

The Case for Using Albuminuria in Staging Chronic Kidney Disease

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The publication of the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for the evaluation, classification, and stratification of chronic kidney disease (CKD) in 2002¹ has greatly raised awareness of CKD and stimulated epidemiologic research investigating the consequences of CKD. Its publication and distribution were also followed by critical commentaries. The authors of these commentaries questioned whether it is correct to claim someone has chronic disease without having firm evidence that that chronic disease will lead to a worse prognosis.^{2,3} They suggested that the CKD staging system be changed—one change among others—by not paying attention to stages 1 and 2 CKD, which are characterized by early signs of renal damage (albuminuria, erythrocyturia, or abnormalities on ultrasonography) and normal or near-normal estimated GFR (eGFR). Critical authors argued that this modification would make the staging system more simple and useful.^{2,3} In this commentary, we suggest that the discounting of stages 1 and 2 CKD is not justified on the basis of recent evidence from various epidemiologic studies and indicate further that there is need to examine more carefully the clinical prognosis of individuals with stage 3 CKD.

RISK FOR ESRD ACCORDING TO CKD STAGES

The main value of a CKD classification system is in providing insight regarding risk for developing ESRD. That renal function often declines gradually makes it more likely that a patient who ends with ESRD will have previously gone through the five levels of severity of CKD; that is, from a normal GFR of >90 ml/min down to a GFR of <15 ml/min. It is unreasonable to assume, however, that all patients with the earlier stages of CKD will likely progress to ESRD. Stages 1 through 3 CKD are present in $\geq 10\%$ of the population,^{4–6} whereas each year going forward fewer than one of the 1000 of those patients will arrive at ESRD. It is also expected that the risk that a patient with stage 1 or 2 CKD would reach ESRD in epidemiologic studies is lower than that for a patient with stage 3 or 4 CKD,

because it requires more time before the lowest patients will have lost all of their residual renal function. It is unclear, however, which signs of kidney damage, expressed as albuminuria (required for stage 1 or 2 but not for stage 3 or 4) or the severity of the loss of filtration capacity (expressed as estimated eGFR) best predicts whether a patient will reach ESRD.

The incidence of ESRD increases with worsening from baseline eGFR (Figure 1). The incidence of ESRD, however, is approximately 100-fold higher when a patient with a given eGFR has dipstick proteinuria compared with patients with similar eGFR but without dipstick proteinuria. In fact, a patient with stage 1 or 2 CKD and with dipstick proteinuria but nearly normal eGFR has a greater risk for reaching ESRD than a patient with stage 3 or even 4 CKD and without a positive dipstick test.⁷ These findings were recently confirmed by data from the Multiple Risk Factor Intervention Trial (MRFIT). Whereas the risk for reaching ESRD for a patient with stage 3 CKD and without dipstick-positive proteinuria was increased only 2.4-fold compared with the population without CKD, it was increased 33-fold for a patient with stage 3 CKD and with a positive dipstick test.⁸ When interpreting these data, it should be realized that only 25% of patients with stage 3 CKD had micro- or macroalbuminuria.^{9,10} Of note, the risk for reaching ESRD was increased 12-fold for a patient with stage 1 or 2 CKD, again a higher risk than for the patient with stage 3 and without a positive dipstick test.⁸ The epidemiologic studies on this topic either used a dipstick test for proteinuria or quantitatively measured albuminuria. It is important to realize that there is not so much difference between these two, because most patients with a 1+ or 2+ dipstick test have micro- instead of

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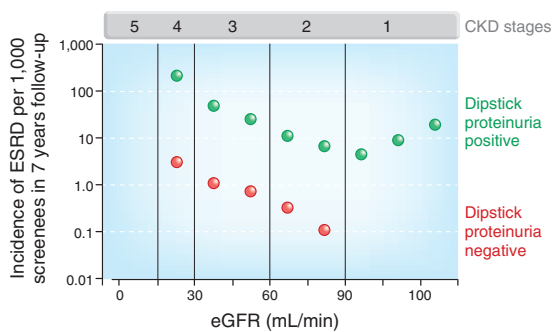


