Renal Medicine 2

Early recognition and prevention of chronic kidney disease

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This is the second in a **Series** of three papers about renal medicine

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Chronic kidney disease is a common disorder and its prevalence is increasing worldwide. Early diagnosis on the basis of presence of proteinuria or reduced estimated glomerular filtration rate could permit early intervention to reduce the risks of cardiovascular events, kidney failure, and death that are associated with chronic kidney disease. In developed countries, screening for the disorder is most efficient when targeted at high-risk groups including elderly people and those with concomitant illness (such as diabetes, hypertension, or cardiovascular disease) or a family history of chronic kidney disease, although the role of screening in developing countries is not yet clear. Effective strategies are available to slow the progression of chronic kidney disease and reduce cardiovascular risk. Treatment of high blood pressure is recommended for all individuals with, or at risk of, chronic kidney disease. Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers is preferred for patients with diabetic chronic kidney disease or those with the proteinuric non-diabetic disorder. Glycaemic control can help prevent the onset of early stages of chronic kidney disease in individuals with diabetes. Use of statins and aspirin is beneficial for most patients with chronic kidney disease who are at high cardiovascular risk, although research is needed to ascertain how to best prevent cardiovascular disease in this cohort. Models of care that facilitate delivery of the many complex aspects of treatment simultaneously could enhance management, although effects on clinical outcomes need further assessment. Novel clinical methods to better identify patients at risk of progression to later stages of chronic kidney disease, including kidney failure, are needed to target management to high-risk subgroups.

Introduction

Chronic kidney disease is a common disorder that is associated with raised risk of cardiovascular disease, kidney failure, and other complications. The ageing of populations along with the growing global prevalence of diabetes and other chronic non-communicable diseases has led to corresponding worldwide increases in prevalence of chronic kidney disease and kidney failure. Strategies for early identification and treatment of people with chronic kidney disease, who are at risk of cardiovascular events and progression to the end stage of chronic kidney disease (kidney failure), are needed worldwide, especially in countries where renal replacement is not readily available. This Review will discuss potential strategies for early identification and treatment of such high-risk patients to reduce morbidity and mortality associated with later stages of chronic kidney disease.

Definition, classification, and staging

Chronic kidney disease is defined by a sustained reduction in glomerular filtration rate or evidence of structural or functional abnormalities of the kidneys on urinalysis, biopsy, or imaging.[1–3] A five-stage classification system for the disorder has been established by the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative and adopted internationally by the Kidney Disease: Improving Global Outcomes (KDIGO) initiative to guide identification of cases and facilitate management (table 1).[2–5] In the clinical setting, glomerular filtration rate is generally estimated on the basis of creatinine concentration in serum and demographic features (age, sex, and ethnic origin) with the Cockcroft-Gault[6] or MDRD (Modification of Diet in Renal Disease) study[7,8] equations. The severity of chronic kidney disease in the five-stage scheme is based mainly on glomerular filtration rate (table 1), although risk of complications at a given rate is modified substantially by the amount of proteinuria. The MDRD study equation was developed in a population with chronic kidney disease from the USA, and its precision and accuracy is reduced with increasing glomerular filtration rate and in different ethnic groups.[7] Unique prediction equations have been derived and validated for other nationalities.[9,10]

Since the concentration of creatinine in serum alone is insensitive to early disease, identification and staging of chronic kidney disease on the basis of estimated glomerular filtration rate was an important advance that facilitated both research and clinical care. Nonetheless,

Search strategy and selection criteria

We searched the Cochrane Library, Medline, and Embase up to the end of August, 2009, with the search terms "chronic kidney disease" or "chronic renal insufficiency" in combination with "diagnosis", "screening", "prevention", "control", "treatment", or "intervention". Largely, we selected publications from the past 10 years from journals with high impact factors but did not exclude frequently referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles were included when they provided comprehensive overviews beyond the scope of this Review. We did not limit by language or date of publication.

controversy continues to surround the existing classification system, specifically with regard to its propensity to overestimate prevalence; its failure to fully incorporate prognostic information from proteinuria; and the potential for misclassification of some people as having chronic kidney disease in the absence of clinically relevant kidney disease.[11] New equations for estimation of glomerular filtration rate from serum creatinine (eg, the Chronic Kidney Disease Epidemiology Collaboration equation) show enhanced precision and accuracy, particularly at high rates, and could overcome some of these limitations.[12] Although current interest exists for use of new markers, such as cystatin C, to detect early chronic kidney disease,[13] or for combination of both serum creatinine and cystatin C for estimation equations to increase accuracy,[14] the clinical role of such markers remains to be defined. The current chronic kidney disease staging system is expected to evolve in response to these considerations, and the KDIGO initiative held an international consensus conference to discuss the issue in late 2009.

Epidemiology

The prevalence of chronic kidney disease has been estimated in several developed countries but remains unknown in much of the developing world.[15] Adoption of standard definitions and use of the MDRD study equation for estimated glomerular filtration rate have facilitated international comparisons. When chronic kidney disease is defined solely by estimated glomerular filtration rates less than 60 mL per min 1·73 m², approximate prevalence is 2·5–11·2% of the adult population across Europe, Asia, North America, and Australia.[15] In the USA, chronic kidney disease by this definition is over 200-fold more common than kidney failure treated by renal replacement therapy; this ratio is several-fold higher in countries of low and middle income with restricted access to renal replacement therapy.[16] The prevalence of chronic kidney disease rises substantially (to 10·5–13·1%) when also defined by presence of microalbuminuria or macroalbuminuria (figure 1).[9,17–22] Up to 25–35% of people older than 65 years meet current criteria for chronic kidney disease,[15] although whether the decline in glomerular filtration rate represents disease or is part of the ageing process is controversial.[23] The frequency of treated kidney failure, however, does increase with age in developed countries.[24] Prevalence of chronic kidney disease in the USA rose from 10·0% to 13·1% between 1988–94 and 1999–2004;[25] the ageing population and growth in the prevalence of diabetes, hypertension, and obesity seem to account partly for this increase.[25]

