The Conundrum of Chronic Kidney Disease Classification and End-Stage Renal Risk Prediction in the Elderly – What Is the Right Approach?

Stein Ivar Hallan^{a, b} Stephan Reinhold Orth^{c, d}

^aDepartment of Medicine, Division of Nephrology, St. Olav University Hospital, and ^bDepartment of Cancer Research and Molecular Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway; ^cDialysis Centre Bad Aibling, Bad Aibling, and ^dDepartment of Internal Medicine II, University of Regensburg, Regensburg, Germany

Key Words

Chronic kidney disease classification • Elderly • End-stage renal disease • Risk • Albumin excretion

Abstract

The worldwide high prevalence of chronic kidney disease (CKD) and the increasing number of patients reaching end-stage renal disease (ESRD) are a matter of major concern. The most widely accepted classification system of CKD is that proposed by the Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002. When applying this system, it has become apparent that the prevalence of CKD is particularly high in elderly subjects. The fact that this system is mainly based on estimated glomerular filtration rate (eGFR), subdividing the severity of CKD into five stages, is a matter of debate. A main issue is that although a reduced eGFR is often encountered in elderly subjects, most of these subjects do not have a renal disease leading to an increased risk of ESRD, i.e. the predictive power of ESRD is unsatisfactory. Recent advances have been put forward to improve (1) estimation of GFR and (2) prediction of ESRD. In this review, we discuss the currently available data with a focus on the elderly and propose an improved classification system of CKD which is characterized by a substantially better diagnostic accuracy for progression

to ESRD. This is simply and cost-effectively accomplished by subdividing stage 3 CKD into two groups (eGFR 30–44 and 45–59 ml/min/1.73 m²) and by complementing all levels of eGFR with information about urinary albumin excretion, i.e. whether normoalbuminuria, microalbuminuria, or macroalbuminuria is present. The consequence should be a revision of the 2002 KDOQI CKD classification system according to these findings, which would be a significant step forward, particularly for elderly CKD patients.

Copyright © 2010 S. Karger AG, Basel

Chronic kidney disease (CKD) has been found to be very common worldwide [1–3]. The prevalence is particularly high in the elderly with 47, 35 and 28% of subjects above age 70 in US, European, and Chinese general populations, respectively, diagnosed as having CKD according to the current Kidney Disease Outcomes Quality Initiative (KDOQI) definition [1–3]. Although a large proportion of new end-stage renal disease (ESRD) cases today comes from this age group, it has become apparent that the risk for progression to kidney failure among elderly CKD patients is low [4]. This has led to a vivid debate whether or not the current KDOQI definition of CKD is valid and appropriate [5–9]. A major concern is

that a large proportion of CKD cases, especially among the elderly, may be misclassified and that their low estimated glomerular filtration rate (eGFR) is just a ‘normal’ reduction of kidney function with increasing age.

Current CKD Classification

The 2002 KDOQI classification system for CKD is mainly based on degrees of reduction in GFR [10]. Stages 1–5 are defined as eGFR ≥90, 60–89, 30–59, 15–29 and <15 ml/min/1.73 m², respectively, and the findings should be consistent for more than 3 months. For stages 1–2 signs of kidney damage (albuminuria, hematuria or sonographic abnormalities) are also required. GFR should be estimated with formulas based on serum creatinine taking age, sex, and other demographics into account. The first publications using the KDOQI system were hampered by estimation formula problems [11, 12]. The first Modification of Diet in Renal Disease (MDRD) study formula was based on an unusually low calibrated serum creatinine method [13], and the use of the Cockcroft-Gault formula results in a too steep decline of kidney function with age [14]. Both problems lead to a substantial underestimation of GFR thereby overestimating the CKD prevalence.

A recalibration of the MDRD formula based on isotope dilution mass spectroscopy traceable serum creatinine values improved performance substantially, and recently the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was published with even better performance [15]. By using the CKD-EPI equation, the mean systematic underestimation at GFR 60 ml/min/1.73 m² and upwards has been reduced from –10.6 to –3.5 ml/min/1.73 m² and precision has increased, resulting in 88.3% of the results being within ±30% of the true GFR (as measured by radiolabeled tracers) compared to 84.7% with the recalibrated MDRD formula [15]. However, for the individual patients there is still a clinically significant inaccuracy (e.g. errors of ±20% are not unusual), and this can – especially in eGFR-dominant systems – lead to misclassification. When using this new equation, the median eGFR in the general population shifts from 85 to 95 ml/min/1.73 m², and a substantial proportion of subjects is reclassified from the 30–59 ml/min/1.73 m² category to the 60–89 ml/min/1.73 m² category, i.e. from stage 3 to stage 2 of the current KDOQI CKD classification [15].

