1

Screening for Chronic Kidney Disease

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1. Introduction

Chronic kidney disease (CKD), defined as reduced excretory kidney function (glomerular filtration rate (GFR) <60 mL/min/1.73m^2) or evidence of kidney damage (such as proteinuria) for a period of at least 3 months, is considered a major global public health problem (Levey, Atkins et al. 2007). The prevalence of CKD has been estimated at between 10-15% in industrialised countries and is increasing, likely as a result of population ageing and the increasing incidence of diabetes, vascular disease and obesity (Chadban, Briganti et al. 2003; Coresh, Astor et al. 2003; Coresh, Selvin et al. 2007; Stevens, O'Donoghue et al. 2007).
A definition and staging system for CKD was introduced in 2002 and has been widely accepted (Table 1) (K/DOQI 2002).

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild reduction in GFR	60–89
3	Moderate reduction in GFR	30–59
4	Severe reduction in GFR	15–29
5	Kidney failure	<15 (or dialysis)

Table 1. National Kidney Foundation CKD classification (K/DOQI 2002)

More recent staging classification systems have attempted to improve CKD risk stratification by incorporating proteinuria (Table 2). Within the continuum of patients with CKD, there is a wide range of disease severities, from patients with an excellent long-term renal prognosis through to patients with end-stage kidney disease (ESKD) who require renal replacement therapy.
Many patients with CKD follow a predictable clinical course following disease initiation, with progressive renal dysfunction ultimately resulting in ESKD. Critically, CKD is clinically silent in up to 90% patients until it has reached an advanced stage (Chadban, Briganti et al. 2003; John, Webb et al. 2004; Nickolas, Frisch et al. 2004), and patients who reach ESKD without prior contact with nephrology services experience greater co-morbidity and poorer survival following initiation of renal replacement therapy (Roderick, Jones et al. 2002; Chan, Dall et al. 2007). There is therefore an opportunity to detect patients with asymptomatic CKD by screening, with the aim of applying therapies to ameliorate disease progression.

eGFR Stage	Albuminuria Stage (uACR value)		
	Normal (<2.5 mg/mmol [M], <3.5 mg/mmol [F])	**Microalbuminuria** (2.5-25 mg/mmol [M], 3.5-35 mg/mmol [F])	**Macroalbuminuria** (>25 mg/mmol [M], >35 mg/mmol [F])
1			
2			
3a			
3b			
4			
5			

* Risks of progressive CKD denoted as low (light grey), moderate (dark gray) and high (black).

Table 2. Modified CKD staging system recommended by the Caring for Australasians with Renal Insufficiency Early CKD Guidelines (Johnson and Toussaint 2011)

Apart from the risk of progression to ESKD, the presence of CKD is a potent risk factor for cardiovascular disease, such that individuals with ESKD have up to a 10- to 20-fold greater risk of cardiac death than age- and sex-matched controls without ESKD (Foley and Parfrey 1998). Moreover, as illustrated in Figure 1, people with earlier stages of CKD are up to 20 times more likely to die, predominantly from cardiovascular disease, than survive to the point of needing dialysis or kidney transplantation (Go, Chertow et al. 2004; Smith, Gullion

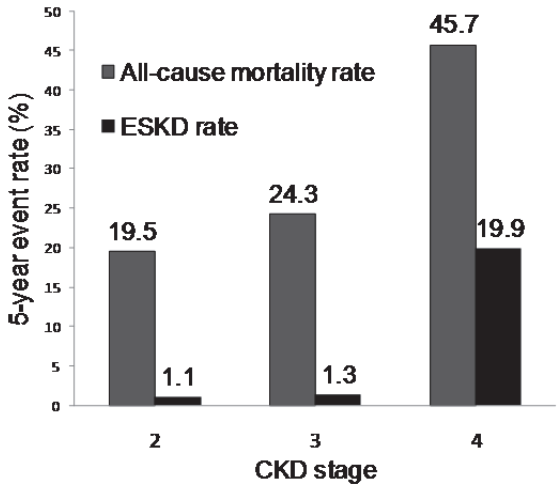

Fig. 1. Five-year event rates for all-cause mortality and end-stage kidney disease in CKD stages 2 to 4 (data derived from (Keith, Nichols et al. 2004)).

et al. 2004; Foley, Murray et al. 2005; Matsushita, van der Velde et al. 2010). As a result, a successful CKD screening programme would identify individuals who are likely to benefit from interventions to reduce heart disease risk.

