GUIDELINES

Early identification and management of chronic kidney disease: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines, which are based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists. Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on bmj.com.

Why read this summary?

Chronic kidney disease is associated with substantial comorbidity including hypertension, cardiovascular disease, anaemia, and renal bone disease. People with chronic kidney disease have a far greater likelihood of cardiovascular death than progression to established renal failure (requiring dialysis or kidney transplantation).[1-4] Chronic kidney disease has been highlighted as a public health problem through the international adoption of the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative staging system and because the prevalence of the disease as defined by the staging system has risen from 10% (in 1988-94) to 13% (in 1999-2004) of the non-institutionalised adult US population.[5-7] The staging system (which comprises five stages, 1-5) defines chronic kidney disease on the basis of either evidence of kidney damage (proteinuria, haematuria, or anatomical abnormality) or an impaired glomerular filtration rate <60 ml/min/1.73 m^2, present on at least two occasions over three months or longer. The use of a threshold of estimated glomerular filtration rate, uncorrected for age or sex, to define disease has been rightly criticised.[8] Nevertheless, based on this definition, the age standardised prevalence of stages 3-5 of chronic kidney disease was 8.5% in a representative UK population.[9]

This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) for identifying and managing chronic kidney disease.

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence. When minimal evidence is available, recommendations are based on the Guideline Development Group's opinion of what constitutes good practice. Evidence levels for the recommendations are given in italics in square brackets.

Classification of chronic kidney disease

Because of evidence about differences in risk of adverse outcomes (particularly cardiovascular disease) with declining glomerular filtration rate, stage 3 should be split into two subcategories defined by glomerular filtration rate (table). [*Based on cohort and observational studies of moderate to high quality*]

The degree of proteinuria is a significant risk factor both for progression of chronic kidney disease and for cardiovascular disease.[10-13] The suffix (p) should be used to denote the presence of proteinuria when staging chronic kidney disease. Proteinuria is defined here as a urinary albumin:creatinine ratio ≥30 mg/mmol (approximately equivalent to a protein:creatinine ratio ≥50 mg/mmol or a urinary protein excretion ≥0.5 g/24 h) (table). [*Based on cohort and observational studies of moderate to high quality*]

Early detection

- Offer people testing for chronic kidney disease (see next section) if they have any of the following risk factors [*based on a review of large cross sectional studies and on the opinion of Guideline Development Group*]:
  - -Diabetes
  - -Hypertension
  - -Cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease, and cerebral vascular disease)
  - -Structural renal tract disease, renal calculi, or prostatic hypertrophy
  - -Multisystem diseases with potential kidney involvement—for example, systemic lupus erythematosus
  - -Family history of stage 5 chronic kidney disease or hereditary kidney disease
  - -Opportunistic haematuria or proteinuria
- Offer people with a diagnosis of chronic kidney disease education and information tailored to the stage and cause of their disease, the associated complications, and the risk of progression. [*Based on evidence from moderate quality randomised controlled trials and cohort studies and on the opinion of Guideline Development Group*]

Measuring renal function

- Estimate glomerular filtration rate from serum creatinine using the IDMS (isotope dilution

mass spectrometry) traceable simplified MDRD (modification of diet in renal disease) equation.[14] [*Based on high quality diagnostic test studies*]

- To detect and identify proteinuria, use urine albumin:creatinine ratio rather than protein: creatinine ratio as the former has greater sensitivity for low levels of proteinuria. For quantification and monitoring of proteinuria, the protein:creatinine ratio can be used as an alternative. Do not use reagent strips to identify proteinuria unless they are capable of measuring albumin at low concentrations and expressing the result as an albumin:creatinine ratio. [*Based on diagnostic test studies of moderate to high quality and on health economic modelling*]
- To detect invisible haematuria, use reagent strips rather than urine microscopy, and keep in mind the following [*based on diagnostic studies of moderate to high quality and on the opinion of the Guideline Development Group*]:

  -Evaluate further if there is a colour change in the reagent strip corresponding to a result of 1+ or more