The CKD-EPI equation should be well suited for use in the elderly, because a total number of 1,592 subjects

Table 1. Prevalence of CKD among the elderly in the USA and in a European population

	NHANES (1999–2006)		HUNT 2 (1995–1997)	
	MDRD	CKD-EPI	MDRD	CKD-EPI
Stage 1	1.2	0.6	4.0	1.5
Stage 2	7.6	8.5	11.5	14.0
Stage 3	35.5	35.3	18.6	18.7
Stage 4	1.9	2.4	0.7	0.9
Total	46.3	46.8	34.8	34.9

Data are percentages of the general population. Prevalence estimates were based on eGFR in subjects aged >70 years. GFR was estimated with the MDRD study equation for use with calibrated serum creatinine values and the CKD-EPI equation. The prevalence estimates for the Norwegian HUNT 2 study were based on the same study sample as previously published [2].

above age 65 was enrolled during development, internal and external validation of this formula [15]. In contrast to middle-aged subjects, there is no shift of the median eGFR in elderly subjects using the CKD-EPI equation. Table 1 shows the prevalence of CKD stages 1 through 4 in elderly subjects from two large population-based studies using the MDRD and the CKD-EPI equations. Independent of the formula used, the CKD prevalence is consistently found to be very high.

Controversies over the Current CKD Classification

There has been a brisk debate over the last couple of years whether the CKD epidemic is fact or fiction. In a series of articles, Glasscock and Winearls [7–9, 16, 17] put forward strong critiques about the current eGFR-focused CKD classification, which in turn, has been strongly defended by the KDOQI chairpersons [5, 6]. The main critique has been related to ‘the improbable high prevalence estimates’, a fixed cutoff for abnormality for all ages, and omission of the possibility that a decline in kidney function may be a normal part of the aging process. The KDOQI 2002 classification system definitely has shortcomings as a renal risk score, but the above mentioned critiques, which are clearly interrelated, also have deficits. First, we have repeatedly learnt over the past 40 years that normality and percentiles are not always the optimal approach for diagnostics and risk stratification. Cutoffs for blood pressure and cholesterol have repeatedly been low-

ered beyond the classical 97.5th percentile, and very large proportions of the general population are now defined as hypertensive or as having hypercholesterolemia [18]. A very high prevalence of CKD in the elderly may therefore indeed be plausible. Second, a number of pathological findings are associated with reduced kidney function in elderly subjects. The prevalence of increased albuminuria is much higher in the elderly compared to the young [19], a phenomenon that is clearly related to pathological processes in the kidney. Histological changes like glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriolar sclerosis, which are typical findings of the common pathway of progressive CKD, are increasingly found with higher age even in the absence of hypertension and diabetes [20]. Figure 1 illustrates such histological alterations in a renal biopsy specimen. Likewise, the cortical thickness is reduced and the overall size of the kidney decreases [20]. All of these changes are considered highly pathological when observed in the younger, and it is difficult to argue that this should not also be the case in the elderly.

Reduced Kidney Function in the Elderly

The reduction of GFR with increasing age deserves special attention. Studies have shown that there is a gradual decline in measured GFR with age [21–23]. The classical work by Davies and Shock [21] showed that mean GFR (measured using the gold standard of inulin clearance) decreased from 123 (SD 16) ml/min/1.73 m² at age 20–29 years to 65 (SD 20) ml/min/1.73 m² at age 80–89 years. This indicates that there is a true reduction in kidney function among the elderly and that this may not only be a phenomenon created by inaccurate or biased equations for estimating GFR. However, the majority of participants in the previous study were in-house patients with acute or chronic infections, atherosclerosis or other diseases and treatments that potentially could influence kidney function although patients with obvious cardio-renal diseases were excluded. On the contrary, there are good indications that the reduction of GFR at higher age is only modest, as long as the subjects investigated are healthy. For instance, Fliser et al. [24] found that this was the case when comparing 10 healthy subjects with a median age of 70 years (range 61–82) with a group of 15 subjects with a median age of 26 years (range 23–32). They also documented that at least until the age of 80 years renal functional reserve, i.e. the increase in GFR after an amino acid load, was preserved in these subjects indepen-

Fig. 1. Histopathological findings in a healthy 70-year-old male subject who was considered as a potential donor in an old-for-old renal transplantation program. eGFR was only slightly reduced (eGFR 65 ml/min/1.73 m²). The picture shows areas with glomerular obliteration (A), tubulointerstitial fibrosis (B), tubular atrophy (C) and vascular sclerosis (D).

dent of gender. Thus, age-related changes of renal function are less severe than previously thought. However, the arterial wall is substantially remodeled with increasing age even in the healthiest subjects. These normal changes caused by the joint effects of biomolecular, cell and matrix modifications are significantly aggravated by classical cardiovascular risk factors such as hypertension, diabetes and smoking, i.e. conditions often encountered in elderly subjects [20, 25]. One of the consequences is increased arterial stiffness, and significant associations have been found even to only small reductions of eGFR and to low-grade albuminuria. The kidneys are, as a low resistance organ, thought to be especially prone to the resulting high pulse pressures, and resulting microcirculation changes lead to kidney dysfunction through ischemia. Decreasing kidney function could then lead to calcium-phosphate depositions and increased oxidative stress setting up a vicious circle as indicated in figure 2 [26, 27].