Figure 1. Incidence of new cases of ESRD according to the severity of GFR impairment and the presence or absence of a dipstick proteinuria test in a 17-yr follow-up of a cohort of 95,252 patients. Dipstick positivity is defined as $\geq 1+$ proteinuria. Adapted from reference⁷.

macroalbuminuria, whereas patients with 3+ proteinuria mostly have microalbuminuria.¹¹

RISK FOR A MORE NEGATIVE SLOPE OF EGFR OVER TIME ACCORDING TO CKD STAGE

The benefits of a staging system should not be limited just to predicting who will finally reach ESRD but should also detect patients who are at risk for accelerated decline in renal function which is associated with morbidity and mortality. For such patients, treatment could be started early to prevent progression of disease (Figure 2). Epidemiologic studies investigating risk factors for accelerated loss of renal function are scarce. To that purpose, one needs studies with sequential follow-up to calculate change in eGFR over time. The more data points of eGFR available and the longer the follow-up, the more reliable the calculated changing slope of eGFR will be. To acquire such data, patients participating in the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, a Dutch population prospective cohort study with sequential follow-up, are screened every 3 to 4 yr. With now three data points available over a period of 6.2 yr, slope calculations are possible.

The data on 6879 patients showed eGFR decline is on average 0.45 ± 1.60 ml/min per 1.73 m²/yr. Adjusted for age and gender, the decline is increased stepwise for each increment in urinary albumin excretion.¹² In each CKD stage, eGFR slopes are always worse in those with albuminuria compared with those without.¹³ The data on slopes in this cohort also allow one to determine the risk factors associated with more progressive loss of eGFR. For example, high BP and plasma glucose are independent predictors of declining renal function in both genders. In men and women, albuminuria also predicted decline in renal function.¹⁴

Of course, even if we are able to identify patients with accelerated loss of renal function in an early phase, it is not yet proved whether the beneficial effect of renoprotective treatment works similarly as when such treatment is started in a later phase (Figure 2); however, assuming this indeed is true,

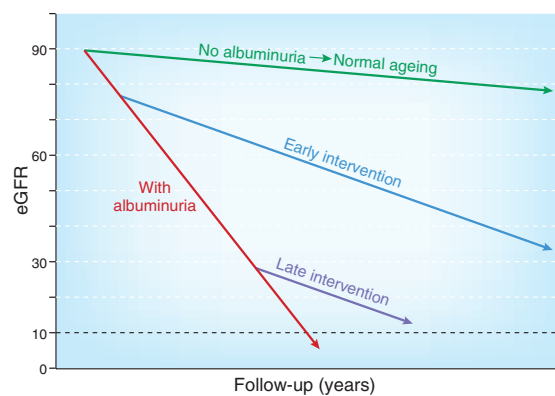


Figure 2. Schematic presentation of the decline in GFR over years in a patient with albuminuria and in a patient with normal urinary albumin excretion. Indicated is the (proven) change in slope when intervention to lower albuminuria is started in a late phase and the (expected) change in slope in case intervention is started early.

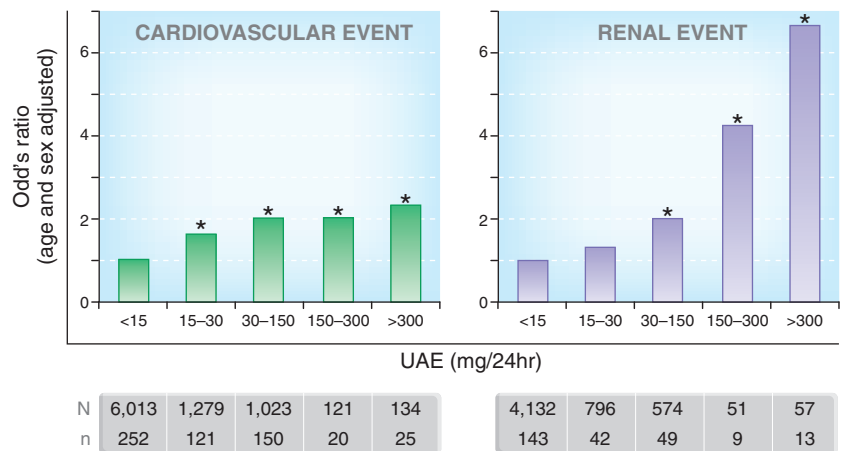
dialysis can be delayed for many more years. Evidence for a beneficial effect of early intervention is sparse. There are data, however, that starting early renoprotective treatment for type 2 diabetes is as effective in retarding progression of microalbuminuria to overt diabetic nephropathy¹⁵ as the start of such treatment in overt diabetic nephropathy to delay progression to ESRD.¹⁶ From these early and late intervention trials, the early start is even more cost-effective than the late start of renoprotective treatment.¹⁷

