Outcomes in CKD: What We Know and What We Need to Know

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Chronic kidney disease • Cardiovascular disease • Age-related risk factors • Classification guidelines • Medicalisation of disease

Abstract

Chronic kidney disease (CKD) is a major public health concern. The high prevalence of reduced estimated glomerular filtration (eGFR) in the elderly has led to speculation as to whether it should really be regarded as a disease in all. Patients with CKD exhibit considerable cardiovascular morbidity and mortality but until recently data regarding the natural history of CKD, particularly in the elderly, has been somewhat lacking. As such the clinical significance of K/DOQI's CKD definition in terms of additional morbidity, mortality and progression to end-stage renal disease (ESRD) remains uncertain. Data have shown that death from cardiovascular disease is far more common than progression to renal replacement therapy in the elderly. Factors which increase the risks of progression to ESRD include younger age, proteinuria and diabetes. Although the elderly have high rates of cardiovascular death, comparatively younger patients with CKD have substantially increased relative risks of death. Specialist renal review should be targeted towards these high-risk patients while the majority of elderly patients can be safely monitored in primary care. It remains doubtful whether labelling all elderly CKD patients with a 'disease' confers any additional benefit.

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Introduction

In recent years chronic kidney disease (CKD) has been identified as a major public health concern worldwide. It has even been suggested that we are in the midst of an 'epidemic' with data from the US indicating that a massive 16.8% of the US population aged ≥ 20 years have K/DOQI CKD stages 1–5 [1] and approximately 9% of the English population are thought to have stages 3–5 based on recent estimates from the NEOERICA project [2, 3].

These estimates have generally been regarded as benchmarks for CKD prevalence and on the face of it seem worryingly high. However, recent data by Foley et al. [4] suggest that the notion of an ensuing 'epidemic' of CKD should certainly be open to question. They found no significant change in the prevalence over 2 time periods when using cystatin C as a measure of kidney function in contrast to the rise in prevalence seen with creatinine-based methods over the same period. There are also some important methodological limitations in the studies mentioned above which have triggered debate among the nephrology community. Only a single creatinine measurement was used to define CKD in both studies with no inclusion of chronicity criteria which could lead to the false inclusion of individuals with transient rises in creatinine. Measuring the mean of several creatinine measurements would allow for less overestimation of prevalence due to underlying intra-individual variation even in non-hospitalised patients but few studies

have adopted this approach [5]. Furthermore, the limitations of creatinine-based equations for estimating glomerular filtration rate (GFR) in population screening are widely documented. These include lack of calibration of creatinine measurements and underestimation of GFR at levels around 60 ml/min/1.73 m². Recent evidence suggests that even at eGFR measurements <60 ml/min/1.73 m² the abbreviated Modification of Diet in Renal Disease (MDRD) formula contains substantial degrees of inaccuracy, resulting in potential for misclassification [6]. These issues are of particular clinical importance, as there is anecdotal evidence in some cases of harm being done to patients, identified with CKD based on K/DOQI's system, who have been commenced on angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists as stipulated by the guidelines for the treatment of CKD [7]. Therefore, the use of eGFR alone as a means of diagnosing CKD should be questioned.

Are we dealing with the tip of an iceberg or is a large number of the population being unnecessarily labelled as suffering from a disease? It is incumbent upon the nephrology community to try and clarify this question in order to avoid unnecessary anxiety and over-investigation and to ensure that already scarce resources for health care provision are directed appropriately. With our increasingly ageing population and the introduction of mandatory eGFR reporting in the UK and in other countries, it is likely that even more patients will be identified as having CKD, placing a significant burden on the health service. It is therefore vital that doctors are aware of the significance of labelling these patients with a new 'disease' and are armed with the knowledge of how to appropriately manage and counsel these patients regarding their diagnosis and prognosis. This review will concentrate on the existing literature in terms of outcomes in early CKD and highlight the gaps in our knowledge.