Despite the theoretical benefits, screening for CKD remains controversial (Glassock and Winearls 2008; Grootendorst, Jager et al. 2009), and although several national and international organisations have made recommendations advocating routine screening for CKD, details regarding approaches to screening vary. This chapter will examine the role and cost-effectiveness of screening for CKD and make recommendations regarding the optimal screening strategy (i.e. who, how, when and what to screen).

2. Methods of screening

The presence of CKD can be readily identified using non-invasive investigations to estimate glomerular filtration rate and to detect proteinuria. Further information about future risk of progressive renal disease and ESKD can be obtained from monitoring blood pressure.

2.1 Proteinuria

Proteinuria is an early marker of kidney damage in many forms of renal disease, such as diabetic nephropathy and glomerulonephritis. Persistent proteinuria has a strong positive correlation with the subsequent development of ESKD. In a Japanese study of community mass screening, 193 of 107,192 subjects were identified as requiring RRT after 10 years of follow-up (Iseki, Iseki et al. 1996). Proteinuria was the strongest predictor of subsequent need for dialysis, with an adjusted odds ratio (OR) of 14.9 (95% confidence interval (CI) 10.9-20.2). Similarly, in a US study that followed 1832 subjects with type 2 diabetes for between 5-40 years, 25 reached ESKD (Humphrey, Ballard et al. 1989). The presence of proteinuria at the time diabetes was identified was the strongest risk factor for reaching ESKD (relative risk (RR) 12.1, CI 4.3-34).

There is also evidence from controlled trials that proteinuria is a risk factor for CKD progression. In the modification of diet in renal disease (MDRD) trial, there was a positive correlation between baseline proteinuria and the rate of decline in GFR (Peterson, Adler et al. 1995). This association was independent of other risk factors for decline in GFR such as blood pressure. Similarly, in a trial of 409 patients with type 1 diabetes, proteinuria was the strongest single risk factor for doubling of serum creatinine (Breyer, Bain et al. 1996).

The presence of proteinuria has also been shown to be an important independent predictor of subsequent cardiovascular disease, both in patients with diabetes and the general population (Mogensen 1984; Rossing, Hougaard et al. 1996; Hillege, Fidler et al. 2002; Romundstad, Holmen et al. 2003; Hallan, Astor et al. 2007).

Taken together, these observations strongly support the inclusion of proteinuria in CKD screening. The gold standard for assessing urinary protein excretion is a timed 24-hour urine collection. However, the difficulties of obtaining an accurately timed and complete urine collection and the inconvenience for the individual performing the collection reduce the utility of this test as a screening tool. Because the rate of creatinine excretion remains approximately stable over a 24-hour period, the creatinine concentration in a spot urine sample can be used as a control for urine concentration, allowing estimation of 24-hour urinary protein or albumin excretion from the urinary protein:creatinine ratio (uPCR) or albumin:creatinine ratio (uACR), respectively (Ginsberg, Chang et al. 1983). Alternatively, urine stick can be used to estimate urinary protein excretion (James, Bee et al. 1978; Allen,

Krauss et al. 1991; Higby, Suiter et al. 1995). However, meta-analysis of data extracted from the primary studies of proteinuria assessment indicate that urine stick testing has a sensitivity of 90% and specificity of 67%, compared to a sensitivity of 95% and specificity of 91% for protein:creatinine ratio (Craig, Barratt et al. 2002). For this reason, uPCR or uACR are the preferred modalities for CKD screening.