RISK FOR CARDIOVASCULAR EVENTS ACCORDING TO STAGES OF CKD

There is evidence that both a higher albuminuria¹⁸ and a lower eGFR¹⁹ are independent of classical cardiovascular risk factors associated with occurrence of cardiovascular events. The question however, is, how reliable these two variables predict cardiovascular events and how they are interrelated, if at all. Recent data from a study of patients after myocardial infarction,²⁰ as well as from two population studies,^{13,21} showed that age- and gender-adjusted hazard ratios for cardiovascular events were not statistically elevated in patients with stage 3 CKD and without albuminuria, whereas they were clearly elevated in patients stage 3 CKD and with albuminuria. It should be stated that some studies did describe a significantly increased cardiovascular risk in patients with stage 3 CKD and without albuminuria^{22,23}; however, this risk was limited to patients with more severely impaired eGFR between 30 and 45 ml/min per 1.73 m². Importantly and similarly as has been described for the risk for developing ESRD, the risk for developing a cardiovascular event in all of these studies was significantly elevated in stages 1 and 2 CKD when compared with patients with no CKD.

Apart from giving evidence of an association between albuminuria and cardiovascular events, it is also important to have

Figure 3. Age- and gender-adjusted risk to develop a cardiovascular event (defined as a fatal or nonfatal myocardial infarction or cerebrovascular accident) and to develop a renal event (defined as an eGFR slope of more than three times the mean of the normal gender-stratified population) in the PREVEND cohort that had at least three eGFR measurements available during 7 yr of follow-up. * $P < 0.05$ versus patients with a urinary albumin excretion <15 mg/d. N = the number of patients with follow-up data available; n = the number of patients with an event.



evidence that lowering albuminuria is associated with a better cardiovascular prognosis. There are indeed data that both in patients with macroalbuminuria²⁴ and patients with microalbuminuria,²⁵ angiotensin-converting enzyme inhibition results in a lowering of albuminuria and a better cardiovascular prognosis. Moreover, the beneficial effect of BP lowering on cardiovascular events is especially due to the effects of that treatment in patients with hypertension and with microalbuminuria.²⁶

The parallel between the impact of albuminuria for cardiovascular and renal risk prediction is thus remarkable. It was always suggested that macroalbuminuria is evidence of a diseased glomerulus, whereas microalbuminuria was a sign of vascular damage and not always considered an enduring renal phenomenon. It therefore was always expected that macroalbuminuria would predict ESRD, whereas microalbuminuria would predict cardiovascular events. Today, macroalbuminuria is also associated with cardiovascular events,^{27,28} and microalbuminuria also predicts ESRD and progressive decline in renal function, both in patients with diabetes^{29,30} and patients with hypertension³¹ and in the general population.^{12–14} Figure 3 compares the association of albuminuria with both cardiovascular and renal events. This figure demonstrates that the association between increasing albuminuria and renal events is at least as steep as the association between albuminuria and cardiovascular events.

CONCLUSIONS

We suggest that if we want to modify the CKD classification system, then we should do so to improve its prognostic value. We should not emphasize so much the risk of stage 3 CKD without albuminuria, especially in patients with an eGFR of 45 to 60 ml/min per 1.73 m². These patients in general are not at increased renal and cardiovascular risk. Conversely, we ought to give more attention to patients with albuminuria, even when their eGFR is not impaired yet. There seems a benefit to starting cardio- and renoprotective treatments with agents interfering in the renin-angiotensin system in those patients. The gain is not only potential prevention of ESRD, but also prevention

of accelerated loss of renal function and new cardiovascular events.

DISCLOSURES

None.

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