CKD and Cardiovascular Disease: the Link

There is now a well-established link between CKD and cardiovascular disease (CVD) with a high prevalence of atherosclerosis, arteriosclerosis and left ventricular hypertrophy in patients with early CKD as well as in patients with end-stage renal disease (ESRD) [8]. The reason for the increased burden remains unclear; it is thought to relate in part to the increased prevalence of the same traditional risk factors present in the general population, but exposure to non-traditional risk factors such

as anaemia and metabolic bone disease are also thought to contribute [9]. There are a few studies which have been able to demonstrate that cardiovascular disease, even in its sub-clinical state, is a risk factor for incident CKD [10, 11]. Recently, Kshirsagar et al. [10] developed a simple model based on routinely available variables (such as hypertension, diabetes and vascular diseases) to reliably predict incident CKD (defined as a single eGFR <60 ml/min/1.73 m²) in middle- to older-aged participants from 2 large community-based cohort studies. However, whilst it may be a beneficial tool to aid early identification and management of CKD and its associated risk factors, its usefulness in determining the future risk of adverse events needs to be questioned as it does not necessarily follow that those identified with incident CKD suffer excess morbidity and mortality. For instance, age >70 years added the greatest predictive capacity in their model. It is thought that GFR physiologically declines with age; therefore, using a cut-off of 60 ml/min/1.73 m² may be normal in these patients and of no adverse consequence, thus falsely raising concern in otherwise healthy older individuals. Furthermore, this study used eGFR calculated from the MDRD formula which has been shown to underestimate true GFR, particularly at levels around 60 ml/min/1.73 m². As many elderly individuals are likely to fall around or just below this mark it is debatable whether they can actually be defined as having CKD, especially as it was defined using only a single creatinine measurement. Nevertheless, this study highlights that efforts at identifying individuals with CKD should focus on individuals with underlying vascular disease, as these are the patients at greatest risk for developing CKD and subsequently cardiovascular events. The elderly clearly have increased risks of developing CKD and vascular disease, but further studies are required to quantify the relationship between senescent GFR decline and its pathological significance as K/DOQI's eGFR threshold may be inaccurate for defining CKD in the very old.

CKD as an independent risk factor for cardiovascular disease has also been the subject of recent debate. Many older studies showing positive associations were performed in populations with known cardiovascular disease or risk factors and therefore do not support the hypothesis that CKD is an independent risk factor for cardiovascular disease [12, 13]. Studies examining more general populations without baseline cardiovascular disease report less powerful associations and certainly no evidence of a causal link. Culleton et al. [14] examined data from 6,233 subjects in the Framingham Heart Study and demonstrated that although CKD was an indepen-

dent risk factor for all cause mortality in men only, it was not an independent risk factor for cardiovascular mortality in either sex. Perhaps one of the most important studies examining a population without baseline cardiovascular disease was by Weiner et al. [15], which pooled results of 22,634 participants from 4 large community based studies: ARIC, Cardiovascular Health Study, Framingham Heart Study and the Framingham Offspring Study. They found that in whites CKD was not an independent risk factor for cardiovascular outcomes such as myocardial infarction, fatal coronary events and stroke but for the primary composite endpoint (including cardiovascular outcomes plus death) it was an independent albeit weakly positive risk factor [hazard ratio (HR): 1.13; 95% confidence interval (CI) 1.02–1.26]. The strength of the association for the primary composite end point in blacks was much more pronounced (HR: 1.76; 95% CI 1.35–2.31) and they hypothesized that there may be much more sub-clinical vascular disease in the black population to account for this result. It is perhaps not surprising that many of these studies demonstrated little or no association with cardiovascular mortality as they consisted of individuals at low risk for cardiovascular disease. These studies also highlight that reduced eGFR may not be an ideal marker of sub-clinical cardiovascular disease due to the inherent problems with using serum creatinine as a measure of filtration, particularly in elderly females. For example, a high creatinine level could represent health in the elderly due to preservation of muscle mass. The use of alternative filtration markers, such as cystatin C, may afford better identification of individuals at risk of CVD events [16].