Chronic kidney disease has many potential causes, which vary in frequency between different populations (figure 2).[1] In developed countries, age, hypertension, diabetes, increased body-mass index, and smoking are associated consistently with chronic kidney disease,[26–28] as is a history of established cardiovascular disease.[29] In the developing world, infectious diseases are also important causes of kidney failure, including infections due to bacteria (tuberculosis in India and the Middle East, streptococcal infection in Africa), viruses (HIV and hepatitis B and C in Africa), and parasites (schistosomiasis in Africa and Latin America, leishmaniasis in Africa and Asia, and malaria in Africa).[30] In Asia, Africa, and the Middle East, chronic kidney disease has been attributed to environmental and occupational exposure to

	Description	GFR (mL per min per 1·73 m²)
–	At risk	≥60 (with risk factors for chronic kidney disease)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mildly diminished GFR	60–89
3*	Moderately reduced GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease (kidney failure)	<15

Modified from reference 1, with permission of Elsevier. GFR=glomerular filtration rate. *UK National Institute for Health and Clinical Excellence guidelines split stage 3 into two subcategories (3A, GFR 45–59 mL per min per 1·73 m²; and 3B, GFR 30–44 mL per min per 1·73 m²) and use the suffix (p) to denote the presence of proteinuria.

Table 1: **Stages of chronic kidney disease, as defined by the Kidney Disease Outcomes Quality Initiative**

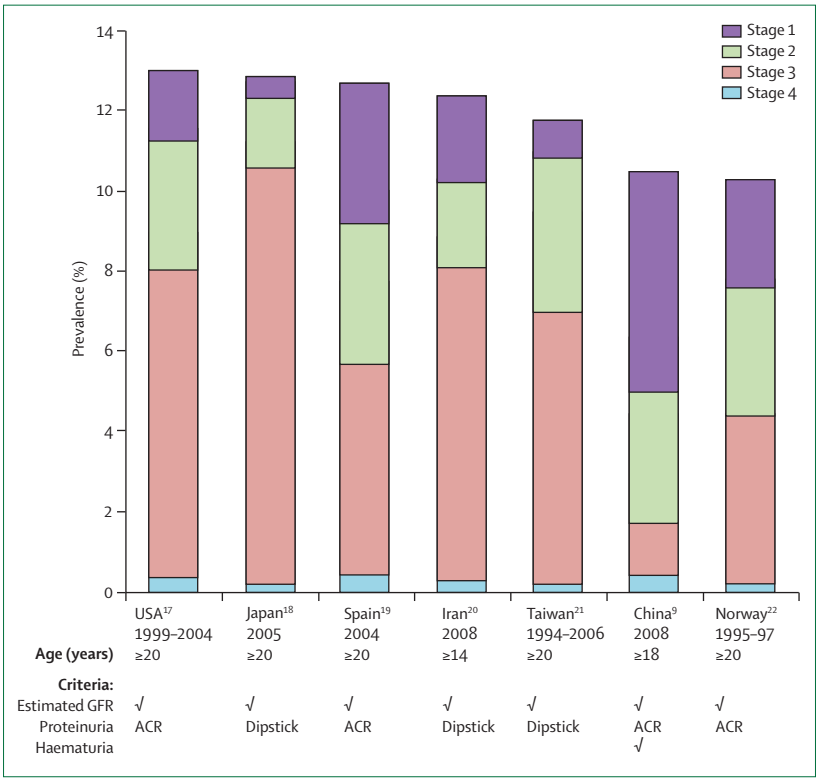

Figure 1: **Population-based estimates of prevalence of chronic kidney disease**
ACR=albumin-to-creatinine ratio. GFR=glomerular filtration rate.

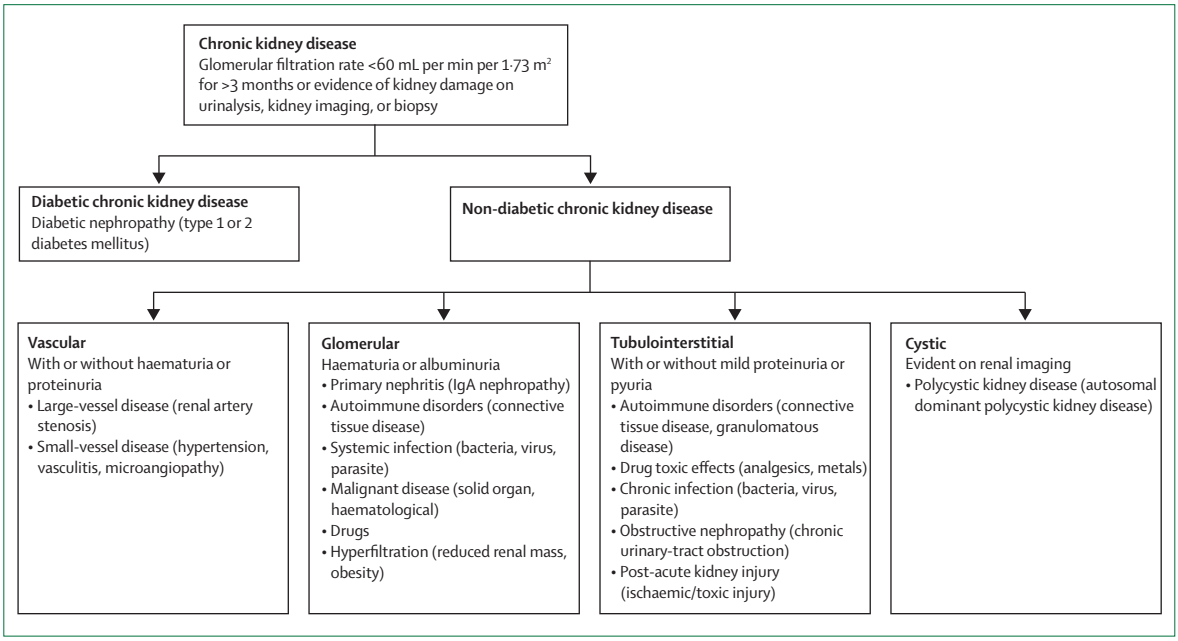

Figure 2: **Classification and selected examples of causes of chronic kidney disease**