  -Do not use urine microscopy to confirm a positive reagent strip test

Managing chronic kidney disease

Identify progressive disease

- At least three estimations of glomerular filtration rate are required over at least 90 days.
- In people with a new finding of reduced estimated glomerular filtration rate, repeat the estimation within two weeks to exclude causes of acute deterioration of glomerular filtration rate—for example, acute kidney injury or initiation of treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers.
- Define progression as a decline in estimated glomerular filtration rate of >5 ml/min/1.73m^2 within one year or as >10 ml/min/1.73m^2 within 5 years.
- Focus particularly on those in whom a rate of decline of glomerular filtration rate (were it to continue at the observed rate) would lead to the need for renal replacement therapy.

[*The above four recommendations are based on observational studies of low to moderate quality and on the opinion of the Guideline Development Group*]

People with chronic kidney disease in the following groups should normally be referred for specialist assessment [*based on the opinion of the Guideline Development Group*]:

- Stage 4 and 5 (with or without diabetes)
- Higher levels of proteinuria (albumin:creatinine ratio ≥70 mg/mmol, approximately equivalent to a protein:creatinine ratio ≥100 mg/mmol or urinary protein excretion ≥1 g/24 h) unless this is known to be due to diabetes and already appropriately treated
- Proteinuria (albumin:creatinine ratio ≥30 mg/mmol, approximately equivalent to a protein:creatinine ratio ≥50 mg/mmol, or urinary protein excretion ≥0.5 g/24 h) together with haematuria
- A rapidly declining estimated glomerular filtration rate (>5 ml/min/1.73 m^2 in one year or >10 ml/min/1.73 m^2 within five years)
- Hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses[15]
- People with or suspected of having rare or genetic causes of chronic kidney disease
- Suspected renal artery stenosis.

Control blood pressure

- Aim to keep systolic blood pressure below 140 mm Hg (target range 120-139 mm Hg) and diastolic blood pressure below 90 mm Hg.
- In people with diabetes and chronic kidney disease or when the albumin:creatinine ratio is ≥70 mg/mmol (protein:creatinine ratio ≥100 mg/mmol or urinary protein excretion ≥1 g/24 h), aim to keep the systolic blood pressure below 130 mm Hg (target range 120-129 mm Hg) and the diastolic blood pressure below 80 mm Hg. [*Based on moderate to high quality meta-analyses and observational studies*]
- Offer angiotensin converting enzyme inhibitors and angiotensin receptor blockers to the following people:

  -Those with diabetes and an albumin:creatinine ratio >2.5 mg/mmol (men) or >3.5 mg/mmol

Recommended modifications to the chronic kidney disease staging system

Stage*	Glomerular filtration rate (ml/min/1.73 m^2)	Description
1	≥90	Normal or increased glomerular filtration rate, with other evidence of kidney damage
2	60-89	Slight decrease in glomerular filtration rate, with other evidence of kidney damage
3A	45-59	Moderate decrease in glomerular filtration rate, with or without other evidence of kidney damage
3B	30-44	
4	15-29	Severe decrease in glomerular filtration rate, with or without other evidence of kidney damage
5	<15	Established renal failure

*Use the suffix (p) to denote the presence of proteinuria.

(women) irrespective of the presence of hypertension or stage of kidney disease
-Those without diabetes but who have hypertension and an albumin:creatinine ratio ≥30 mg/mmol (protein:creatinine ratio ≥50 mg/mmol or urinary protein excretion ≥0.5 g/24 h)
-Those without diabetes but who have an albumin:creatinine ratio ≥70 mg/mmol (protein:creatinine ratio ≥100 mg/mmol or urinary protein excretion ≥1 g/24 h) irrespective of the presence of hypertension or cardiovascular disease.