The relationship between albuminuria and cardiovascular disease in the general population has also been examined. In the Prevention of Renal and Vascular End Stage Disease (PREVEND) study, a doubling of urine albumin concentration was associated with a 29% increase in relative risk for cardiovascular mortality [17]. Culeton et al. [18] also found that dipstick proteinuria was associated with all-cause mortality in elderly men and women and with cardiovascular mortality in women. One of the limitations of this study was that it did not quantify the proteinuria; dipstick measurements are known to be insensitive. Furthermore, although the relationship seen was statistically significant, the association was very weak and in no way supports a causal relationship between proteinuria and cardiovascular events. The exact mechanism behind the relationship between albuminuria and increased cardiovascular risk is unknown but it is likely that it is simply a marker of underlying vascular

disease, or indeed of its severity and duration, rather than a predictor.

Despite there being no clear evidence of any direct causal relationship between CKD and cardiovascular disease, K/DOQI announced that CKD should be regarded as one of the 'highest risk' groups for cardiovascular morbidity and mortality, suggesting that the use of cardiovascular secondary prevention should be considered beneficial for the CKD patient in the same way as other high-risk groups [19]. It should be noted, however, that composite end points do not measure a disease and these outcome measures have been criticised for being used for statistical convenience [20].

From What Do They Die?

Given the high prevalence of CKD in the elderly and their associated cardiovascular morbidity, it is not surprising that several studies have demonstrated that cardiovascular disease is the predominant cause of death in these individuals. Two studies from the United Kingdom illustrate this finding. John et al. [21] identified unreferred CKD patients and followed them to establish the influence of non-referral on outcomes. They included all patients with a creatinine level of $\geq 180 \mu\text{mol/l}$ in men and $\geq 135 \mu\text{mol/l}$ in women in East Kent, a population with slightly more elderly than the general population. During a mean follow-up of 31.3 months, nearly 40% of the cohort had died with the most common cause of death being cardiovascular disease. Drey et al. [22] found similar results; in their cohort of incident CKD patients in Southampton and South-West Hampshire, 46% had died of cardiovascular disease during a mean follow-up of 5.5 years. It seems plausible that the high cardiovascular mortality seen in these patients may be a reflection of their underlying cardiovascular co-morbidities and that reduced eGFR with or without proteinuria are markers for underlying vascular disease in the elderly, whether visible or not. Many elderly patients will have had CKD identified opportunistically as part of routine primary care chronic disease management programs (e.g. hypertension registers). They are, therefore, likely to already be receiving treatment for underlying vascular co-morbidity. If this is not the case, the often incidental finding of a reduced eGFR in the elderly should prompt an enquiry into underlying vascular risk factors and, if necessary, optimisation of secondary cardiovascular prevention.

How Common Is Progression of Kidney Disease?

Studies have consistently shown that in patients with CKD death is far more common than progression of kidney disease [22–24]. Keith et al. [23] identified 27,998 patients enrolled in the Kaiser Permanente health plan with $\text{eGFR} < 90 \text{ ml/min/1.73 m}^2$ on at least 2 occasions spaced apart by 90 days. Subjects were followed-up for 66 months or until death or initiation of renal replacement therapy (RRT). Death was found to be significantly more common in each stage of CKD compared with the frequency of RRT: 19.5% in stage 2, 24.3% in stage 3 and 45.7% in stage 4 died compared with rates of RRT of 1.1, 1.3 and 19.9% in each stage, respectively [23]. Two other population-based studies have also demonstrated that the risks of death far exceed progression to RRT [22, 24]. Drey et al. [22] found that only 4% of those with creatinine $> 150 \mu\text{mol/l}$ progressed to RRT compared with 69% who had died during the 5.5-year follow-up. Foley et al. [24] examined a 5% sample of the Medicare population and found that the rates per 100 patient-years were significantly higher for death than progression to RRT in CKD patients with and without diabetes. These studies were all carried out in selected populations, i.e. patients who had had blood sampling for a particular reason and who may have been less well and therefore at greater risk of dying from cardiovascular disease, thus leading to a degree of bias. A study by Hallan et al. [25] in a large unselected cohort found notably lower cardiovascular mortality rates for stage 3 CKD than in the aforementioned studies, but rates of progression to ESRD were even lower (4.2 per 100 person-years and 0.1 per 100 person-years, respectively).

