.73m²), and with drugs that have a low therapeutic ratio in renal impairment³.

1. BMJ 2006; 333:733-7
2. Br J Renal Med 2005; 10:15-18
3. Br J Renal Med 2006; 11:5-8
4. Pharm J 2006; 277:403-4

The Renal Association has produced a patient information leaflet. I've adapted it a little using information from reference 2.

CKD PATIENT INFORMATION LEAFLET

What is chronic kidney disease?

Kidneys take waste out of the blood, which then leaves the body in urine. The kidneys also play a role in controlling your blood pressure. Chronic kidney disease means that for some reason this is not working as well as expected. Our kidney function gets less efficient as we get older anyway but CKD is deterioration in kidney function faster than would be normally expected for age. There is a big reserve of kidney function – you usually only start to feel unwell if it falls below one-third of its normal amount.

How do you know about chronic kidney disease?

Most people with kidney disease have no symptoms. It is usually diagnosed after blood or urine tests. A new blood test now makes it much easier to recognise a problem with the kidneys. There are 5 stages of CKD but it is only at stage 4 or later that you are likely to notice any symptoms.

How common is chronic kidney disease?

About five per cent of the population have kidneys that show signs of damage. Most of these people have mild kidney damage.

What causes chronic kidney disease?

For many people the cause is not known but it is more common in people who have diabetes, high blood pressure or heart problems. It can also be caused by inflammation or swelling in the kidneys or a past history of urine infections.

Will it get worse?

Kidney damage is usually permanent but most people with kidney disease will find it gets worse very slowly. A small number of people will get much worse and need dialysis or a transplant.

Why does it matter?

People with kidney disease are more likely to have heart attacks and strokes so it is important to do things that help prevent this. This includes lowering blood pressure, lowering cholesterol, taking aspirin and not smoking. It is also important to avoid certain drugs that can damage the kidneys and you should always tell your pharmacist about your kidney problem if you are buying medication over the counter.

Will I need to go to hospital?

Most people can be looked after by their GP with regular blood tests, blood pressure checks and a review of any symptoms. A small number of people such as those whose kidney function is getting worse will need out patient hospital assessment.

Do I need a special diet?

Depending on your blood test results, a dietician may advise you on a special diet. A diet that is low in salt can also help in controlling blood pressure and problems with fluid retention. Most people need this. You may also be asked to restrict the potassium and/or phosphate in your diet.