To separate the effect of toxins and diseases that may injure the kidneys over time and the ‘natural aging’ caused by replicative senescence and oxidative stress, we must study a population that is very unlikely to have any kind of kidney disease and no cardiovascular risk factors. Kidney donors are probably the most valid study group to analyze this problem. These subjects undergo all available noninvasive tests to ensure that donation will have

Fig. 2. The effect of aging on kidney failure progression [adapted from 20]. Aging leads to structural fatigue and stiffening of elastic arteries and, in turn, increased pulse wave velocity and increased transmission of energy to fragile microvessels in the kidney. Ischemia in the perfusion areas of the glomerular and peritubular capillary networks leads to persistent structural damage (measured as reduced eGFR) as well as more reversible functional changes indicating ongoing CKD progression (measured as albuminuria due to reduced reabsorption and/or degradation of albumin in proximal tubules).

no negative influence on their future health. A pooled analysis of measured GFR in 1,040 kidney donors showed that there was only a modest reduction of kidney function over time [14]. Median GFR (2.5th and 97.5th percentiles) was 110 ml/min/1.73 m² (80–150) at age 25, 95 ml/min/1.73 m² (70–125) at age 50, and 80 ml/min/1.73 m² (60–110) at age 75, which corresponds to a reduction in GFR of 0.6 ml/min/1.73 m² per year. Figure 3 shows that estimation of GFR using the CKD-EPI formula in 1,027 subjects from the HUNT 2 study eligible for kidney donation gave very similar results. Inclusion criteria for this healthy group were absence of macroalbuminuria, cardiovascular disease (CVD), diabetes mellitus and malignancy as well as presence of normotension, normal serum creatinine, body mass index <35 and the self-reporting of good or excellent general health [14]. The median eGFR at age 75 was exactly the same as measured GFR in kid-

ney donors reported in the literature (80 vs. 81 ml/min/1.73 m²), while the eGFR values at younger ages were slightly higher (97 vs. 94 ml/min/1.73 m² at age 50). In this cohort, the 5th percentile, which has been suggested as a lower limit of normal kidney function, was above 60 ml/min/1.73 m² even for 80-year-old subjects. Clearly, the 5th percentile is substantially lower if estimated in the general population versus a very healthy population like potential kidney donors, and it would be principally wrong to use percentiles derived from the total general population for decision making. Therefore, it seems clear indeed that there is a normal decline in kidney function with age, but the decline is not as steep as had often been claimed in the past. The important conclusion is that even among the elderly an eGFR below 60 indicates a pathological reduction in kidney function!

Cardiovascular Disease Risk in Elderly CKD Patients

CVD is the most imminent threat for patients with CKD. It is not until CKD patients have progressed to stage 4 that the risk for future ESRD exceeds the risk of cardiovascular death [28]. The reason for this extremely increased CVD risk is both an increased prevalence of traditional cardiovascular risk factors in elderly subjects and several novel risk factors associated with CKD [29]. Anemia, electrolyte disturbances, hyperparathyroidism, metabolic acidosis, and others contribute to the increased risk. In a substantial number of CKD patients one or more of these risk factors start to appear at a GFR of 60 ml/min/1.73 m² [30]. However, the relative risk associated with traditional risk factors like hypertension and hypercholesterolemia is lower in the elderly compared with younger subjects [31, 32]. In the oldest, there are even indications of a reversed causation for several traditional CVD risk factors (body mass index, blood pressure, and cholesterol) [33]. In this context, it also has to be kept in mind that the major risk equations used today, i.e. the U.S. Framingham Score and the European System for Cardiac Operative Risk Evaluation (or SCORE), are based on data derived from populations below the age of 70 years.

Albuminuria has long been recognized as an important predictor of increased cardiovascular mortality in the general population as well as in different subgroups including the elderly [34, 35]. Since eGFR emerged as an important CVD risk factor the combined assessment of these two parameters seems prudent. Several studies have found that both lower eGFR and increasing albuminuria

Fig. 3. eGFR in healthy potential kidney donors versus the unselected general population. Figures show 5th, 50th, and 95th percentiles by age. Data based on the total HUNT 2 study ($n = 65,123$) versus subjects fulfilling the criteria for kidney donation ($n = 1,027$) from the same population. GFR was estimated with the CKD-EPI equation.