The natural history of progression in certain conditions such as polycystic kidney disease and diabetic nephropathy is well documented with these diseases often following a predictable linear decline. However, much less is known about the rates and nature of progression in general population-based cohorts of CKD, particularly in the elderly. A recent paper by Conway et al. [26] examined the outcomes of 396 patients with stage 4 CKD patients referred to nephrology clinics in south east Scotland and Northern Ireland. Over 70% of the cohort was > 65 years old. Those aged > 74 years declined at a rate of $0.86 \text{ ml/min/1.73 m}^2/\text{year}$ and over 25% of the cohort was discharged back to primary care with stable renal function, dying before requiring RRT. A study carried out by Hemmelgarn et al. [27] in 2006 included 10,184 subjects aged 66 years and older and found that the rate of decline in eGFR for men and women without diabetes was 1.4 and $0.8 \text{ ml/min/1.73 m}^2$ per year, respectively. Those who

started with a baseline $\text{eGFR} < 30 \text{ ml/min}$ had the greatest rates of decline along with those with diabetes. The majority of subjects had stable function and, in fact, 40% had evidence of an *increase* in their mean eGFR over the 2-year follow-up period.

Two further studies report rates of progression in population cohorts of CKD. A population-based study in Iceland examined the prevalence and progression of CKD in an unselected population [28]. Progression of renal disease was defined as a reduction in $\text{eGFR} > 1 \text{ ml/min/1.73 m}^2/\text{year}$. They reported that 27 out of 41 patients had progressive disease. Of these, 17 progressed to ESRD during a median follow-up of 7 years and 27% of patients with CKD had stable renal function at a median follow-up of 11 years. In the study by John et al. [21] the majority of patients had stable renal function with only 20% of patients showing a decline $> 2 \text{ ml/min/1.73 m}^2/\text{year}$.

So, for the majority of patients, death is far more common than the progression of kidney disease, with elderly patients by and large having little or no progression of kidney impairment, with their declining eGFR comparable to previous estimates of physiological age-related decline [29].

What Are the Risk Factors for Progression of Kidney Disease?

One of the challenges in CKD research has been identifying and understanding the risk factors for its progression. There are a number of factors which have been shown to influence the risk of progression of kidney disease but few have examined the unselected general population. Younger age appears to be linked with faster rates of decline in kidney function and progression to ESRD. In the study by Conway et al. [26], those > 74 years progressed at a much slower rate than the younger age groups. Similarly, a study by Evans et al. [30], investigating the outcomes of an unselected Swedish population with advanced CKD, found an inverse relationship between age and decline in renal function. These findings may simply reflect the type of underlying renal disease in these populations, as older patients are likely to have vascular causes with less chance of progression compared with younger patients who are more likely to have progressive glomerular disease. In contrast, Eriksen et al. [31] found that, although the risk of progression to ESRD was reduced in elderly individuals, the rate of decline in function was greater. Factors such as greater acceptance of younger patients onto dialysis programs and higher com-

peting risks of death among the elderly may account for this apparent discrepancy.

The effects of gender on the progression of kidney disease have also been explored. Data have shown that males are more likely to progress to RRT than females. It has been postulated that hormones play a role, with oestrogen having a protective effect, or alternatively, testosterone having a detrimental effect [32]. A meta-analysis of 68 studies including 11,345 patients with CKD found a higher rate of decline in renal function in men, regardless of the underlying cause of renal disease [33]. Two other studies found that male gender was linked with greater risks of progression to RRT than females [30, 31]. These findings may help explain the gender differences evident in our dialysis populations.

Naturally, the level of baseline eGFR is an important predictor of the risk of decline in function and development of ESRD. This was demonstrated by Hallan et al. [25], with 8-year follow-up of the HUNT 2 study – a cross-sectional study set in Norway with 65,604 participants. They showed a graded relationship with incidence rates of ESRD of 0.04, 0.2 and 2.6 per 100 patient-years in the eGFR groups 45–59 ml/min/1.73 m², 30–44 and <30 ml/min/1.73 m², respectively.

It is also worth dwelling on a paper by Eriksen et al. [34], who analysed the effects of changing the K/DOQI chronicity criterion on outcomes including progression. They found that in patients with CKD stage 4 there were greater rates of initiation of RRT or developing eGFR <15 ml/min/1.73 m² in those defined as stage 4 using a 9-month criterion compared with those defined using 6-month chronicity criteria. They also found that the rates of progression were greater in the longer chronicity groups than the shorter chronicity group, in those with stage 4 CKD. This data suggests that including serial measurements of creatinine and use of robust chronicity criteria could add important renal prognostic information and supports the argument for a radical change to the current CKD classification.