There is diurnal variation in urinary protein excretion, with the highest level of proteinuria in the afternoon and therefore where possible, spot urine testing for proteinuria should be performed on an early morning (first urinary void of day) sample. However, a number of studies have demonstrated that random urine samples are still acceptable if first void samples are impractical (Price, Newall et al. 2005; Cote, Brown et al. 2008; Witte, Lambers Heerspink et al. 2009). Importantly, transient increases in urinary protein excretion are seen in several circumstances other than CKD, including urine infection, febrile illness, heart failure and hyperglycaemia (Table 2). As a result, patients should only be labelled as having CKD if proteinuria persists for at least three months.

Urinary tract infection
High dietary protein intake
Congestive cardiac failure
Acute febrile illness
Heavy exercise within 24 hours
Menstruation or vaginal discharge
Drugs – e.g. non-steroidal anti-inflammatory drugs, ACE inhibitors, ARBs, calcineurin inhibitors

Table 2. Factors that may affect urinary protein excretion

2.2 Renal function

Glomerular filtration rate, or GFR, is determined by the total number of functional nephrons, and is considered the best overall measure of excretory kidney function. Furthermore, GFR is central to the current definition of CKD. Several equations have been derived that permit estimation of GFR from the serum concentration of renally-excreted endogenous molecules – typically creatinine. Creatinine is both filtered at the glomerulus and secreted in the proximal tubule, and therefore falls short of being a model molecule with which to assess GFR. This is particularly significant in patients with low GFRs, in whom tubular creatinine secretion contributes a greater proportion of total renal creatinine clearance. Nevertheless, several equations have been generated that allow estimation of GFR using serum creatinine levels. The first equation to be used widely in clinical practice was described in 1976 (Box 1) and estimates creatinine clearance (Cockcroft and Gault 1976). While useful for monitoring the clinical course of an individual patient or making dose adjustments of medications, the inclusion of body weight as a variable reduces the applicability of this formula for population screening.

More recent equations have been generated using data from large trials in which simultaneous data for serum creatinine and GFR measured by the renal clearance of radioactive isotopes, such as [^{51}Cr]-ethylenediaminetetraacetic acid, [^{125}I]-iothalamate or [^{99}Tcm]-diethylenetriaminepentaacetic acid, were available. At present, an equation generated using data from the modification of diet in renal disease trial (Box 2) is in widespread clinical use for GFR estimation (Levey, Bosch et al. 1999).

Creatinine clearance (ml/min) =

$$\frac{1.23 \times \left(140 - age\ (years)\right)}{serum\ creatinine\ (\mu mol/L)} \times 0.85\ (if\ female)$$

Box 1. Cockcroft and Gault equation

GFR (ml/min/1.73m^2) =

$$175 \times \left\{\frac{serum\ creatinine\ (\mu mol/L)}{1.004} \times 0.011312\right\}^{-1.154} \times (age\ in\ years)^{-0.203} \times 0.742\ (if\ female) \times 1.212\ (if\ black)$$

Box 2. Simplified modification of diet in renal disease (MDRD) formula

An advantage of the MDRD equation over the Cockcroft-Gault equation is that the former only requires knowledge of the serum creatinine, age and ethnicity. MDRD eGFR is currently reported automatically whenever a serum creatinine assay is requested in several countries including Australia and the UK. A significant problem with the MDRD equation is that the accuracy of the approximation to isotopic GFR varies with renal function. While it is acceptably accurate in patients with low GFR, it performs less well in patients with normal or near normal renal function (GFR >60ml/min/1.73m^2). The MDRD equation tends to underestimate GFR in patients with normal or near-normal renal function, which is of particular concern for the purpose of CKD screening, since this increases the probability of inappropriately labelling healthy individuals with CKD.

