

Higher Incidence of ESRD than Mortality in the AASK Study

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An estimated 15.5 million individuals in the United States have stage 3 chronic kidney disease (CKD).¹ In contrast, the number of individuals with ESRD approximates 525,000.² This suggests that most people with stage 3 CKD will die before reaching the need for renal replacement therapy. This is what most observational studies have found.³⁻⁷ In an analysis of Kaiser data, Go *et al.*³ found an increasing risk for mortality and cardiovascular disease with lower levels of estimated GFR (eGFR). In those with an eGFR <60 ml/min per 1.73 m², there were 25,621 deaths during follow-up, in contrast to 3171 individuals who began dialysis. In the Medicare population, the rate of death in individuals with CKD but without diabetes is >10 times greater than the risk for ESRD.

In this issue of *JASN*, Alves *et al.*⁸ evaluate the incidence of ESRD *versus* all-cause and cardiovascular mortality before ESRD in the African American Study of Kidney Disease and Hypertension (AASK). Their study combined the trial period and then a noninterventional cohort period for a total of 11 years of follow-up. In this study, the rate of ESRD was 1.8 times greater than mortality. Does this reflect a higher risk for ESRD or a lower risk for mortality in this population compared with other study populations? There are reasons to think both explanations may be involved.

As discussed by the authors, the findings could relate to higher risk for progression to ESRD in black individuals.⁹ The higher risk for ESRD in black individuals is a consistent finding, although the relative relationship of death to ESRD has varied. Choi *et al.*,¹⁰ in an analysis of veterans, found the risk for ESRD was higher in black individuals at all levels of eGFR. The difference in risk was most marked at higher levels of eGFR; however, except for individuals with an eGFR <30 ml/min per 1.73 m², the risk for death was higher than the risk for ESRD for both black and white individuals. In the

Medicare population, the risk for ESRD was higher in black compared with white individuals, but the risk for death was also higher,¹¹ a finding also supported by studying younger black adults in the Third National Health and Nutrition Examination Survey (NHANES III) data set.¹² The authors cite the study by Derose *et al.*¹³ as consistent with their findings of higher rates of ESRD in comparison with total mortality. Looking at the raw data, however, the cumulative incident of death from study entry was greater than ESRD in black individuals in those with an eGFR \geq 30 ml/min per 1.73 m². With longer survival, the risk for ESRD became greater than death, although this could reflect survival bias. What is notable is that the ratio of death/ESRD was smaller in black compared with white individuals (2.7 *versus* 7.3, respectively), so although the higher risk for progression may be one contributor to the findings seen, the findings may be more reflective of a high risk for ESRD in the setting of a lower-than-usual risk for mortality (2.2/100 patient-years).

AASK was a randomized, controlled study. Individuals who participate in research studies are often different from those who do not.^{14,15} This is due to exclusion criteria that eliminate a subset of individuals, as well as differences in those who agree to participate compared with those who do not. In AASK, it is possible these individuals were healthier and at lower risk for mortality than the general population of those with CKD. This hypothesis is consistent with the long-term follow-up of the Modification of Diet in Renal Disease study. In this randomized study, the risk for ESRD was also higher than the risk for mortality before dialysis.¹⁶ The mean age at the start of the study was approximately 55 years, which is younger than the age in previous studies. The majority of individuals with CKD are older¹; however, the risk for dying before ESRD increases with older age.^{4,11} This was also seen in this study, in which those who were older than 55 years were one of the few groups who had a higher rate for death before dialysis. Thus, the findings may reflect the earlier risk for progression to ESRD in younger black individuals.

There are some other notable findings. Although the risk for ESRD more than death was true for most subgroups in the study, individuals who had a low level of proteinuria (protein/creatinine ratio \leq 0.22) and higher baseline eGFR (>40 ml/min per 1.73 m²) also had higher mortality than ESRD rates. In those with proteinuria, the mortality rate was slightly higher (2.7 *versus* 2.0 patient-years), but the progression to ESRD was more than five times higher (10.5 *versus* 1.8/100 patient-years). This highlights the importance of proteinuria as a risk factor for progression to ESRD.¹⁷ Because angiotensin-converting enzyme inhibitors were shown in AASK to be more beneficial in individuals with proteinuria,¹⁸ the findings indicate a potential target group and therapy.

In summary, the literature suggests that the risk for death

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before dialysis is not uniform. Whether this should have an impact on clinical care is not yet clear. Although it could affect the focus on preparing for dialysis or transplantation evaluation, we would need to improve our risk prediction on an individual level before this could be initiated. Perhaps we could institute therapies to generate the low mortality rate seen in AASK. The authors propose tight BP control as one possible explanation for their finding, although they were not adequately powered to assess the effect of BP control on cardiovascular mortality. The upcoming Systolic Blood Pressure Intervention Trial (SPRINT) will also help clarify which groups benefit from tight BP control with regard to mortality and ESRD.

DISCLOSURES

None.

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See related article, "Rate of ESRD Exceeds Mortality among African Americans with Hypertensive Nephrosclerosis," on pages ●●●●–●●●●.