Table 2. Data from the literature on the association between eGFR and albuminuria and cardiovascular mortality risk in elderly subjects

Study	Age group	Variable	Relative risk	Study conclusion
UK [53] (general practice)	≥ 75 years	proteinuria (dipstick neg./pos.) eGFR (>60 , $45-59$, $30-44$, <30)	NS 1.0, 1.6, 1.7, 4.5	GFR is an independent strong risk factor, especially in men
Japan [54] (general population)	≥ 80 years	eGFR (>60 , <60)	1.0, 4.6	CKD increases CVD risk in very elderly individuals
US (Cardiovascular Health Study) [55] (general population)	≥ 65 years	albuminuria (quintiles) eGFR (quintiles)	1.0, 1.2, 1.4, 1.6, 2.1 1.0, 1.1, 1.6, 1.8, 2.5	albuminuria and GFR are graded independent risk factors for CVD
Taiwan (Elderly Health Examination Program study) [56] (general population)	≥ 65 years	eGFR (>60 , $45-59$, $30-44$, <30)	1.0, 1.3, 2.4, 3.6	late-stage CKD is a significant risk factor in the elderly
Norway (HUNT study) [39] (general population)	≥ 70 years	albuminuria (quintiles) ^a eGFR (>60 , $45-59$, $30-44$, <30)	1.0, 1.4, 2.1, 2.4, 2.7 1.0, 1.4, 2.6, 2.5	albuminuria and GFR are strong independent risk factors, especially when combined and in the elderly

Relative risk given for albuminuria and GFR are adjusted for each other and age, sex, diabetes, hypertension, and other relevant cardiovascular risk factors. NS = Nonsignificant.

^a Unpublished data from reference [39], new categorization to improve comparison with other studies.

are significant independent cardiovascular risk factors. Table 2 shows data from some studies based on elderly subjects. These, as well as other general population-based studies [36–41], are quite heterogeneous regarding study design and patient characteristics. Thus, it is not possible to give good pooled estimates of the association between CKD and cardiovascular mortality.

Such research is, however, underway in the Kidney Disease Improving Global Outcomes (KDIGO) organization [6], and it is likely that more than 100,000 elderly subjects with data on eGFR and albuminuria will be included into a meta-analysis. The presence of CKD has already been included as a new major risk factor for CVD in general clinical guidelines [42], and the data

Table 3. Data from the literature on the association between eGFR and albuminuria and kidney failure risk in elderly subjects

Study	Age group	Variable	Relative risk	Study conclusion
Japan (Okinawa study) [47] (general population)	≥71 years	proteinuria (0, trace, 1 to 4+) eGFR (>79, 64–79, 50–64, <50)	1.0, 4.7, 9.4, 14.1, 18.8, 23.5, 28.3 1.0, 9.8, 19.6, 29.4	dipstick screening useful, especially in the elderly
Norway (HUNT study) [51] (general population)	≥70 years ^a	albuminuria (normo, micro, macro) eGFR (>60, 45–59, 30–44, <30)	1.0, 8.2, 26.3 1.0, 3.3, 10.4, 30.3	major independent risk factors for kidney failure

Relative risk given for albuminuria and GFR are adjusted for each other and age, sex, diabetes, hypertension, and other relevant risk factors.

^a Unpublished data [from 51], i.e. a subanalysis of the elderly.

shown in table 2 very consistently document that low eGFR and increasing albuminuria are strong independent cardiovascular risk factors. It has also been shown that the additional predictive power of a combined eGFR-albumin:creatinine ratio (ACR) variable is especially high among the elderly [39]. This is probably due to the reduced risk associated with traditional risk factors and CKD working as a marker of subclinical atherosclerosis in the elderly. Indeed, there are substantial experimental, epidemiological and clinical data suggesting that CKD is a marker of subclinical atherosclerosis [20]. Inclusion of kidney function and damage, i.e. eGFR and albuminuria, in future CVD risk equations seems reasonable, and a close collaboration with the cardiology societies will be very important.

Risk of Progression to Kidney Failure in Elderly CKD Patients

The risk of progression to kidney failure is of major interest for CKD patients and nephrologists. Developing renal risk scores are therefore urged by nephrology leaders [43]. In this process, we should ensure that the risk scores to be developed are also suitable for use among the elderly. The largest proportion of incident dialysis patients comes from this group of CKD patients, which also is the most difficult to evaluate concerning the need of intensive prophylactic treatment and follow-up. The currently available knowledge for the specific subgroup of the elderly is more limited concerning kidney disease progression than for CVD risk estimation. Table 3 shows that low eGFR and increased ACR are important independent risk factors in several populations, and a subanalysis of the HUNT 2 study indicates that this also proves true for the elderly.