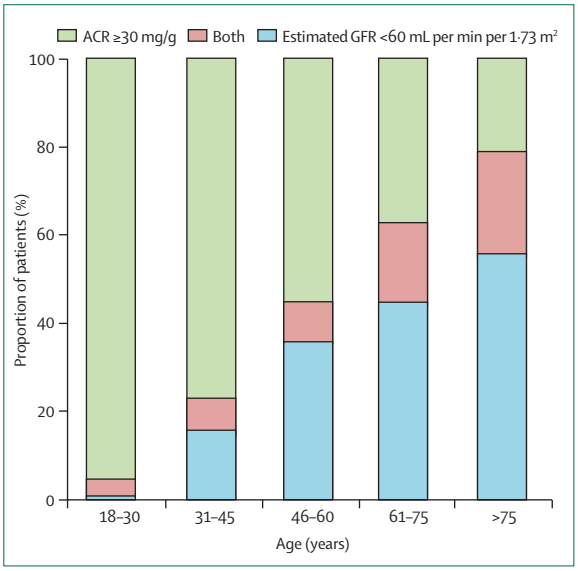

Figure 3: **Proportions of patients with chronic kidney disease identified by albumin-to-creatinine ratio, estimated glomerular filtration rate, or both**
ACR=albumin-to-creatinine ratio. GFR=glomerular filtration rate. Data taken from the US National Health and Nutrition Examination Survey, 1999–2004. Adapted from reference 58, with permission of Elsevier.

chemicals, including lead, cadmium, and mercury.[31,32] The rapidly increasing burden of chronic non-communicable diseases that has been seen in many developing nations will probably lead to striking corresponding rises in prevalence of chronic kidney disease and kidney failure in these countries over the next two decades.[30,33]

Cardiovascular disease is the leading cause of mortality in chronic kidney disease,[34,35] and even mild reductions in glomerular filtration rate are associated with excess cardiovascular risk.[36] At any given level of kidney function, raised amounts of proteinuria are associated with increased cardiovascular morbidity and mortality.[37–39] In patients with cardiovascular disease, diabetes, or hypertension, presence of chronic kidney disease (especially with proteinuria) is a so-called risk multiplier that identifies the subset of individuals who are most likely to have adverse outcomes.[40] Additional disorders that accompany chronic kidney disease include infection,[41] acute kidney injury,[42] cognitive dysfunction,[43] and impaired physical functioning.[44]

Because availability of renal replacement therapies is limited in countries of low and middle income, most patients around the world with chronic kidney disease will die from kidney failure without receiving dialysis or transplantation.[31] In developed countries, many more people will die from cardiovascular disease rather than progress to kidney failure requiring renal replacement.[36,45,46] A low estimated glomerular filtration rate at presentation and the amount of proteinuria are the strongest independent risk factors for kidney failure.[47,48] Reduction in level of proteinuria over time correlates with a slowing of the rate of decline in glomerular filtration rate, making proteinuria an important prognostic variable and potential therapeutic target.[49,50]

Strategies for early recognition

Early identification of patients with chronic kidney disease is desirable because interventions can then be implemented to reduce risk of cardiovascular events or progression to kidney failure. The high prevalence of

	n	Study population			Background treatment	Control treatment	Intervention treatment	Study duration (years)	Relative risk reduction with intervention
		Inclusion criteria	Kidney function	Proteinuria					
ACE inhibitors									
Jafar (2001)[83]	1860	Non-diabetic chronic kidney disease	Mean serum creatinine 203 mmol/L	Mean 1·8 g per day	Concomitant antihypertensive drugs	Placebo, nifedipine, atenolol, or acebutolol	ACE inhibitor (captropril, enalapril, cilazapril, benazepril, or ramipril)	2–4	37% reduction in kidney failure*; 38% reduction in composite of doubling of serum creatinine or kidney failure
AASK (Agodoa; 2001)[84]	653	African-American with hypertensive chronic kidney disease	GFR 20–65 mL per min per 1·73 m²	Median 112 mg per day	Other antihypertensive drugs, plus randomised to mean arterial blood pressure goal of 102–107 mm Hg or <92 mm Hg	Amlodipine	Ramipril 2·5–10 mg once daily	3	38% reduction in composite of 50% or 25 mL per min per 1·73 m² decrease in GFR, kidney failure, or death*
ALLHAT (2005)[88]	31 897	Hypertension and ≥1 other coronary disease risk factor (38% diabetes mellitus)	18% with estimated GFR <60 mL per min per 1·73 m²	NR	Other antihypertensive drugs to achieve blood pressure <140/90 mm Hg	Chlorthalidone	Lisinopril 10–40 mg daily	4·9	No significant reduction in kidney failure for all patients or in stratum with baseline estimated GFR <60 mL per min per 1·73 m²
Hou (2006)[85]	224	Non-diabetic chronic kidney disease with persistent proteinuria	Serum creatinine 274–442 mmol/L	>0·3 g per day	Goal blood pressure <130/80 mm Hg	Other open-label antihypertensive drug	Benazepril 10 mg twice daily	3·4	43% reduction in composite of doubling of serum creatinine, kidney failure, or death*
Angiotensin-receptor blockers									
TRANSCEND (2009)[92]	5927	Documented cardiovascular disease with end-organ damage (36% diabetes mellitus), intolerant of ACE inhibitors	Mean serum creatinine 92 mmol/L	10% with microalbuminuria, 1% with macroalbuminuria	..	Placebo	Telmisartan 80 mg daily	4·7	No reduction in composite of doubling of serum creatinine, kidney failure, or death
ACE inhibitor and angiotensin-receptor blocker combination									
ONTARGET (2008)[91,93]	25 620	Cardiovascular disease or diabetes (38% diabetes mellitus) with end-organ damage	Mean serum creatinine 94 mmol/L	13% with microalbuminuria, 4% with macroalbuminuria	..	Telmisartan or ramipril alone	Ramipril 10 mg daily and telmisartan 80 mg daily	4·7	Increased risk of doubling of serum creatinine, dialysis, or death with combination

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chronic kidney disease,[15] absence of symptoms until disease is advanced, accessibility of laboratory tests for diagnosis and prognostication,[51] and availability of treatments that prevent complications suggest that screening for chronic kidney disease could be worthwhile. However, the role of population-based screening remains controversial.[52] Screening for proteinuria is appealing because it is easy to undertake, predicts cardiovascular morbidity and mortality, and might be a better predictor of future decline in glomerular filtration rate than a reduction in estimated glomerular filtration rate.[53] However, on the basis of data from the USA, annual dipstick testing to detect proteinuria in all adults older than 50 years is not cost effective unless restricted to high-risk groups (eg, older individuals or those with diabetes or hypertension).[54,55] Projections of an analysis from Norway suggested that screening for a reduction in estimated glomerular filtration rate would be most effective if targeted at people with hypertension, diabetes, or those older than 55 years of age, although risk of kidney failure in those detected would remain low.[56] Data from the general US population indicate that albuminuria is the most typical marker of chronic kidney disease in young adults, whereas reduced estimated glomerular filtration rate is the most frequent abnormality in elderly people with the disorder (figure 3).[57,58] Albuminuria and estimated glomerular filtration rate might have complementary roles in screening different age groups, and use of the two variables together could be efficient for identification of people at high risk of progression to kidney failure.