- For people without diabetes but who have hypertension and an albumin:creatinine ratio <30 mg/mmol (protein:creatinine ratio <50 mg/mmol or urinary protein excretion <0.5 g/24 h), offer a choice of antihypertensive treatment to prevent or ameliorate progression of chronic kidney disease. [*Based on high quality meta-analyses, randomised controlled trials, health economic analysis, and NICE guidelines on hypertension and type 2 diabetes*[15 16]]

Manage increased cardiovascular disease risk

- Offer antiplatelet drugs for the secondary prevention of cardiovascular disease. Be aware of the increased risk of minor bleeding in people with chronic kidney disease who are given multiple antiplatelet drugs. [*Based on moderate quality randomised controlled trials and cohort studies*]
- The use of statins for primary prevention of cardiovascular disease in people with chronic kidney disease should not differ from the use in people without kidney disease and should be based on existing risk tables for people with and without diabetes. [*Based on the opinion of the Guideline Development Group*]
- Offer statins for the secondary prevention of cardiovascular disease irrespective of baseline lipid values. [*Based on evidence from high quality meta-analysis and randomised controlled trials*]

Identify anaemia associated with chronic kidney disease

- Check blood haemoglobin concentration in people with stage 3B, 4, and 5 to identify anaemia (haemoglobin <110 g/l) [*Based on the opinion of the Guideline Development Group and on NICE's guideline on anaemia*[17]]

Overcoming barriers

The Guideline Development Group discussed at length the fact that the classification for chronic kidney disease can label people as having a disease solely on the basis of a glomerular filtration rate.[8] Do people with impaired renal function, which does not decline much over time and leads to no overt symptoms, have a disease? Chronic kidney disease is increasingly prevalent with increased age. People aged over 70 years who have an estimated glomerular filtration rate in the range 45-59 ml/min/1.73 m^2 that is stable over time and who have no other evidence of kidney damage are unlikely to experience complications related to chronic kidney disease. Further research is needed to determine whether or not this is a function of ageing and/or a consequence of the use of the MDRD (modification of diet in renal disease) equation to estimate glomerular filtration rate.

The reagent strip is still the method of choice for detecting blood in urine, but relinquishing the reagent strip for detecting proteinuria will be a major change in practice. Albumin is the principal component of proteinuria in glomerular disease. Reagent strips in clinical practice predominantly detect albumin, not total protein, but are not reliably quantitative. The albumin:creatinine ratio has far greater sensitivity than the protein:creatinine ratio for detecting low levels of proteinuria and is better for identifying chronic kidney disease early. There is strong evidence linking urinary albumin excretion to cardiovascular events and kidney disease progression in people with and without diabetes.[18-22] However, the literature on chronic kidney disease in patients without diabetes has been largely predicated on 24 h urinary total protein excretion, which correlates directly with the protein:creatinine ratio, and a specialist may have clinical reasons for using this ratio to quantify and monitor important levels of proteinuria.

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1 Drey N, Roderick P, Mullee M, Rogerson M. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis* 2003;42:677-84.
2 John R, Webb M, Young A, Stevens PE. Unreferred chronic kidney disease: a longitudinal study. *Am J Kidney Dis* 2004;43:825-35.
3 Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;164:659-63.
4 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
5 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(suppl 1):S1-266.
6 Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: third national health and nutrition examination survey. *Am J Kidney Dis* 2003;41:1-12.
7 Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038-47.