The answer to improving detection of those at risk of ESRD perhaps lies with the presence of proteinuria. Several studies have illustrated that proteinuria is a better marker than eGFR alone for the development of progressive kidney disease in both diabetics and non-diabetics with renal disease and therefore may be a valuable inclusion within a screening strategy. Iseki et al. [35] examined the prevalence of low creatinine clearance and the risk of developing ESRD in an unselected Japanese population and reported that the cumulative incidence of ESRD per 1,000 patients over an 18-year follow-up was low in those

without proteinuria at 1.1 in stage 3, 7.6 in stage 4 and 242 in stage 5 compared to rates of 69.8, 368 and 722 for stages 3, 4 and 5, respectively, in those with 2+ or more of proteinuria. Similarly, the Multiple Risk Factor Intervention Trial (MRFIT) showed that the risk of developing ESRD after adjusting for other confounding factors was greater for those with proteinuria and eGFR of ≥ 60 ml/min/1.73 m² compared to those without proteinuria and eGFR <60 ml/min/1.73 m² [36]. Halbesma et al. [37] examined rates of progression in subjects from the PREVENDE study; they found that the rates of progression were not significantly different between those in the control group and those with low eGFR, but those with macroalbuminuria had a significantly greater decline in renal function compared to the control group (7.2 ml/min/1.73 m²/year vs. 2.6 ml/min/1.73 m²/year).

None of the above studies have been able to report the effects of eGFR combined with the entire albuminuria spectrum in a Caucasian population on the hard end point of developing ESRD. Hallan et al. [38] recently set out to test a predictive model for ESRD which has overcome these limitations. Data from the HUNT 2 study was used to construct a multivariate model to predict progression to ESRD. They found that eGFR and albuminuria were independently and strongly associated with progression to ESRD but using both variables together vastly improved diagnostic accuracy, suggesting that all eGFR values should be accompanied by urine information to provide optimal classification and prognostic information. ESRD was defined as starting RRT or death with a documented stable eGFR <15 ml/min/1.73 m² or other indications for RRT before death. This robust method minimized survival bias as it included patients who had died before being taken onto dialysis with a diagnosis of ESRD. However, this definition would have missed the few patients with eGFR <15 ml/min/1.73 m² who remained free of dialysis and alive at the end of the 10-year follow-up, potentially leading to a misclassification bias, but it was felt that this degree of bias was insignificant. The limits of this study were that only a subgroup of the population were invited for albuminuria screening and they excluded 38 patients with stage 3 to 4 CKD who required RRT. It is known that some individuals require RRT at a higher GFR than universally accepted as 'end-stage'; for example, diabetics are often required to start dialysis earlier than other groups due to problems with fluid balance, leading to a potential source of misclassification bias. Therefore, that study's defined end point of ESRD may be less useful than the knowledge of rates of progression in such individuals.

What is not clear is whether proteinuria depicts an increased risk of developing more progressive disease or again merely represents a marker of more underlying aggressive and advanced disease. Nevertheless, a combination of eGFR and albuminuria clearly allows practitioners to focus attention on the small group of individuals at risk of progression.

Does the Degree of Mortality Risk Vary among Individuals?

In addition to its role in predicting progression, proteinuria appears to be a better marker than eGFR alone for determining mortality risk. Keith et al. [23] found that the risk of death doubled and the rate of RRT was 10-fold higher in the stage 2 population with proteinuria compared with those with eGFR of 60–89 ml/min/1.73 m² and no proteinuria, highlighting the additional risks of albuminuria. In a recent analysis of the PREVEND study Brantsma et al. [39] showed that among subjects with stage 3 CKD without albuminuria, their adjusted risks of cardiovascular events were essentially no different to those without CKD.

