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Not All Deaths in CKD Are from a Broken Heart

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CKD is common, but outcomes remain poor, with a high incidence of death as eGFR declines.1 Two studies published in this issue of JASN examine the association between reduced kidney function and specific causes of death.2,3 Navaneethan et al.2 used electronic health records and a linked mortality registry from the state of Ohio in the United States to study adults with two eGFR values <60 ml/min per 1.73 m². Thompson et al.3 used administrative health care data and linked laboratory information from the province of Alberta in Canada to study all adult deaths stratified by recent eGFR and urine protein results. Reliably ascertaining an individual’s cause of death is notoriously difficult, even in prospective cohort studies with central adjudication. In both of these retrospective analyses, administrative personnel recorded the cause of death in routine care using the International Classification of Diseases 10th Revision system. With this method of ascertainment, we expect that many deaths were classified incorrectly. Reasons for misclassification include scenarios with multiple causes of death, ill-defined causes of death, and a lack of autopsy data. Nonetheless, these studies by Navaneethan et al.2 and Thompson et al.3 provide several important messages for our consideration.

Both studies confirm that a greater proportion of deaths is attributable to cardiovascular diseases as eGFR declines. Some would say this association between low eGFR and a higher risk of death “from a broken heart” is already well appreciated by the nephrology community.4 As might be expected, in the Alberta study, after adjustment for age and sex, 33% of deaths were attributed to cardiovascular disease when the eGFR was 45–59 ml/min per 1.73 m², and 40% of deaths were attributed to cardiovascular disease when the eGFR was 15–29 ml/min per 1.73 m².3 Similarly, in the Ohio study, the 3-year probability of mortality from cardiovascular disease increased in a graded manner as eGFR declined (from approximately 3% when the eGFR was 60 ml/min per 1.73 m² to 7.5% when the eGFR was 10 ml/min per 1.73 m²).2 The Alberta study provides new insights into the nature of these cardiovascular deaths. As eGFR declined, a greater proportion of people died from cardiac failure and valvular disease rather than ischemic heart disease. This finding is consistent with prior data of chronic fluid overload coupled with anemia and chronic hypertension producing a high cardiac output state, leading to mechanical trauma.5 Valvular calcification is also prominent in CKD, where it is attributed to chronic inflammation and impairments of calcium phosphate metabolism.6

There are other prominent causes of death in CKD beyond a broken heart. In the Alberta study, infection accounted for 3% of deaths in those with an eGFR of 45–59 ml/min per 1.73 m² and 5% of deaths in those with an eGFR of 15–29 ml/min per 1.73 m². A similar graded relationship between CKD stage and severe infection requiring hospitalization was also observed in a recent meta-analysis.7 Better infection control may prevent some of these deaths. For example, in the study by Navaneethan et al.,2 approximately 10% of all CKD deaths were attributed to diabetic-related infections. Perhaps better diabetic foot care will prevent some deaths.

In the Ohio study, the 3-year probability of mortality from cancer was approximately 2.5%, and this percentage remained unchanged through all stages of eGFR. Similar findings were observed in the Alberta cohort. Large population-based cohort studies suggest a graded association between reduced eGFR and cancer risk.8,9 However, the direction and the causality of this association require clarification. Although in the Ohio study, approximately 20% of those with CKD had cancer, it is unclear whether these cancers developed before or after the onset of CKD. Cancers, such as multiple myeloma and lymphoma, are established risk factors for CKD, whereas 1 in 10 patients has CKD in the setting of solid-organ malignancies.10 In other analyses restricted to those with cancer, CKD was associated with at least a 2-fold higher risk of death from cancer.11

Where do we go from here? These two studies shed new light on the association between reduced eGFR and cause of death.2,3 While we continue to search for therapies to prevent cardiovascular deaths in CKD, we also need to focus on strategies to prevent nonvascular deaths from infection and cancer. For example, the benefit of screening to reduce cancer-related deaths in CKD remains largely unknown.12 These studies serve as a call to bridge the gap between
pathogenic understanding, experimental data, clinical testing, and high-quality care. We urgently need proven strategies to prevent deaths in CKD. Sadly, the results of intervention trials in CKD (for example, of antiplatelet and lipid-lowering therapies to prevent major cardiovascular events) have been disappointing or modest at best.\textsuperscript{13,14} Let us stop the heart break by working together on large-scale, practice-changing research. Finally, not all deaths should be prevented at the expense of quality of life, and we need to listen carefully to our patients and their families to ensure that we provide care according to their values and preferences.

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**DISCLOSURES**

None.

**REFERENCES**