However, the current CKD definition has a low specificity. Only a minor portion of those classified as CKD patients progress to kidney failure [44, 45]. There has recently been some important progress on risk stratification; combining eGFR and albuminuria at all levels are now considered as the way forward [46]. This is based on previous reports with certain shortcomings [47–50] and a recent comprehensive analysis on the improved classification of CKD using these principles [51]. Previous reports have shown that the relative risk for ESRD increases strongly with decreasing eGFR and increasing albuminuria, independently of each other. However, some of the studies were based on men with high CVD risk or African-Americans with hypertensive nephrosclerosis [48, 50], some did not adjust for relevant confounders [47, 50], and some only tested for macroalbuminuria [47]. Furthermore, all previous studies have only reported relative risk estimates for ESRD exclusively, although this is regarded as a less suitable/relevant measure for risk prediction and classification [52].

Based on 65,000 subjects from the population-based HUNT 2 study with 10.3 years of follow-up, we found that eGFR and ACR were the major risk predictors after adjusting for other known risk factors [51]. They were also synergistic implying increased discrimination when used together. Age, sex, hypertension, diabetes, and other cardiovascular risk factors did not increase predictive value. We also performed receiver operating characteristics analysis, which describes how well a model discriminates those CKD cases progressing to ESRD from those cases not progressing. This confirmed that eGFR discriminates better than ACR when equal importance is given to sensitivity and specificity. However, for screening related situations a very low false-positive rate is needed, and in this case eGFR and ACR had equal diagnostic accuracy. Both strongly outperformed a model including all other known risk factors, and combining eGFR and ACR significantly

Table 4. Suggestion for a new CKD classification providing clear information about the future ESRD risk, even in the elderly

	eGFR ≥ 60	eGFR 45–59	eGFR 30–44	eGFR 15–29
<i>Adjusted relative risk</i>				
Normal ACR	1.0 (ref.)	11.7	25.3	120
Microalbuminuria	18.2	60.9	183	765
Macroalbuminuria	110	302	934	982
<i>Absolute risk</i>				
Incidence rate (per 100,000 person-years)	Reference	Low risk	Moderate risk	High risk
	4	69	586	3,938

Data are derived from 11,241 subjects from the HUNT 2 study above age 70. The categories of the combined eGFR-ACR were defined and grouped into low, medium and high risk as suggested in the original article [51]. The relative risks are adjusted for age, sex, diabetes, blood pressure, antihypertensive medication, lipids, and physical activity. The absolute risk is the observed incidence of progression to kidney failure defined as starting renal replacement therapy or CKD-related death with a documented eGFR <15 ml/min/1.73 m² during a 10.3-year observation period.

improved diagnostic accuracy. We therefore recently proposed a new classification system for CKD based on four eGFR categories (≥ 60 , 45–59, 30–44, <30 ml/min/1.73 m²) that are further subdivided by three ACR categories (normal, microalbuminuria, macroalbuminuria) [51]. Importantly, we showed that this classification system could reduce the number of CKD patients referred to specialists by 70% without losing CKD cases that would progress to ESRD in the future. These results need to be confirmed in other cohorts, and a joint effort to do so is on its way within the KDIGO organization [6]. Fifty CKD cohorts including more than a million subjects worldwide will be analyzed following the same analytical approach as in the previous 2009 HUNT 2 study, with the first results expected during 2010. The new CKD classification system that we present here also provides clear information about kidney failure risk in the elderly. Importantly, we have also recently been able to show that this CKD classification system provides strong predictive information on CVD risk in the elderly as well [39].

Should Normoalbuminuric Elderly Subjects with eGFR 30–59 ml/min/1.73 m² Be Classified as CKD Patients?

CKD stage 3 in the elderly has been one of the main problems fuelling the debate on the current CKD classification. Including information on albuminuria in all CKD patients substantially improves risk prediction [51]. However, subjects with eGFR 30–59 ml/min/1.73 m²

without micro- or macroalbuminuria remain problematic as far as classification is concerned. The question is whether these subjects really have CKD? This question is indeed of major clinical importance, because this group comprises a large number of subjects. Prevalence and relative risk estimates for serious outcomes in this group of subjects are given in table 5 (based on data of the HUNT 2 study). We have provided evidence above that eGFR <60 ml/min/1.73 m² is not normal even in the elderly, as long as unbiased estimation formulas are used. Furthermore, the relative risk for ESRD is substantially increased (more than 10 times) in this group, although the absolute risk is still very low. The absolute risk for cardiovascular morbidity and mortality is high in this age group, and we see that a slight reduction in eGFR is associated with a strong increased risk even in the absence of microalbuminuria. The same is found for total mortality. Therefore, we conclude that eGFR in the range of 45–59 ml/min/1.73 m² should be classified as CKD.