Screening with urinalysis to detect glomerulonephritis has been done routinely for all working adults and school-aged children (age 6–18 years) in Japan since the 1970s, and this strategy seems to have lowered the incidence of

	n	Study population			Background treatment	Control treatment	Intervention treatment	Study duration (years)	Relative risk reduction with intervention
		Inclusion criteria	Kidney function	Proteinuria					
(Continued from previous page)									
Blood pressure target									
MDRD study (1994)[76]	840	Chronic kidney disease, excluding patients with diabetes receiving insulin	Substudy A, GFR 25–55 mL per min per 1·73 m²; substudy B, GFR 13–24 mL per min per 1·73 m²	Substudy A, 0·9 g per day; substudy B, 1·4 g per day	Also randomised to usual or low-protein diet	Usual mean arterial blood pressure target ≤107 mm Hg for patients age ≤60 years and ≤113 mm Hg for patients ≥61 years of age	Low mean arterial blood pressure target of 92 mm Hg for patients age 60 years and ≤98 mm Hg for patients ≥61 years	2·2	No significant reduction in kidney failure or death†
AASK (Wright; 2002)[77]	1094	African-American with hypertensive chronic kidney disease	GFR 20–65 mL per min per 1·73 m²	Mean 0·6 g per day	Randomised to metoprolol, ramipril, or amlodipine, plus use of other antihypertensives to achieve blood pressure targets	Usual blood pressure goal, mean arterial blood pressure 102–107 mm Hg	Lower blood pressure goal, mean arterial blood pressure ≤92 mm Hg	4	No reduction in composite of 50% or 25 mL per min per 1·73 m² decrease in GFR or death*
REIN-2 (2005)[79]	335	Non-diabetic nephropathy with persistent proteinuria	Creatinine clearance <70 mL per min per 1·73 m²	≥1 g per day	Ramipril 2·5–5 mg daily	Diastolic blood pressure <90 mm Hg	Addition of amlodipine to target blood pressure <130/80 mm Hg	1·6	Study stopped after first interim analysis due to futility; no reduction in kidney failure*

ACE=angiotensin-converting-enzyme. AASK=African-American Study of Kidney Disease. GFR=glomerular filtration rate. ALLHAT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. NR=not reported. TRANSCEND=Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. ONTARGET=Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial. MDRD=Modification of Diet in Renal Disease. REIN=Ramipril Efficacy In Nephropathy. *Primary endpoint of study. †Secondary endpoint of study.

***Table 2*: Randomised controlled trials of prevention or early intervention for non-diabetic chronic kidney disease**

kidney failure secondary to glomerulonephritis.[59] In the USA, the National Kidney Foundation's Kidney Early Evaluation Program (KEEP) is a community-based initiative that recruits adults at high risk of chronic kidney disease for a health-screening questionnaire and measurement of serum creatinine, urine microalbumin, and albumin-to-creatinine ratio.[58,60] This targeted approach has been successful for identification of an enriched population with chronic kidney disease for follow-up with a doctor or at a local public health centre.[60] Mass screening for kidney disease might also be feasible in developing countries,[61] although the health and economic effects of such programmes need further evaluation.[61] If screening is done, health systems must be able to provide appropriate medical care for individuals with newly detected chronic kidney disease.[52]

Diagnostic testing for chronic kidney disease is advocated for several groups of patients who seek medical attention for other reasons,[52] especially those with diabetes, hypertension, cardiovascular disease, structural renal-tract disease, autoimmune diseases with potential for kidney involvement, and a family history of chronic kidney disease or hereditary kidney disease.[62–64] A risk score based on information available routinely (ie, age, sex, hypertension, diabetes, cardiovascular disease, anaemia) has been developed to enhance identification of individuals with occult chronic kidney disease in the USA,[29] but similar methods are not available for other populations.

Automated reporting of estimated glomerular filtration rate has been initiated in laboratories worldwide to facilitate early detection of chronic kidney disease,[65] although its role remains contentious.[66,67] Introduction of reporting of estimated glomerular filtration rate, accompanied by education of doctors, increased the recognition of chronic kidney disease from 27% to 85% of cases.[68] Although automated reporting of estimated glomerular filtration rate boosts the number of referrals to nephrologists, with the greatest rises in women, elderly people, and individuals with stage 3 chronic kidney disease,[69,70] it might also lead to unnecessary referrals and overwhelm health resources. Whether automatic estimated glomerular filtration rate reporting enhances care of high-risk individuals and clinical outcomes is under investigation.[71]