In an attempt to improve GFR estimation, a new creatinine-based eGFR equation was developed that includes a two-slope "spline" to improve accuracy in patients with good renal function (Levey, Stevens et al. 2009). Unlike the MDRD formula, which was developed from a population with CKD, the CKD-EPI formula was developed and validated in a large heterogeneous population with and without known CKD including subjects with diabetes, potential kidney donors and transplant recipients. Analyses using the CKD-EPI equation (Box 3) indicate that it is more accurate than the MDRD equation in individuals with a GFR >60ml/min/1.73m^2, and performs with equivalent accuracy to the MDRD equation when the GFR is <60 (Levey and Stevens 2010; Stevens, Claybon et al. 2011). Subsequent epidemiologic evaluations in North American (Matsushita K et al. 2010) and Australian general population studies (White, Polkinghorne et al. 2010) have shown that the CKD-EPI equation more appropriately categorises individuals with respect to long-term clinical risks of end-stage kidney disease, coronary heart disease, stroke and/or all-cause mortality than the MDRD equation. In particular, 1.9% of the AusDiab study population was re-classified as not having CKD and such re-classified individuals were predominantly younger women with a favourable cardiovascular risk profile and absence of significant albuminuria.

GFR (ml/min/1.73m²) =

$$141 \times \min\left(\frac{serum\ creatinine}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{serum\ creatinine}{\kappa}, 1\right)^{-1.209} \times 0.993^{\text{age}}$$

$$\times 1.018\ (if\ female)$$

$$\times 1.159\ (if\ black)$$

$$\kappa = 0.7\ , \alpha = -0.329\ if\ female$$

$$\kappa = 0.9\ , \alpha = -0.411\ if\ male$$

$$\min = \text{the minimum of } \frac{serum\ creatinine}{\kappa} \text{ or } 1$$

$$\max = \text{the maximum of } \frac{serum\ creatinine}{\kappa} \text{ or } 1$$

Box 3. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

Finally, equations are available that permit estimation of GFR from serum levels of an alternative renally-excreted endogenous molecule, cystatin C (Stevens, Coresh et al. 2006). Cystatin C is a 122-amino acid protein ubiquitously expressed in all nucleated cells that is freely filtered at the glomerulus, whereupon 99% of filtered cystatin C is reabsorbed and catabolised in the proximal tubule (Tenstad, Roald et al. 1996; Roald, Aukland et al. 2004). There is some evidence that cystatin C, like creatinine, is secreted in the proximal tubule. Early data suggest that estimated GFR based either on the serum level of cystatin C or the combination of cystatin C and creatinine may be more accurate than creatinine-only equations (Madero, Sarnak et al. 2006; Groesbeck, Kottgen et al. 2008; Kottgen, Selvin et al. 2008; Stevens, Coresh et al. 2008). At present, the relatively high cost of assaying cystatin C and the need for further validation of the potential benefits over creatinine as a filtration marker mean that this approach is not ready for use as a screening tool.

2.3 Hypertension

Systemic blood pressure is an important and modifiable risk factor for CKD progression (Haroun, Jaar et al. 2003). Furthermore, long-term population studies indicate that hypertension is a potent predictor of subsequent development of ESKD. For instance, in the Multiple Risk Factor Intervention Trial (MRFIT), a strong graded independent relationship between blood pressure and later ESKD development was observed (Klag, Whelton et al. 1996). The strength of the association between hypertension and ESKD risk was much greater for systolic blood pressure than diastolic blood pressure.

It remains unclear whether hypertension (other than accelerated or malignant hypertension) is causally related to, or a consequence of progressive renal impairment. Furthermore, no studies have specifically examined blood pressure as a screening tool for detecting patients with CKD. However, the strong epidemiological link between blood pressure and ESKD suggests that patients with hypertension should be monitored for the development of CKD.

3. Evidence of benefit from screening for CKD

There is little point in screening for a disease unless interventions are available that can improve outcomes following diagnosis. Unfortunately, there are no prospective randomised

trials that have addressed whether screening for CKD leads to improvement in important outcomes such as progression of renal dysfunction or co-morbidity from cardiovascular disease. Despite this, there is an increasing evidence base to support a range of interventions in patients with CKD, providing indirect support for identifying these individuals at an earlier stage of disease. Specific therapies are available for a limited number of renal diseases, such as recombinant alpha-galactosidase in patients with Fabry disease. Immunosuppressive therapy can ameliorate disease progression in several immunologically-mediated renal diseases, such as lupus nephropathy. Importantly however, there are data to support the application of certain therapies in a broad range of patients with CKD, particularly blood pressure control and the use of HMG-CoA reductase inhibitors (statins).