8 Glassock RJ, Winearls C. An epidemic of chronic kidney disease: fact or fiction? *Nephrology Dialysis and Transplantation* 2008;23:1117-21.
9 Stevens PE, O'Donoghue DJ, de Lusignan S, van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. *Kidney Int* 2007;72:92-9.
10 Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003;63:1468-74.
11 Klausen K, Borch JK, Feldt RB, Jensen G, Clausen P, Scharling H, et al. Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004;110:32-5.
12 Hillege HL, Fidler V, Diercks GF, van Gilst WH, de ZD, van Veldhuisen DJ, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002;106:1777-82.
13 Arnlov J, Evans JC, Meigs JB, Wang TJ, Fox CS, Levy D, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham heart study. *Circulation* 2005;112:969-75.
14 Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F. Expressing the MDRD study equation for estimating GFR with standardised serum creatinine values. *Clin Chem* 2007;53:766-72
15 National Institute for Health and Clinical Excellence. *Hypertension: management of hypertension in adults in primary care*. 2006. (Clinical guideline 34.) www.nice.org.uk/guidance/index.jsp?action=byID&o=10986
16 National Institute for Health and Clinical Excellence. *Type 2 diabetes: the management of type 2 diabetes (update)*. 2008. (Clinical guideline 66.) www.nice.org.uk/CG66.
17 National Institute for Health and Clinical Excellence. *Anaemia management in people with chronic kidney disease (CKD)*. 2006. (Clinical guideline 39.) www.nice.org.uk/CG39.
18 Foster MC, Hwang SJ, Larson MG, Parikh NI, Meigs JB, Vasan RS, et al. Cross-classification of microalbuminuria and reduced glomerular filtration rate: associations between cardiovascular disease risk factors and clinical outcomes. *Arch Intern Med* 2007;167:1386-92.
19 Hallan S, Astor B, Romundstad S, Aasarod K, Kvenild K, Coresh J. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: the HUNT II study. *Arch Intern Med* 2007;167:2490-6.
20 Cirillo M, Lanti MP, Menotti A, Laurenzi M, Mancini M, Zanchetti A, et al. Definition of kidney dysfunction as a cardiovascular risk factor: use of urinary albumin excretion and estimated glomerular filtration rate. *Arch Intern Med* 2008;168:617-24.
21 Brantsma AH, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT. Extended prognostic value of urinary albumin excretion for cardiovascular events. *J Am Soc Nephrol* 2008;19:1785-91.
22 Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT, et al. Cardiovascular and renal outcome in subjects with K/DOQI stage 1-3 chronic kidney disease: the importance of urinary albumin excretion. *Nephrol Dial Transplant* 2008; advance access 18 Jul, doi:10.1093/ndt/gfn356

Commentary: Controversies in NICE guidance on chronic kidney disease

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New NICE guidelines seek to improve health outcomes for individuals with chronic kidney disease. They emphasise the role of primary care in dealing with two important questions: how should we assess and reduce the risk of cardiovascular events that are present among all patients with chronic kidney disease; and how can we identify the minority of individuals who are likely to progress to advanced kidney disease (and require specialist nephrological services)?

Definition and staging

One of the most controversial issues in writing such guidelines is the definition of chronic kidney disease, which relies on the ability to estimate glomerular filtration rate (GFR). As the NICE authors recognise, the current, creatinine based formulas are woefully inadequate among the 90-95% of the population who have "normal" or "moderately impaired" kidney function (GFR >45 ml/min/1.73m^2).

The staging system based on GFR largely ignores other measures of kidney damage—proteinuria, for example—which are useful indicators of the risk of progression of renal disease. The consequence is that many individuals (particularly those aged over 70 years) are given a diagnostic label of stage 3 disease. Although such patients are at increased risk of death and cardiovascular events, they are unlikely to develop advanced kidney disease. Labelling them as having "kidney disease" may be unnecessarily worrying for patients and unduly distracting for doctors.[1] In this respect, the NICE recommendations to split stage 3 disease into stage 3A and 3B (45-59 and 30-44 ml/min/1.73m^2, respectively), and to use the suffix "p" for all patients with important proteinuria, should help identify those at highest risk of renal progression and its complications.

Cardiovascular and renal outcomes

The guidelines acknowledge the competing risks of renal progression and death.[2] They emphasise the importance of tackling cardiovascular risk in all patients with chronic kidney disease, and reserve referral to specialist nephrological services largely for people with metabolic complications or who are likely to require renal replacement therapy. However, reliable tools with which to estimate the risks of renal progression, cardiovascular events, or death among these patients are currently lacking.