Prevention and intervention

Initial management of chronic kidney disease entails identification of reversible disorders (such as urinary-tract obstruction, infection, or autoimmune disease) that could respond to specific treatment and lead to stabilisation or improvement in kidney function. Irrespective of underlying

	n	Study population			Background treatment	Control treatment	Intervention treatment	Study duration (years)	Relative risk reduction with intervention
		Inclusion criteria	Kidney function	Proteinuria					
ACE inhibitors									
Lewis (1993)[96]	409	100% type 1 diabetes	Serum creatinine <221 mmol/L	≥500 mg per day	Target blood pressure <140/90 mm Hg	Placebo	Captopril 25 mg three times daily	3	50% in composite of death, dialysis, and transplantation; 48% reduction in risk of doubling of serum creatinine*
HOPE (2000)[100]	2272	100% type 2 diabetes (subgroup)	Mean 94 mmol/L	32% micro-albuminuria	..	Placebo	Ramipril	4·5	27% reduction in new overt nephropathy
BENEDICT (2004)[101]	1204	100% type 2 diabetes	Serum creatinine <133 mmol/L	Normal	Additional antihypertensive drugs to target blood pressure 120/80 mm Hg	Placebo	Trandalopril or trandalopril plus verapamil	3·6	Delayed onset of new microalbuminuria by factors of 2·6 (for trandalopril plus verapamil) and 2·1 (for trandalopril)*
ADVANCE (2007)[103]	11140	100% type 2 diabetes	Mean serum creatinine 87 mmol/L	26% micro-albuminuria	Other antihypertensive drugs at discretion of doctor	Placebo	Perindopril 4 mg plus indapamide 1·25 mg	4·3	21% reduction in composite of new microalbuminuria, doubling of serum creatinine to ≥200 mmol/L, renal replacement therapy, or death due to renal disease†
Angiotensin-receptor blockers									
IDNT (2001)[98]	1715	100% type 2 diabetes	Serum creatinine <265 mmol/L	≥900 mg per 24 h	Other antihypertensive drugs targeting blood pressure <135/85 mm Hg	Placebo or amlodipine	Irbesartan 75–300 mg daily	2·6	20% (*vs* placebo) and 23% (*vs* amlodipine) reductions in composite of doubling of serum creatinine concentration, kidney failure, or death*
RENAAL (2001)[97]	1513	100% type 2 diabetes	Serum creatinine <265 mmol/L	>500 mg per day	Other antihypertensive drugs targeting blood pressure <140/90 mm Hg	Placebo	Losartan 50–100 mg daily	3·4	16% reduction in composite of doubling of serum creatinine, kidney failure, or death*
IRMA (2001)[99]	590	100% type 2 diabetes	Serum creatinine ≤113 mmol/L in men, ≤97 mmol/L in women	100% micro-albuminuria	Other antihypertensive drugs targeting blood pressure <135/85 mm Hg	Placebo	Irbesartan 150 mg or 300 mg daily	2	39% (for 150 mg) and 70% (for 300 mg) reductions in new overt nephropathy*
DIRECT (2009)[104]	5231	64% type 1 diabetes, 36% type 2 diabetes	Serum creatinine <110 mmol/L in women, <130 mmol/L in men	Normal	Other antihypertensive drugs if blood pressure >140/90 mm Hg	Placebo	Candesartan 16–32 mg daily	4·7	No reduction in incidence of new microalbuminuria†

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cause, typical goals of management for all patients with chronic kidney disease include prevention of cardiovascular events and reduction of the rate of progression of the disorder (thereby delaying or preventing kidney failure and other complications). Many clinical trials have been undertaken solely in patients with non-diabetic chronic kidney disease (table 2) or in those with diabetic chronic kidney disease (table 3). Pharmacological therapy for these two groups is discussed below.

Pharmacological treatment of non-diabetic chronic kidney disease

Treatment of hypertension is the mainstay of management to slow the progression of chronic kidney disease and reduce cardiovascular risk.[72] Observational work has indicated an increased risk of progression of chronic kidney disease and of kidney failure as blood pressure rises above 130/80 mm Hg.[73–75] The current recommended blood pressure target for patients with chronic kidney disease is 125–135/75–85 mm Hg, but all guidelines advocate a goal lower than that for the general population.[1,4,5] Findings of the MDRD[76] and AASK studies[77] did not show substantial reductions in incidence of kidney failure or death, or decline of glomerular filtration rate when a lower mean arterial blood pressure of 92 mm Hg (equivalent to <125/75 mm Hg) was targeted. Although some suggestion of benefit has been made with such goals in specific subgroups (eg, patients with proteinuria >1 g per day)[75,76] or with extended follow-up,[78] this outcome remains uncertain. The REIN-2 study

	n	Study population			Background treatment	Control treatment	Intervention treatment	Study duration (years)	Relative risk reduction with intervention
		Inclusion criteria	Kidney function	Proteinuria					
(Continued from previous page)									
Glycaemic control									
DCCT (2000)[109]	1441	100% type 1 diabetes	Mean creatinine clearance 129 mL per min	Normal or micro-albuminuria	Diet and exercise education	Insulin twice daily	Insulin ≥3 times daily targeting blood glucose <6·7 mmol/L preprandial, <10 mmol/L postprandial, and HbA_{1c} <6%	6·5	34% reduction in new microalbuminuria and 56% reduction in new albuminuria†
Kumamoto study (1995)[110]	110	100% type 2 diabetes	Serum creatinine <132 mmol/L	<300 mg per day	..	1–2 daily injections intermediate-acting insulin	≥3 times daily injections rapid-acting and intermediate-acting insulin targeting fasting blood glucose <7·7 mmol/L, postprandial blood glucose <11 mmol/L, HbA_{1c} about 7·0%	6	70% reduction in new microalbuminuria or new nephropathy
UKPDS (1998)[95]	3867	100% type 2 diabetes	Serum creatinine <175 mmol/L	1·9% proteinuria	Dietary advice	Maintain fasting blood glucose <15 mmol/L with sulphonylurea or insulin, plus metformin if obese	Fasting blood glucose <6 mmol/L, preprandial blood glucose 4–7 mmol/L with sulphonylurea, insulin	10	30% and 42% non-significant reductions in new microalbuminuria†

ACE=angiotensin-converting-enzyme. HOPE=Heart Outcomes Prevention Evaluation. BENEDICT=Bergamo Nephrologic Diabetes Complications Trial. ADVANCE=Action in Diabetes and Vascular disease: preterax and diamicron-MR Controlled Evaluation. IDNT=Irbesartan in Diabetic Nephropathy Trial. RENAAL=Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan. IRMA=Irebesartan in patients with type 2 Diabetes and Microalbuminuria. DIRECT=Diabetic Retinopathy Candesartan Trials. DCCT=Diabetes Control and Complications. HbA_{1c}=glycosylated haemoglobin. UKPDS=UK Prospective Diabetes Study. *Primary endpoint of study. †Secondary endpoint of study.