3.1 Blood pressure lowering

Multiple studies have evaluated the impact of anti-hypertensive agents in patients with CKD. There is strong and consistent evidence from these data that antihypertensives, and in particular agents that inhibit the action of angiotensin II, reduce proteinuria (Gansevoort, Sluiter et al. 1995; Atkins, Briganti et al. 2005; Kunz, Friedrich et al. 2008; Parving, Persson et al. 2008), as well as the rate of progression of CKD (Peterson, Adler et al. 1995; Maschio, Alberti et al. 1996; Giatras, Lau et al. 1997; GISEN 1997; Jafar, Schmid et al. 2001; Strippoli, Bonifati et al. 2006). These data provide compelling support for blood pressure control in patients with CKD.

3.2 Lipid lowering

Until the recent publication of the SHARP trial (Baigent, Landray et al. 2011), there were no primary studies of lipid lowering in patients with CKD that were not on renal replacement therapy. Many patients with overt CKD were excluded from the early large trials showing a beneficial effect of statins on all cause mortality in both secondary and primary prevention studies (Wright, Flapan et al. 1994; Shepherd, Cobbe et al. 1995). Nevertheless, post-hoc analyses have identified many patients with modest renal impairment that were included in the trials. These data suggest that within these trials, similar benefits from statin use occurred in patients with or without modest renal impairment (Shepherd, Kastelein et al. 2008; Navaneethan, Nigwekar et al. 2009). In contrast, two randomised controlled trials specifically evaluating statin use in patients on dialysis found no evidence of improvement in mortality or cardiovascular endpoints, despite significant reductions in serum cholesterol levels (Wanner, Krane et al. 2005; Fellstrom, Jardine et al. 2009). The SHARP trial goes some way to bridge the gulf between these apparently contradictory findings. 9270 patients with CKD (serum creatinine >150 µmol/L in men or >130 µmol/L in women) were randomised to receive simvastatin plus ezetimibe or placebo (Baigent, Landray et al. 2011). The active treatment group experienced significantly fewer major atherosclerotic events (a composite endpoint of non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke, or any arterial revascularisation procedure) – (RR 0.83, 95% CI 0.74–0.94; p=0.0021). There was no significant difference in mortality rate between the two groups. Overall, these data indicate that patients with CKD are likely to benefit from statin use.

4. Who should be screened for CKD?

Epidemiological studies indicate that many of the patients identified with CKD have a low probability of progressing to ESKD. As a result, most of the published guidelines on CKD

screening have recommended targeted screening of groups considered to be at high risk of developing progressive CKD, such as individuals with diabetes or hypertension. This strategy will increase the cost-effectiveness of screening, at the expense of missing individuals who could benefit from CKD screening. For example, many individuals will have unrecognised risk factors for CKD – for example undiagnosed diabetes – and will therefore be omitted from targeted CKD screening. An 8 year follow-up of a cross sectional health survey (the HUNT II study) involving 65,604 people (70.6 % of all adults aged ≥20 years in Nord-Trøndelag County, Norway) found that screening people with hypertension, diabetes mellitus, or age >55 years was the most effective strategy to detect patients with CKD, such that 93.2% (95% CI 92.4-94.0%) of all CKD patients would be identified resulting in a number needed to screen of 8.7 (8.5 to 9.0). Nevertheless, the risk of end stage kidney disease among those detected was low (1.2% over 8 years) (Hallan, Dahl et al. 2006). Other strategies of targeting (e.g. only people with diabetes and hypertension) detected a lower percentage of CKD (44.2%) and were less effective. Another study reporting on the performance of similar screening strategies is the United States (US) Kidney Early Evaluation Program (KEEP), which targets individuals with diabetes, hypertension, or family history of diabetes or hypertension or CKD. Using this strategy, 7 people with diabetes or hypertension or with first degree relatives with diabetes, hypertension or kidney disease needed to be screened for one case of CKD to be found (Vassalotti, Li et al. 2009). An Australian report by Howard *et al.* using cost-effectiveness modelling outlined the potential effectiveness of screening and intensive management of the most important CKD risk factors - diabetes, hypertension and proteinuria (Howard, White et al. 2010). Cost-effectiveness was modelled in terms of the effect on overall mortality, on cardiovascular mortality and morbidity and on progression to ESKD and the report determined that a strategy based on screening of 50 to 69 year olds in general practice, plus intensive management of diabetes, hypertension and proteinuria, would be cost-effective. Similarly, a US cost-effectiveness study found that early detection of urine protein to slow progression of CKD and decrease mortality was not cost-effective unless selectively directed toward high-risk groups (older persons and persons with hypertension) (Boulware, Jaar et al. 2003). The CARI Guidelines recommend that patients should be screened with eGFR, urine albumin:creatinine ratio (uACR) and a BP measurement at least annually during routine primary health encounters if they have at least one of the CKD risk factors listed in Figure 2.