However, it is the effect of the eGFR level that has perhaps attracted more attention due to the widespread use of the K/DOQI staging system along with eGFR reporting across the world. A study by Go et al. [40] of 1.1 million adults enrolled in the Kaiser Permanente Renal Registry found an independent, graded association between the level of eGFR and the risks of death after adjusting for confounders including age, co-morbidity and gender. The adjusted HR for death was 1.2 for those with an eGFR level of 45–59 ml/min/1.73 m², 1.8 for eGFR 30–44, rising significantly to 3.2 for eGFR 15–29 and to 5.9 for an eGFR level <15 ml/min/1.73 m². It is worth noting, however, that in a subgroup of patients with repeat creatinine measurements to ascertain chronicity, the risk of death was no different in individuals with eGFR 45–59 ml/min/1.73 m² compared to those with eGFR >60 ml/min/1.73 m². Two other studies have reported similar findings showing that the degree of mortality risk may also differ substantially within stage 3, with some advocating the need for finer classification of the K/DOQI staging system to account for these differences [25, 41].

There is now emerging evidence that the degree of mortality risk in CKD populations may be age-dependent. Many of the studies examining CKD and mortality risk have been conducted in younger populations, such as those by Hallan et al. [25] (median age 49 years) and Go

et al. [40] (mean age 52 years). The high risks seen in these population studies may be due to less baseline prevalence of vascular co-morbidities in the young and therefore greater relative risks. Studies which have specifically examined elderly populations have found weaker associations [42]. In particular the Cardiovascular Health Study, whose participants were 65 years and older, found very weak albeit positive associations with cardiovascular events and death (HR between 1.04–1.07 for all events for every 10 ml reduction in GFR) [43]. Results from the same population later found that cystatin C was a much stronger predictor of the risk of death and CVD events than creatinine, again highlighting that equations based on serum creatinine may be inappropriate for use in predicting mortality risk in elderly individuals [44]. Furthermore, a recent paper by Roderick et al. [45] showed that the all-cause mortality risk in patients >75 years was only significantly increased for eGFR <45 with the greatest risks for cardiovascular death. In addition, they found that women had distinctly lower hazards of death compared with men, which could be explained by underlying inaccuracies of the MDRD equation in females or simply by biological differences. One of the major limitations of this study was the use of only a single creatinine measurement and the lack of calibration of the creatinine assay. In a study by O'Hare et al. [41], examining over 2.5 million subjects, age-related attenuation in mortality risk and CKD was demonstrated. In this study, there was no increase in the relative risk of mortality in those aged >65 years with a persistent eGFR of 50–59 ml/min and, likewise, no increase in risk in those with eGFR of 40–49 ml/min in those aged >75 years. However, there was a significantly increased risk of mortality in the lower age groups across all ranges of eGFR, apart from eGFR <15 ml/min/1.73 m² at which point older age groups had similar relative risks of death compared to younger age groups. In fact, they found a *decreased* independent risk of mortality in those aged >45 years with eGFR of 50–59 ml when chronicity was established, again highlighting the importance of serial measurements in predicting prognosis. A more recent study by Raymond et al. [46] echoed these findings, placing further emphasis on the apparent lack of increased mortality risk in the elderly, particularly with eGFR in the range of 45–59 ml/min/1.73 m².

It is less clear what the effects of proteinuria in the older patient are on mortality risk. The paper by Roderick et al. [45] showed that dipstick proteinuria did not add to the risk stratification of CVD mortality, but only a single dipstick test was used which is not a very sensitive measure of proteinuria. In addition, as mentioned above, Culleton

et al. [18] found only weak associations with dipstick proteinuria and all-cause mortality in both sexes, but no association for CVD mortality and males. In contrast, Hallan et al. [47] found that eGFR and microalbuminuria synergistically improved cardiovascular risk stratification to a greater degree in patients >70 years than in those who were younger, suggesting that the traditional risk factors are less predictive in the elderly. As discussed earlier, it is more likely that proteinuria is a marker of sub-clinical CVD rather than a predictor per se.

What these studies show is that CKD is a risk factor for cardiovascular morbidity and mortality but only in subgroups of individuals with more advanced disease or proteinuria.

Conclusions

Many have criticised the K/DOQI for fuelling a surge of startled individuals labelled (rightly or wrongly) with a 'disease' of which they may otherwise never have been aware. In their defence, K/DOQI has enabled clinicians to become more aware of the condition, aided in the adjustment of drug dosages and empowered clinicians to deal with the considerable morbidity and mortality associated with having CKD.