***Table 3*: Randomised controlled trials of prevention or early intervention for diabetic chronic kidney disease**

examined the effect of addition of a non-dihydropyridine calcium-channel blocker to background treatment with an angiotensin-converting-enzyme inhibitor to achieve a lower-than-usual target blood pressure of less than 130/80 mm Hg. The study was terminated after the first interim analysis when data indicated that the combined intervention to achieve lower blood pressure would not show a reduction in the primary outcome of kidney failure.[79] Whether achievement of reduced levels of blood pressure with alternative antihypertensive combinations, or maintenance of these levels of blood pressure for a prolonged period, can further preserve kidney function remains unclear.[78]

Angiotensin-converting-enzyme inhibitors are the best-studied agents for slowing the progression of non-diabetic kidney disease. Their effectiveness has been shown most clearly in individuals with proteinuric chronic kidney disease, and they are recommended as first-line treatment in this subgroup.[1,4,5] Pooled results from 11 randomised controlled trials (including data from the landmark Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency[80] and REIN-1[81,82] studies) indicated that risk of kidney failure or doubling of creatinine concentration in serum was reduced by about 40% with an angiotensin-converting-enzyme inhibitor compared with other classes of antihypertensive drugs in patients with chronic kidney disease and proteinuria greater than 0·5 g per day.[83] In the AASK study, an angiotensin-converting-enzyme inhibitor reduced the risk of loss of kidney function, kidney failure, or death by almost 40% compared with a dihydropyridine calcium-channel blocker in African-American people with hypertensive nephropathy, despite similar levels of blood pressure control.[84] In a randomised trial by Hou and colleagues in China, the renal benefits of angiotensin-converting-enzyme inhibition extended to patients with later stages of chronic kidney disease with proteinuria.[85] Acute renal failure and hyperkalaemia were infrequent complications of these drugs in trial settings, although their use requires careful laboratory monitoring of electrolyte concentrations, with introduction and dose-adjustment in real-world clinical settings.[86] Small increases in the amounts of potassium and creatinine in serum are typical and usually tolerated; however, inhibition of the angiotensin system should be avoided in women planning pregnancy.[87]

No evidence is available to favour angiotensin-converting-enzyme inhibitors specifically over other antihypertensive drugs for prevention of renal outcomes in patients without diabetes or with early chronic kidney disease without proteinuria. Secondary analysis of data of the ALLHAT trial showed no difference in rates of kidney failure in individuals treated with an angiotensin-converting-enzyme inhibitor, dihydropyridine calcium-channel blocker, or thiazide diuretic, even in the subgroup with a baseline estimated glomerular filtration rate less than 60 mL per min per 1·73 m^2.[88] Urine protein quantification was not done in the ALLHAT study; however, in view of the population studied, proteinuria was probably rare, which could account for the absence

of any beneficial effects of angiotensin-converting-enzyme-inhibitor treatment on risk of kidney failure.[88] Although use of an angiotensin-converting-enzyme inhibitor reduced risk of cardiovascular events in patients with mild renal insufficiency in the HOPE study,[89] whether this outcome is independent of effects on blood pressure is unclear.

The effects of angiotensin-receptor blockers on progression of non-diabetic chronic kidney disease are less well studied than those of angiotensin-converting-enzyme inhibitors. Angiotensin-receptor blockers are effective antihypertensive drugs in patients with chronic kidney disease and reduce proteinuria to a similar level as angiotensin-converting-enzyme inhibitors.[90] On this basis, they are a good alternative for patients who cannot tolerate an angiotensin-converting-enzyme inhibitor because of cough or angio-oedema.[91,92] As far as we know, no studies have been undertaken to establish effectiveness of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers specifically for primary prevention of chronic kidney disease in patients without diabetes. Findings of the TRANSCEND study showed no effect of an angiotensin-receptor blocker for primary prevention of renal disease in a population with cardiovascular disease, preserved kidney function, and no proteinuria.[92]

Combination treatment with an angiotensin-converting-enzyme inhibitor and an angiotensin-receptor blocker reduces proteinuria by a greater amount than either agent alone and, thus, has the potential to provide additional renoprotection.[90] In the ONTARGET study, the combination of angiotensin-converting-enzyme inhibitor and angiotensin-receptor blocker was associated with heightened risk of dialysis (acute or chronic), doubling of creatinine concentration in serum, or death in people with well preserved glomerular filtration rate and infrequent proteinuria.[93] Without definitive evidence, the increased risk of adverse effects with combination treatment could outweigh the potential benefits for patients at low risk of progression;[91,93] whether this conclusion applies to individuals with progressive disease needs further study.

Many patients with chronic kidney disease will need several antihypertensive drugs to control their blood pressure.[4,5] Antihypertensives from any class can be added, although decisions should be made after consideration of comorbidities. Thiazide or loop diuretics help to reduce blood pressure, and loop diuretics can control extracellular volume fluid overload and hyperkalaemia as glomerular filtration rate declines.[86] Add-on treatment with non-dihydropyridine calcium-channel blockers might lessen proteinuria further,[94] but conclusive data for long-term benefits are scarce.

Pharmacological treatment of diabetic chronic kidney disease

Treatment of high blood pressure in patients with diabetes mellitus is advocated irrespective of the presence of chronic kidney disease. In the UK Prospective Diabetes Study (UKPDS), reduction of blood pressure diminished the risk of diabetes-related death, stroke, and microvascular endpoints such as retinopathy.[95] Findings of observational studies support blood-pressure targets for patients with diabetic chronic kidney disease similar to those for individuals with non-diabetic chronic kidney disease.[74]

Angiotensin-converting-enzyme inhibition shows clear renal benefits in patients with diabetic nephropathy. Angiotensin-converting-enzyme inhibitors decrease the risk of death, dialysis, or transplant in individuals with type 1 diabetes and established nephropathy.[96] Similarly, in patients with nephropathy due to type 2 diabetes, findings of the RENAAL[97] and IDNT[98] studies showed that treatment with an angiotensin-receptor blocker resulted in 16–20% reductions in risk of doubling of serum creatinine, kidney failure, or death. The effects of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers for primary prevention of diabetic nephropathy have been variable. Results from the IRMA study[99] and a subgroup analysis of patients with diabetes enrolled in the HOPE study[100] suggested that the onset of macroalbuminuria is decreased in patients treated with angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers. In individuals with type 2 diabetes, normal renal function, and normoalbuminuria in the BENEDICT study,[101] use of ramipril (with or without verapamil) delayed new onset of microalbuminuria. Reductions in incidence of new cases of microalbuminuria with angiotensin-converting-enzyme inhibition were also reported in two other large randomised controlled trials in patients with type 2 diabetes (EUCLID and ADVANCE)[102,103] but not in a secondary analysis of the DIRECT studies.[104]