5. Conclusions

CKD is common, and can be readily detected using non-invasive assays. It causes considerable co-morbidity and premature mortality, and is frequently asymptomatic until disease has progressed to the point that there is little scope to modify disease progression or limit co-morbidity. At present, it is unclear whether screening for CKD has a beneficial effect on outcome. However, increasing evidence supports a range of interventions in patients with CKD, including blood pressure reduction, angiotensin-converting enzyme inhibition or angiotensin receptor blockade to reduce proteinuria and statin use to reduce cardiovascular events. Therefore, CKD fits many of the principles proposed by the WHO for population health screening programmes (Table 4). General population screening does not appear to be a cost-effective approach, and instead screening should be performed in individuals who have an elevated risk for CKD. An illustrative example of how a CKD screening programme may be organised is shown in Figure 2.

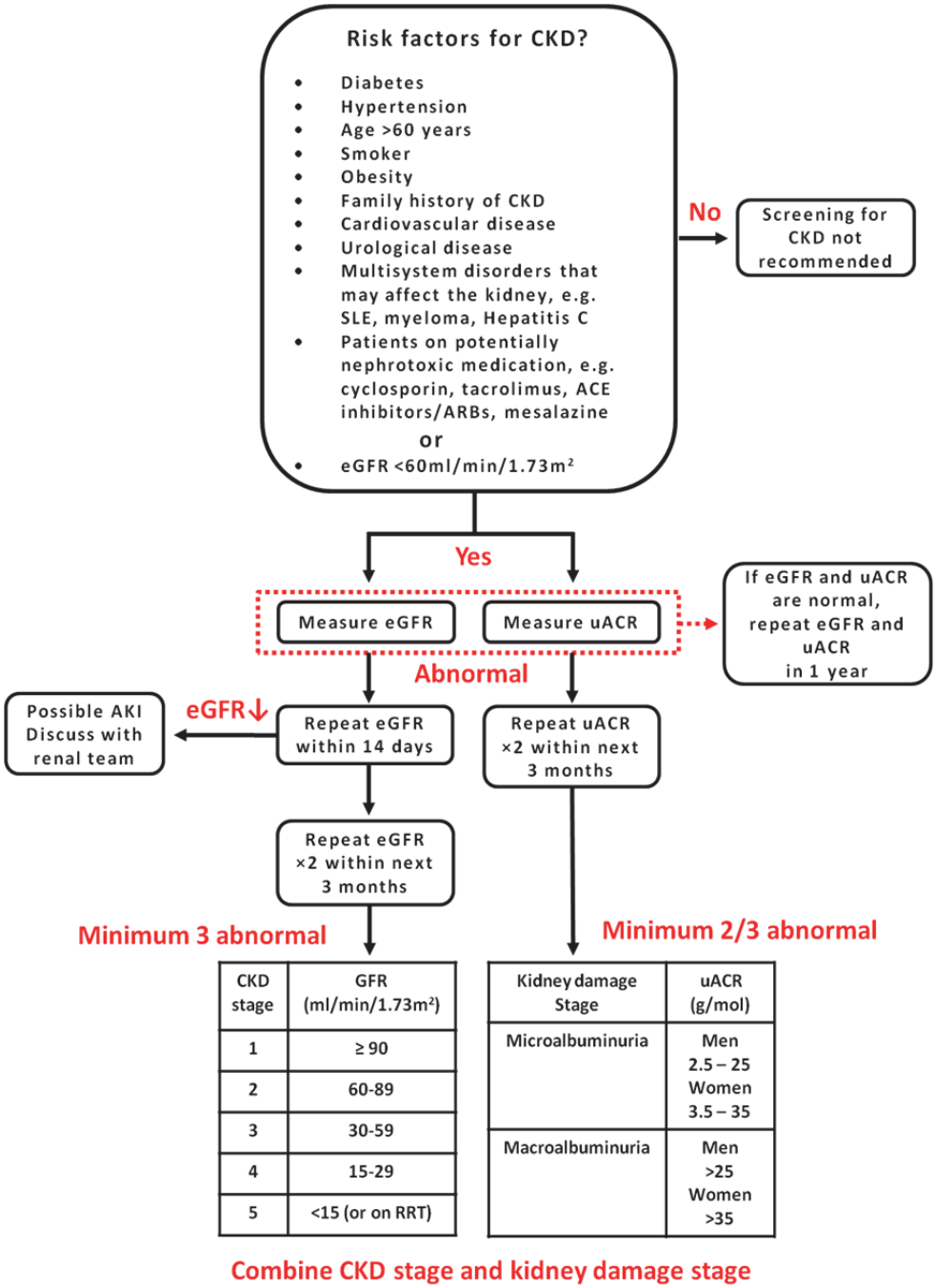

Fig. 2. Recommended approach to screening for CKD

The condition should be an important health problem.
There should be a treatment for the condition.
Facilities for diagnosis and treatment should be available.
There should be a latent stage of the disease.
There should be a test or examination for the condition.
The test should be acceptable to the population.
The natural history of the disease should be adequately understood.
There should be an agreed policy on whom to treat.
The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
Case-finding should be a continuous process, not just a "once and for all" project.

Table 4. World Health Organisation Principles of Screening (Jungner and Wilson 1968)