Reducing the risk of vascular events is an important goal for all patients with chronic kidney disease (regardless of risk of renal progression). Among those with moderately impaired kidney function (stage 3A ±p), treatments that lower cholesterol are likely to produce reductions in relative risk that are similar to those seen in the general population.[3] However, the situation among patients with advanced disease is much less clear. The risk of vascular events is greatly

increased in this group, but structural heart disease (resulting in progressive pump failure and sudden cardiac death) is more common than classical myocardial infarction—a pattern reminiscent of advanced heart failure. Randomised trials of statins in patients with end stage renal disease have so far failed to show significant reductions in vascular events, although trials are ongoing.[4] Large trials of blood pressure lowering have not been carried out in such patients, and there are some concerns regarding the tolerability and safety of such drugs in this group. The recommendation to maintain systolic blood pressure within a target range (rather than below an upper limit) is not supported by reliable evidence.

Slowing the rate of renal progression is particularly important for the minority of patients (those with proteinuria) who might develop advanced kidney disease. Although renin-angiotensin system blockade may be superior to other antihypertensive agents in slowing progression, aggressive treatment of blood pressure is required to reduce vascular risk in all patients, and most people will require multiple drugs.

Improving the evidence base for guidelines

The research base in chronic kidney disease is not as mature as that in other chronic diseases, such as diabetes, and the recommendations for new research emphasise the uncertainty in many areas, including the measurement of kidney function (particularly in older and ethnic populations) and the assessment and treatment of cardiovascular risk. The authors have generally resisted the temptation to make strong statements in areas where there is inadequate evidence to support them, instead using sound clinical judgment where evidence is difficult to find or supply (such as for referral criteria). Although some will be disappointed by the adoption of an unproved staging system, these guidelines are likely to be valuable to general practitioners who manage the majority of such patients. It is now imperative that the attention of funders, academics, and the renal and primary care communities is focused on improving the evidence base on which future versions will be founded.[5]

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1 Glassock RJ, Winearls C. Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008;3:1563-8.
2 O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 2007;18:2758-65.
3 Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2004;110:1557-63.
4 Baigent C, Landray M. Study of heart and renal protection (SHARP). *Kidney Int Suppl* 2003;84:S207-10.
5 Himmelfarb J. Chronic kidney disease and the public health: gaps in evidence from interventional trials. *JAMA* 2007;297:2630-3.

A memorable patient

Welcome to Mr Miracle

I first met Mr M four years ago during a teaching session to medical students. He had had diabetes for 75 years and was attending the outpatient clinic for a plantar foot ulcer. His diabetes was diagnosed at the age of 3 years in 1929. Although insulin was first used in humans in 1922, it was expensive and only became widely available in the mid-1930s. In 1929 insulin treatment was not widely available or known about, and M's doctor simply advised a strict starvation diet that was low in carbohydrates. His parents were told that his diabetes was untreatable and that he would be expected to die within a year. His father was advised to take him to a hospice for his inevitable death and not to send him to school.

M's father, however, had heard of a doctor in London who was treating patients with diabetes with a miracle drug and, as M was becoming rapidly more unwell, took him by train to King's College Hospital in London to be treated with insulin by Dr R D Lawrence, the co-founder of the British Diabetes Association (now Diabetes UK) and one of the first to campaign for insulin to be used widely for all, regardless of their status. M duly received insulin treatment and rapidly got better.

Indeed, he survived 79 years with insulin treatment until his recent death at the age of 82. He had lived with only a few complications of diabetes until the last 10 years of his life.

During the time that I had the pleasure of meeting Mr M, I learnt a vast amount about the difficulties experienced by people with type 1 diabetes. He remembered being deliberately made to have a hypoglycaemic episode. He had to take a strict carbohydrate diet, weighing foods with scales. He was taught to use thick glass syringes, which were expensive and needed autoclaving regularly. Needles were thick and had to be reused and sharpened by hand to prolong their life. He had to boil his urine to test it using home made kits. Adjustments of insulin were based on symptoms of hypoglycaemia as home blood glucose recording, taken for granted these days, wasn't available. Despite failing health in his later years, M always remained optimistic and positive.

I always introduced Mr M to medical students as a miracle. He had reminded me that less than a century ago insulin dependent diabetes had a hopeless prognosis. The discovery, isolation in the laboratory, and subsequent clinical use of insulin reminds me of the miracle drug I use on a daily basis.

Patient consent not required: patient anonymised, dead, or hypothetical.

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