However, it is clear that for the majority of elderly patients with CKD their renal impairment will not progress and that they will succumb to cardiovascular disease before ESRD ensues. The vast majority of such patients could be managed appropriately in primary care.

On the other hand, we need to exercise vigilance for the select group of higher-risk individuals, those who can be identified by their younger age or the presence of proteinuria; these are the patients who are likely to gain the most from early nephrology referral and intervention.

Despite considerable research in CKD in recent years, a number of questions remain unanswered:

- How much of the increased cardiovascular risk seen in the CKD population is due to traditional risk factors and how much can be attributed to so-called non-traditional factors?
- Are there better therapies that can be developed and targeted against these non-traditional risk factors?
- Should all elderly patients with stage 3 CKD be labelled with a 'disease' and start new cardiovascular protective medications given that the mortality risk for some of these individuals may not be as high as previously thought?
- To what extent do standard cardiovascular preventative measures impact on risk in the elderly?
- Will new markers of filtration be better at predicting adverse events, particularly in elderly populations?
- Perhaps most importantly in view of the recent Hallan et al. [38] study, can we change the current CKD classification system to enable enhanced identification of those at high risk of progression and minimise the anxiety-provoking detection of the low risk?

There is a need to exercise caution in adopting new definitions of disease before fully understanding its natural history. The nephrology community must address these questions now and reconsider the current definition and classification of CKD in the light of recent and further research.

References

- Centers for Disease Control and Prevention (CDC): Prevalence of chronic kidney disease and associated risk factors – United States, 1999–2004. *MMWR Morb Mortal Wkly Rep* 2007;56:161–165.
- 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;72:92–99.
- Chronic kidney disease (stages 3–5) prevalence estimates using data from the NEOERICA study [homepage on the Internet]. www.apho.org.uk/resource/item.aspx?RID=63798 (accessed April 20, 2009).
- Foley RN, Wang C, Snyder JJ, Collins AJ: Cystatin C levels in US adults, 1988–1994 versus 1999–2002: NHANES. *Clin J Am Soc Nephrol* 2009;4:965–972.
- Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al: Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002;39:920–929.
- Botev R, Mallie J, Couchoud C, Schuck O, Fauvel J, Wetzels JFM, et al: Estimating glomerular filtration rate: Cockcroft-Gault and Modification of Diet in Renal Disease formulas compared to renal inulin clearance. *Clin J Am Soc Nephrol* 2009;4:899–906.
- Glasscock RJ, Winearls C: An epidemic of chronic kidney disease: fact or fiction? *Nephrol Dial Transplant* 2008;23:1117–1121.
- Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 1998;9:S16–S23.
- Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ: Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J* 2006;151:492–500.
- Kshirsagar AV, Bang H, Bombardier AS, Vupputuri S, Shoham DA, Kern LM, et al: A simple algorithm to predict incident kidney disease. *Arch Intern Med* 2008;168:2466–2473.
- Chonchol M, Gnahn H, Sander D: Impact of subclinical carotid atherosclerosis on incident chronic kidney disease in the elderly. *Nephrol Dial Transplant* 2008;23:2593–2598.
- Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. *Ann Intern Med* 2001;134:629–636.