The clinical priorities in individuals detected to have CKD during screening will vary depending on the patient population. It is likely that many elderly patients with relatively poor excretory renal function (CKD stage 4-5) will be identified. However, many of these individuals are likely to have relatively stable renal function and to die either from alternative health issues or cardiovascular disease (O'Hare, Choi et al. 2007). In this population the principal benefit of CKD identification will be the potential to reduce the risk of cardiovascular complications. Younger patients with CKD are more likely to progress to ESKD, and the priorities will be both to ameliorate renal disease progression as well as to reduce cardiovascular co-morbidity (Menon, Wang et al. 2008).

6. Online resources

- National Kidney Foundation http://www.kidney.org/professionals/kdoqi/
- Kidney Disease Improving Global Outcomes (KDIGO) http://www.kdigo.org/
- Caring for Australians with Renal Impairment http://www.cari.org.au/
- UK Renal Association http://www.renal.org/home.aspx
- European Renal Association http://www.era-edta.org/
- UK NICE CKD guidelines http://www.nice.org.uk/CG73

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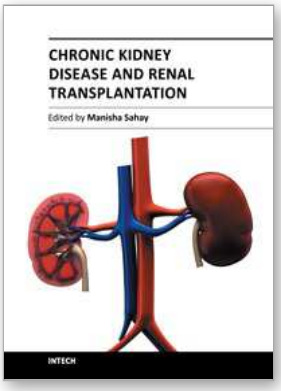

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This valuable resource covers inpatient and outpatient approaches to chronic renal disease and renal transplant with clinical practicality. This first section of the book discusses chronic disease under distinct topics, each providing the readers with state-of-the-art information about the disease and its management. It discusses the fresh perspectives on the current state of chronic kidney disease. The text highlights not just the medical aspects but also the psychosocial issues associated with chronic kidney disease. The latest approaches are reviewed through line diagrams that clearly depict recent advances. The second section of the book deals with issues related to transplant. It provides effective and up-to-date insight into caring for your transplant patients.

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