Summary and Clinical Implications for the Handling of Elderly CKD Patients

Based on the above discussed data, the following considerations are of major importance in the diagnostic and therapeutic decision making when dealing with suspected CKD cases:

- (1) Estimation of GFR should be based on the recalibrated MDRD formula or, even better, on the CKD-EPI equation. This notion does not only hold true for the el-

Table 5. Risk for serious outcomes in elderly subjects with stage 3 CKD by presence or absence of microalbuminuria

	eGFR ≥ 60 ml/min/1.73 m ²		eGFR 45–59 ml/min/1.73 m ²		eGFR 30–44 ml/min/1.73 m ²	
	NA	MA	NA	MA	NA	MA
Prevalence	66%	15%	11%	4%	3%	1%
ESRD risk	1.0	20.0 ^c	11.4 ^c	55.0 ^c	19.5 ^c	221.4 ^c
CV mortality risk	1.0	1.1	1.2 ^b	1.5 ^c	1.6 ^c	2.2 ^c
Total mortality risk	1.0	1.1 ^a	1.1 ^a	1.3 ^c	1.4 ^c	1.7 ^c

Data are based on subjects aged ≥ 70 years from the HUNT 2 study. NA = Normoalbuminuria; MA = microalbuminuria. Hazard ratios are adjusted for age and sex. ^a $p < 0.05$, ^b $p < 0.01$, ^c $p < 0.001$.

derly, but also the young. However, eGFR still has a clinically significant inaccuracy necessitating the use of other markers of kidney damage to enable an accurate diagnosis of CKD.

- (2) Studies in healthy subjects show that there is a natural loss of GFR with increasing age, but this decrease is only minor and 95% of octogenarians have eGFR > 60 ml/min/1.73 m². An eGFR of 45–59 ml/min/1.73 m² is a significant and independent renal risk factor in elderly subjects from the general population. Therefore, even in very old subjects GFR levels below 60 ml/min/1.73 m² have to be regarded as pathological and should be defined as CKD (despite the fact that the absolute risk to progress to kidney failure is low in this subgroup).
- (3) Estimation of GFR should be complemented by measurement of urinary ACR in all subjects with an eGFR < 60 ml/min/1.73 m². For renal (but not cardiovascular) risk prediction, a dipstick test for the detection of macroalbuminuria is sufficient in those with eGFR > 60 ml/min/1.73 m². The new CKD classification that we have recently proposed is given in table 4 and is based on eGFR and urinary albumin excretion. The advantage of this classification compared to the current KDOQI classification system is a substantially improved prediction of the future ESRD risk. We also find that renal risk stratification based on the combined eGFR-ACR approach is efficient in the elderly, which is of major clinical importance since the prevalence of CKD is very high in this subgroup.
- (4) In patients recognized to be at moderate or high renal risk the search for a primary or secondary renal disease and/or underlying vascular risk factors is mandatory. The treatment of the underlying cause should follow current state-of-the-art therapies/guidelines,

irrespective of the age of the patient. Specific and un-specific therapeutic and prophylactic interventions with the aim to prevent or retard progression to ESRD are certainly poorly studied areas among the highest age groups, but diagnosing and treating CKD even in the oldest is more than justified based on the current knowledge.

Acknowledgements

The HUNT Study is a collaboration between the HUNT Research Center, Faculty of Medicine, Norwegian University of Science and Technology, the Norwegian Institute of Public Health, Nord-Trøndelag County Council, and Central Norway Regional Health Authority. The authors thank the health service and people of Nord-Trøndelag for their endurance and participation.

We also thank Prof. K. Amann, Head of the Nephropathology Department of the University of Erlangen-Nürnberg, Germany, for providing figure 1.

References

- 1 Coresh J, Selvin E, Stevens LA, et al: Prevalence of chronic kidney disease in the United States. *JAMA* 2007;298:2038–2047.
- 2 Hallan SI, Coresh J, Astor BC, et al: International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 2006;17:2275–2284.
- 3 Zhang L, Zhang P, Wang F, et al: Prevalence and factors associated with CKD: a population study from Beijing. *Am J Kidney Dis* 2008;51:373–384.
- 4 U.S. Renal Data System: USRDS Annual Data Reports (2000–2009): Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, National Institutes of Health, 2010. <http://www.usrds.org/adr.htm> (accessed March 22, 2010).