The renoprotective effects of angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers seem to be clinically equivalent in patients with diabetic nephropathy on the basis of longitudinal measurements of glomerular filtration rate.[105] Dual blockade of the renin–angiotensin system with an angiotensin-converting-enzyme inhibitor and an angiotensin-receptor blocker reduces proteinuria in patients with diabetic nephropathy but the effects on clinically relevant renal outcomes are unknown[90] pending results from ongoing studies.[106] Further lowering of albuminuria has been noted in patients with diabetic nephropathy when a direct renin inhibitor (aliskiren) was added to an angiotensin-receptor blocker.[107] A randomised controlled trial (ALTITUDE) examining the effect of addition of aliskiren to conventional treatment (including an angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker) on cardiovascular and renal outcomes is in progress.[108]

Poor glycaemic control has been associated with increased risk of diabetic nephropathy and with rapid progression of chronic kidney disease. Findings of the Diabetes Control and Complications (DCCT) study

	Recommendation
Lifestyle changes	
Smoking	Recommend smoking cessation
Diet	Sodium intake <100 mmol (2·3 g) per day Consider oral sodium bicarbonate supplementation if acidotic
Weight	Body-mass index <25 kg/m^2; waist circumference <102 cm for men and <88 cm for women
Exercise	When feasible, 30–60 min of moderate intensity dynamic exercise (walking, jogging, cycling, or swimming) 4–7 days per week
Hypertension	
Treatment goal	<125–130/75–80 mm Hg
Pharmacotherapy	Proteinuric chronic kidney disease (urine albumin-to-creatinine ratio ≥30 mg/mmol or random urine protein equivalent to ≥500 mg per day) should include an ACE inhibitor or an angiotensin-receptor blocker Non-proteinuric chronic kidney disease might use either an ACE inhibitor, an angiotensin-receptor blocker, a thiazide diuretic, a β blocker (in patients <60 years, or with existing ischaemic heart disease), or a long-acting calcium-channel blocker
Diabetes mellitus	
Treatment goal	HbA_{1c} <7·0%, fasting plasma glucose 4–7 mmol/L
Pharmacotherapy	Metformin acceptable for stage 1–2 chronic kidney disease, and stable stage 3 chronic kidney disease Repaglinide acceptable with no dose adjustment Short-acting sulphonylureas (eg, gliclazide) are preferred over long-acting agents Sulphonylureas and insulin need dose adjustment
Dyslipidaemia	
Treatment goal	LDL-cholesterol targets for patients with stage 3–4 chronic kidney disease should follow guidelines for the general population
Pharmacotherapy	Statins preferred Fibrates need dose adjustments Bile acid sequestrants, statins, niacins, ezetimibe do not need dose adjustments
Antiplatelets	
Pharmacotherapy	Aspirin 81 mg daily if high risk or established cardiovascular disease and no contraindication

ACE=angiotensin-converting enzyme. HbA_{1c}=glycosylated haemoglobin.

Table 4: **Management of patients with early stages of chronic kidney disease**

showed that targeting of glycosylated haemoglobin (HbA_{1c}) to a level less than 6% reduced the incidence of new cases of microalbuminuria or macroalbuminuria in patients with type 1 diabetes.[109] Similar renal benefits with intensive glycaemic control have been recorded in randomised controlled trials that enrolled people with type 2 diabetes.[95,110] However, risk of hypoglycaemic events with tight glucose control can be raised in patients with a low glomerular filtration rate because many sulphonylurea drugs and insulin need renal clearance. Thus, the risk-to-benefit ratio of tight glycaemic control should be considered carefully in individuals with low glomerular filtration rate outside the context of a clinical trial.

Other pharmacological treatments to reduce cardiovascular risk

Since few trials have been undertaken specifically in populations with chronic kidney disease, we need to either extrapolate data from randomised controlled trials done in the general population or rely on subgroup analyses of people with chronic kidney disease enrolled in such trials. Although findings of randomised controlled trials of statins undertaken in haemodialysis patients have shown no survival benefits, subgroup results from trials undertaken in the general population suggest that statins significantly reduce all-cause mortality and cardiovascular events in individuals with an estimated glomerular filtration rate of 30–60 mL per min per 1·73 m^2.[111] Although secondary analysis of data from cardiovascular randomised controlled trials suggests that statins diminish proteinuria and could result in a small reduction in rate of loss of kidney function,[112] the true renal benefits of these drugs are uncertain.

Aspirin is prescribed frequently to patients with chronic kidney disease because of its established net benefit for secondary prevention of cardiovascular events in the general population, including those in whom chronic kidney disease is typical, such as individuals with hypertension or diabetes.[113] Whether aspirin has a beneficial effect on progressive loss of kidney function (and whether its beneficial effects on cardiovascular disease outweigh the risk of bleeding associated with advanced chronic kidney disease) remains uncertain. Data from small studies show no increase in major bleeding rates or other adverse events in patients with chronic kidney disease treated with low-dose aspirin.[114] In the absence of a large-scale trial, use of low-dose aspirin or other antiplatelet agents must be individualised on the basis of every patient's cardiovascular and bleeding risks.[113]

Additional aspects of medical care

A high frequency of medical encounters, impaired renal clearance of drugs in patients with reduced estimated glomerular filtration rate, and use of agents with potential nephrotoxic effects are all factors that could increase risk of iatrogenic complications in individuals with chronic kidney disease. Patients in the USA admitted to hospital with reduced glomerular filtration rates had increased rates of hip fracture, metabolic derangements, and complications of anaesthesia during surgical admission, and more frequent infections as a result of medical care.[115] Increasing our awareness of chronic kidney disease, appropriate drug dosing in patients with reduced estimated glomerular filtration rate,[116] and minimisation of exposure to nephrotoxic agents such as iodinated radiocontrast agents[117] and phosphate-based enemas[118] might diminish complications.