- 13 Ruilope LM, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H, et al: Renal function and intensive lowering of blood pressure in hypertensive participants of the Hypertension Optimal Treatment (HOT) study. *J Am Soc Nephrol* 2001;12:218–225.
- 14 Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D: Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999;56:2214–2219.
- 15 Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al: Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004;15:1307–1315.
- 16 Menon V, Shlipak MG, Wang X, Coresh J, Greene T, Stevens L, et al: Cystatin C as a risk factor for outcomes in chronic kidney disease. *Ann Intern Med* 2007;147:19–27.
- 17 Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE: Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002;106:1777–1782.
- 18 Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. *Am J Med* 2000;109:1–8.
- 19 Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW: American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003;42:1050–1065.
- 20 Ferreira-Gonzalez I, Busse JW, Heels-Ansell D, Montori VM, Akl EA, Bryant DM, et al: Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *BMJ* 2007;334:786.
- 21 John R, Webb M, Young A, Stevens PE: Unreferred chronic kidney disease: a longitudinal study. *Am J Kidney Dis* 2004;43:825–835.
- 22 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;42:677–684.
- 23 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;164:659–663.
- 24 Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005;16:489–495.
- 25 Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Holmen J, et al: Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ Online* 2006;333:1047.
- 26 Conway B, Webster A, Ramsay G, Morgan N, Neary J, Whitworth C, et al: Predicting mortality and uptake of renal replacement therapy in patients with stage 4 chronic kidney disease. *Nephrol Dial Transplant* 2009;24:1930–1937.
- 27 Hemmelgarn BR, Zhang J, Manns BJ, Tonelli M, Larsen E, Ghali WA, et al: Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int* 2006;69:2155–2161.
- 28 Magnuson RL, Indridason OS, Sigvaldason H, Sigfusson N, Palsson R: Prevalence and progression of CRF in Iceland: a population-based study. *Am J Kidney Dis* 2002;40:955–963.
- 29 Lindeman RD, Tobin J, Shock NW: Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 1985;33:278–285.
- 30 Evans M, Fryzek JP, Elinder CG, Cohen SS, McLaughlin JK, Nyren O, et al: The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. *Am J Kidney Dis* 2005;46:863–870.
- 31 Eriksen BO, Ingebretsen OC: The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;69:375–382.
- 32 Silbiger SR, Neugarten J: The role of gender in the progression of renal disease. *Adv Ren Replace Ther* 2003;10:3–14.
- 33 Neugarten J, Acharya A, Silbiger SR: Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol* 2000;11:319–329.
- 34 Eriksen BO, Ingebretsen OC: In chronic kidney disease staging the use of the chronicity criterion affects prognosis and the rate of progression. *Kidney Int* 2007;72:1242–1248.
- 35 Iseki K, Kinjo K, Iseki C, Takishita S: Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. *Am J Kidney Dis* 2004;44:806–814.
- 36 Ishani A, Grandits GA, Grimm RH, Svendsen KH, Collins AJ, Prineas RJ, et al: Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the Multiple Risk Factor Intervention Trial. *J Am Soc Nephrol* 2006;17:1444–1452.
- 37 Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al: Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol* 2006;17:2582–2590.
- 38 Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR: Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009;20:1069–1077.
- 39 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;23:3851–3858.
- 40 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;351:1296–1305.
- 41 O'Hare AM, Bertenthal D, Covinsky KE, Landefeld CS, Sen S, Mehta K, et al: Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol* 2006;17:846–853.
- 42 Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al: Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;17:2034–2047.
- 43 Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, et al: Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int* 2003;63:1121–1129.
- 44 Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, et al: Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005;352:2049–2060.
- 45 Roderick PJ, Atkins RJ, Smeeth L, Mylne A, Nitsch DD, Hubbard RB, et al: CKD and mortality risk in older people: a community-based population study in the United Kingdom. *Am J Kidney Dis* 2009;53:950–960.
- 46 Raymond NT, Zehnder D, Smith SC, Stinson JA, Lehnert H, Higgins RM: Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrol Dial Transplant* 2007;22:3214–3220.
- 47 Hallan S, Astor B, Romundstad S, Aasarod K, Kvenild K, Coresh J: Association of kidney function and albuminuria with cardiovascular mortality in older versus younger individuals: the HUNT II study. *Arch Intern Med* 2007;167:2490–2496.

Editorial Comment

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This minireview by Laura Clark and Izhar Khan provides the reader with an excellent updated critical analysis of the data relating to CKD, its definition, classification as well as natural history and prognosis. The authors examine in details the impact of gender and age on outcomes, namely ESRD and CVD. Their review makes the point, argued by many, that caution should be adopted when embracing new definitions of disease in certain subgroups of individuals such as the elderly. It cautions against medicalisation of normality and questions wheth-

er changes in the current CKD classification are warranted based on better definition of those at risk of ESRD or CVD progression. This task has been taken up by the not-for-profit organization Kidney Disease: Improving Global Outcomes or KDIGO, who in 2009 is organising a conference to revisit the definition and classification of CKD based on outcome measures. KDIGO aims to use available evidence-based knowledge of CKD outcomes to examine the validity of the current classification of CKD.