- 5 Coresh J, Stevens LA, Levey AS: Chronic kidney disease is common: what do we do next? *Nephrol Dial Transplant* 2008;23:1122–1125.
- 6 Eknayan G: Chronic kidney disease definition and classification: no need for a rush to judgment. *Kidney Int* 2009;75:1015–1018.
- 7 Glassock RJ, Winearls C: Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008;3:1563–1568.
- 8 Glassock RJ, Winearls C: CKD – fiction not fact. *Nephrol Dial Transplant* 2008;23:2695–2696.
- 9 Glassock RJ, Winearls CG: eGFR: Readjusting its rating. *Clin J Am Soc Nephrol* 2009;4: 867–869.
- 10 K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Kidney Disease Outcome Quality Initiative*. *Am J Kidney Dis* 2002;39(suppl 2):1–246.
- 11 Chadban SJ, Brigganti EM, Kerr PG, et al: Prevalence of kidney damage in Australian adults: the AusDiab kidney study. *J Am Soc Nephrol* 2003;14(7 suppl 2):S131–S138.
- 12 Clase CM, Garg AX, Kiberd BA: Prevalence of low glomerular filtration rate in nondiabetic Americans: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol* 2002;13:1338–1349.
- 13 Coresh J, Astor BC, McQuillan G, 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.
- 14 Hallan S, Astor BC, Lydersen S: Estimating glomerular filtration rate in the general population: the second Health Survey of Nord Trøndelag (HUNT II). *Nephrol Dial Transplant* 2006;21:1525–1533.
- 15 Levey AS, Stevens LA, Schmid CH, et al: A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.
- 16 Glassock RJ, Winearls C: An epidemic of chronic kidney disease: fact or fiction? *Nephrol Dial Transplant* 2008;23:1117–1121.
- 17 Glassock RJ, Winearls C: Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008;3:1563–1568.
- 18 Getz L, Kirkengen AL, Hetlevik I, Romundstad S, Sigurdsson JA: Ethical dilemmas arising from implementation of the European guidelines on cardiovascular disease prevention in clinical practice. A descriptive epidemiological study. *Scand J Prim Health Care* 2004;22:202–208.
- 19 Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM: Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. *Kidney Int* 2002;61:2165–2175.
- 20 Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG: The aging kidney. *Kidney Int* 2008;74:710–720.
- 21 Davies DF, Shock NW: Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest* 1950;29:496–507.
- 22 Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P: Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol* 2005;16: 763–773.
- 23 Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW: The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol* 1976;31:155–163.
- 24 Fliser D, Zeier M, Nowack R, Ritz E: Renal functional reserve in healthy elderly subjects. *J Am Soc Nephrol* 1993;3:1371–1377.
- 25 Wang M, Monticone RE, Lakatta EG: Arterial aging: a journey into subclinical arterial disease. *Curr Opin Nephrol Hypertens* 2010; 19:201–207.
- 26 Hermans MM, Henry R, Dekker JM, et al: Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: the Hoorn Study. *J Am Soc Nephrol* 2007;18: 1942–1952.
- 27 Peralta CA, Katz R, Madero M, et al: The differential association of kidney dysfunction with small and large arterial elasticity: the multiethnic study of atherosclerosis. *Am J Epidemiol* 2009;169:740–748.
- 28 de Jong PE, van der Velde M, Gansevoort RT, Zoccali C: Screening for chronic kidney disease: where does Europe go? *Clin J Am Soc Nephrol* 2008;3:616–623.
- 29 Yamamoto S, Kon V: Mechanisms for increased cardiovascular disease in chronic kidney dysfunction. *Curr Opin Nephrol Hypertens* 2009;18:181–188.
- 30 Moranne O, Froissart M, Rossert J, et al: Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009;20: 164–171.
- 31 Lewington S, Clarke R, Qizilbash N, et al: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913.
- 32 Harris T, Feldman JJ, Kleinman JC, Ettinger WH, Makuc DM, Schatzkin AG: The low cholesterol-mortality association in a national cohort. *J Clin Epidemiol* 1992;45:595–601.
- 33 Vischer UM, Safar ME, Safar H, et al: Cardiometabolic determinants of mortality in a geriatric population: is there a 'reverse metabolic syndrome'? *Diabetes Metab* 2009;35: 108–114.
- 34 Damsgaard EM, Frøland A, Jørgensen OD, Mogensen CE: Microalbuminuria as predictor of increased mortality in elderly people. *BMJ* 1990;300:297–300.
- 35 Perkovic V, Verdon C, Ninomiya T, et al: The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. *PLoS Med* 2008;5:e207.
- 36 Astor BC, Hallan SI, Miller ER III, Yeung E, Coresh J: Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol* 2008;167:1226–1234.
- 37 de Boer IH, Katz R, Cao JJ, et al: Cystatin C, albuminuria, and mortality among older adults with diabetes. *Diabetes Care* 2009;32: 1833–1838.
- 38 Farbom P, Wahlstrand B, Almgren P, et al: Interaction between renal function and microalbuminuria for cardiovascular risk in hypertension: the nordic diltiazem study. *Hypertension* 2008;52:115–122.
- 39 Hallan S, Astor B, Romundstad S, Aasarød 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.
- 40 Ninomiya T, Perkovic V, de Galan BE, et al: Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009; 20:1813–1821.
- 41 Vlek AL, van der Graaf Y, Spiering W, Algra A, Visseren FL, SMART Study Group: Cardiovascular events and all-cause mortality by albuminuria and decreased glomerular filtration rate in patients with vascular disease. *J Intern Med* 2008;264:351–360.
- 42 Mancia G, De Backer G, Dominiczak A, et al: 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105–1187.
- 43 Taal MW, Brenner BM: Predicting initiation and progression of chronic kidney disease: developing renal risk scores. *Kidney Int* 2006;70:1694–1705.
- 44 Hallan SI, Dahl K, Oien CM, et al: Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ* 2006;333:1047.
- 45 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.
- 46 Ikizler TA: CKD classification: time to move beyond KDOQI. *J Am Soc Nephrol* 2009;20: 929–930.
- 47 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.