Non-pharmacological treatment

Limitation of dietary sodium intake to less than 100 mmol per day is advocated frequently to prevent or manage hypertension.[4] The effects of dietary protein restriction on prevention of progression of chronic kidney disease have been controversial owing to the features of study design and because of inconclusive and conflicting data of individual randomised controlled trials.[119] Results from meta-analyses suggest that kidney

failure or death could be reduced with severe or very low protein intake in trial settings.[119] Nonetheless, because of the risks of malnutrition and need for additional nutritional monitoring, severe protein restriction is not generally implemented for patients with chronic kidney disease.[4] Data from a small single-centre randomised trial reported that oral supplementation with sodium bicarbonate slowed the rate of decline in kidney function and reduced the rate of progression to kidney failure in individuals with a glomerular filtration rate lower than 30 mL per min per 1·73 m² and low concentration in serum of bicarbonate.[120] Smoking is associated with increased risk of progressive chronic kidney disease[26,121] and kidney failure or death related to chronic kidney disease,[27,122] and thus smoking cessation is encouraged.

Findings of large observational studies suggest that obesity is associated with development of chronic kidney disease,[26] progression to kidney failure,[123] and mortality related to chronic kidney disease,[122] although how much of this effect is mediated by diabetes, hypertension, and dyslipidaemia remains uncertain.[28,124] Weight gain increases the risk of chronic kidney disease, even in patients with normal starting weight,[125] and should be avoided, whereas weight loss is recommended for individuals who are overweight because of its known benefits for glycaemic control and blood pressure.[28]

Table 4 summarises recommended management of patients with chronic kidney disease. Notably, since generic versions of all drugs in table 4 are available, these treatments are affordable for individuals in developing countries.

Delivery of care

Caring for patients with chronic kidney disease is complex, and data from many studies indicate lower-than-expected rates of use of recommended treatments, even in people at high risk of kidney failure or cardiovascular disease.[126] In the UK, only a fifth of patients with diabetes and chronic kidney disease had a blood pressure of 130/80 mm Hg or less, and fewer than half were receiving an angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker.[127] Furthermore, only 50% of those with stage 3–5 chronic kidney disease were prescribed an antiplatelet agent or a lipid-lowering treatment, suggesting that the management of these patients in primary-care settings could be enhanced considerably.[127] An algorithm-based, primary-care, disease-management programme for patients with chronic kidney disease—based on automated reporting of estimated glomerular filtration rate—led to better controlled blood pressure and blood cholesterol, and reduced the rate of kidney function loss.[71]

Most cases of non-progressive chronic kidney disease can be managed without referral to a nephrologist, and specialist referral can be reserved for patients with an estimated glomerular filtration rate less than 30 mL min per 1·73 per m², rapidly declining kidney function (>5 mL per min per 1·73 m² over 1 year), persistent proteinuria, or uncontrolled hypertension or diabetes.[4,5] Specialist involvement might also be helpful to manage renal anaemia (if erythropoiesis-stimulating agents are used) and metabolic complications of chronic kidney disease (ie, hyperphosphataemia, secondary hyperparathyroidism, or renal osteodystrophy).[4,5] Late referral of individuals with advanced chronic kidney disease (<3–4 months before the requirement for renal replacement therapy) has been associated consistently with poor outcomes;[128,129] thus, timely referral of high-risk patients should be encouraged.[130]

In a randomised controlled trial of a multifactorial intervention of tight glucose regulation, use of renin–angiotensin system blockers, aspirin, and lipid-lowering agents, 48% and 57% reductions in risks of all-cause and cardiovascular mortality,[131] respectively, were recorded in patients with type 2 diabetes and microalbuminuria, raising the possibility that this approach would also be effective in chronic kidney disease. Findings of several observational studies have shown associations between care in a multidisciplinary chronic kidney disease clinic and better clinical outcomes,[132,133] and preliminary economic analyses suggest that such an approach would be cost effective.[134] A multimodal intervention for patients with chronic kidney disease and proteinuria in Italy lowered blood pressure, cholesterol, and proteinuria further than in historical controls, achieving disease remission or regression in 50% of patients who would have been otherwise expected to progress rapidly to kidney failure with historical management.[135] However, in a randomised controlled trial of multidisciplinary case management for patients with chronic kidney disease, no benefits were recorded on renal function, health services use, or mortality over 5 years of follow-up, perhaps because of small sample size.[136] Although many nephrologists think that multidisciplinary chronic kidney disease clinics are beneficial, convincing evidence of their effectiveness for clinically relevant outcomes is currently absent.

Further challenges and directions

Better clinical methods are needed to distinguish patients at risk of adverse renal and cardiovascular outcomes to permit best use of resources. The use of predictive techniques that combine estimated glomerular filtration rate and proteinuria might represent one such potential advance. Novel biomarkers could help to identify individuals at risk of progressive chronic kidney disease and kidney failure in the future. Although effective interventions to slow the progression of diabetic and non-diabetic chronic kidney disease have been described, many patients with chronic kidney disease continue to develop kidney failure, and enhanced therapeutic approaches are needed. Therapeutic agents that target other causal and pathophysiological processes of kidney disease hold promise but remain experimental.

The current evidence base to guide other aspects of chronic kidney disease management is smaller than that for many other frequent chronic diseases. Assessment of usual cardiovascular treatments is needed in patients with chronic kidney disease, as are trials to evaluate many drugs currently used to manage related disorders of mineral metabolism and bone disease. The risks and benefits of typical drug combinations also need further investigation in populations with chronic kidney disease specifically, particularly in view of the high prevalence of polypharmacy and potential for toxic effects of drugs in such patients.

Further research on the merits of novel methods for case-identification and care delivery in diverse settings is needed because of the high and growing global prevalence of chronic kidney disease. In view of the severely restricted availability of dialysis in countries of low and middle incomes, such research is especially urgent outside the developed world. For all health systems (irrespective of resources), multi-intervention clinics and programmes that enhance care of patients in primary-practice settings are attractive alternatives to conventional models that merit further study.

Contributors

MTJ wrote the first draft of the manuscript with assistance from MT and BRH. All authors contributed equally to the literature search, interpretation of retrieved publications, and planning and revision of the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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