- 48 Ishani A, Grandits GA, Grimm RH, 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.
- 49 Keane WF, Zhang Z, Lyle PA, et al: Risk scores for predicting outcomes in patients with type 2 diabetes and nephropathy: the RENAAL Study. *Clin J Am Soc Nephrol* 2006;1:761–767.
- 50 Lea J, Greene T, Hebert L, et al: The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. *Arch Intern Med* 2005;165:947–953.
- 51 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.
- 52 Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P: Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. *Am J Epidemiol* 2004;159:882–890.
- 53 Roderick PJ, Atkins RJ, Smeeth L, 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.
- 54 Kagiya S, Matsumura K, Ansai T, et al: Chronic kidney disease increases cardiovascular mortality in 80-year-old subjects in Japan. *Hypertens Res* 2008;31:2053–2058.
- 55 Rifkin DE, Katz R, Chonchol M, et al: Albuminuria, impaired kidney function and cardiovascular outcomes or mortality in the elderly. *Nephrol Dial Transplant* 2010;25:1560–1567.
- 56 Hwang SJ, Lin MY, Chen HC, et al: Increased risk of mortality in the elderly population with late-stage chronic kidney disease: a cohort study in Taiwan. *Nephrol Dial Transplant* 2008;23:3192–3198.

Editorial Comment

M. El Nahas, Sheffield

The minireview by Hallan and Orth is timely as it discusses the controversial issue of CKD definition and prognosis in the elderly. Most CKD surveys reporting a significant prevalence (~10%) of CKD within the population merely reflect the fact that a large percentage (40–60%) of elderly individuals have decreased GFR. I recently argued that such a decrease in age-related kidney function, which is not universal, may be a manifestation of diffuse vascular damage, with the kidney being one of many end organs affected; I called it cardio-kidney damage [1]. Hallan and Orth suggest that in order to identify elderly individuals at increased risk of ESRD or death, the KDOQI CKD classification should be revised by subdividing CKD stage 3 into CKD3a and CKD3b and qualifying the severity of proteinuria. This goes along with the recommendations made by the UK National Institute for Health and Clinical Excellence (NICE) for the revised CKD classification issued in 2008 (<http://www.nice.org.uk/Guidance/CG73>). They also support the recommendations made by the KDIGO Consensus Conference held in London in 2009. These recommendations are supported by recently published data from the Chronic Kidney Disease Prognosis Consortium showing an association

between decreased GFR and raised albuminuria with increased mortality in the general population [2]. Clearly, a growing body of data is suggesting that elderly individuals with underlying, overt or covert, cardiovascular pathology have microalbuminuria (a sign of atherosclerosis and endothelial dysfunction) and a reduced GFR (a sign of renal underperfusion and ischemia). It is therefore not too surprising that these markers of CVD predict mortality. Whether they add much to current CVD risk stratification and scoring is debatable, but there is no doubt that the recommendations of Hallan and Orth, UK NICE and KDIGO will help nephrologists to identify elderly patients at higher risk and direct healthcare resources to address their underlying risk factors: most likely progressive cardiovascular in nature.

References

- 1 El Nahas M: Cardio-kidney-damage: a unifying concept. *Kidney Int* 2010;78:14–18.
- 2 Chronic Kidney Disease Prognosis Consortium: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;375:2073–2081.