The Natural History of Chronic Kidney Disease Revisited—A 72-Month Mayo Health System Hypertension Clinic Practice-Based Research Network Prospective Report on End-Stage Renal Disease and Death Rates in 100 High-Risk Chronic Kidney Disease Patients: A Call for Circumspection

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The natural history of chronic kidney disease (CKD), in general, remains conjectural. Current literature on rates of progression to end-stage renal disease (ESRD) as compared with mortality in CKD shows conflicts. A study of 27,998 patients in managed care reported a 5-year ESRD rate of 20% and a death rate of 50%. In 1666 patients in the Modification of Diet in Renal Disease study, a much higher ESRD rate of 60% after 88 months was reported (four times the death rate); among patients older than 65 years, the death rate approximated the ESRD rate. More than 20 million Americans have CKD [estimated glomerular filtration rate (eGFR) < 60 mL/min). Annually, approximately 100,000 new U.S. patients develop ESRD, accounting for a casual annual ESRD rate of only 0.5% among the U.S. CKD population. Similarly, this author's anecdotal experience suggests a more benign CKD outcome than is suggested by the two foregoing studies. A 72-month prospective report of an aging cohort of 100 CKD patients, high risk because they all experienced acute kidney injury at study entry, is presented. The finding of an approximately 18% ESRD rate and 13% death rate after 4 years contrasts sharply with the two studies cited earlier. Several factors—prospective as compared with retrospective analysis, varying patient age and other variables, managed care as compared with other care, and other unknown variables—play important roles in CKD outcome. This author agrees with researchers who recently emphasized the heterogeneity of the CKD population. Patient prognosis and management must be individualized.

Introduction

A March 2007 report from the U.S. Centers for Disease Control and Prevention indicated that 16.5% of the U.S. population 20 years of age and older had chronic kidney disease (CKD), meaning an estimated glomerular filtration rate (eGFR) below 60 mL/min, according

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to the 1999–2004 National Health and Nutrition Examination Survey (1). This percentage represents more than 20 million Americans. On the other hand, approximately one third of a million Americans currently have end-stage renal disease (ESRD) requiring some form of renal replacement therapy, with about 100,000 new ESRD entrants reported annually (2).

The natural history of CKD in the general population is unclear, because the reports in the literature have been highly conflicting (3,4). In 2004, from among 27,998 CKD participants drawn from a database in a managed care organization (51% stage II CKD, 6% stage III CKD, 40% stage IV CKD, and 3% stage V CKD; mean age 62 years), Keith *et al.* reported a cumulative 5-year ESRD rate of 20% and a death rate of 50% (3). Conversely, in 2008, from among 1666 nondiabetic CKD patients in the Modification of Diet in Renal Disease (MDRD) cohort (15% stage II CKD, 46% stage III CKD, 28% stage IV CKD, and 9% stage V CKD; mean age 50 years), Menon *et al.* demonstrated a much higher ESRD rate of 60% after 88 months, a figure four times the death rate (4). In this MDRD cohort, only among subjects older than 65 years did the rate for death approximate that for ESRD (4). Assuming that all ESRD in the United States derived solely from a base CKD population of more than 20 million, a U.S. annual ESRD incidence of 100,000 gives a rough annual incident ESRD rate of only 0.5%, a ratio that flies in the face of the statistics provided by Keith *et al.* and Menon *et al.* in their respective publications (1–4).

Cognizant of these facts, and recognizing my own anecdotal experience of better renal and patient outcomes in CKD patients in general as compared with suggestions from current literature, the present article reports ESRD and mortality data from a prospective analysis of 100 high-risk CKD patients followed in the Mayo Health System's hypertension clinic since September 2002. This cohort has been variously reported in previous publications (5,6).

Patients and methods

Over a 30-month recruiting period between September 2002 and March 2005, in a northwestern Wisconsin hypertension clinic practice, this study prospectively enrolled 100 Caucasian CKD patients who were exhibiting a 25% or greater increase in baseline serum creatinine and who were concurrently using an angiotensin converting-enzyme inhibitor or an angiotensin II receptor blocker, or both (5,6). Blockade of the renin–angiotensin–aldosterone system (RAAS) was discontinued, and otherwise standard nephrology care was followed. Prospective monitoring of serum creatinine, eGFR by the MDRD equation, and urinary albumin-to-creatinine ratio (5,6) continued. A robust network of interconnected electronic medical record (EMR) systems in the various clinics within the Luther Midelfort site of the Mayo Health System Practice-Based Research Network (PBRN) allowed for monitoring and tracking of individual patient outcomes—including such events as hospitalizations, surgical procedures, ESRD, and death—in very great detail and almost in real time. In August 2008, a 72-month analysis of this cohort, with a mean follow-up of 4 years, was completed.

Results

The 100 patients enrolled over the 30-month period included 52 men and 48 women. Mean age at enrollment was 71.5 years (range: 25 – 92 years), with 75% being 65 years and older; 63%, 70 years and older; and 23%, more than 80 years (5). Mean serum creatinine at enrollment was 3.2 ± 2.1 mg/dL (range: 1.2 – 18.7 mg/dL; $p = 0.0000001$). Mean enrollment eGFR was 22.1 ± 8.8 mL/min per 1.73 m^2 body surface area (BSA) ($p < 0.001$). At study entry, CKD staging by eGFR would show that 24% were at stage III, 56% at stage IV, and 15% at stage V. Generally, as described elsewhere, eGFR improved after RAAS blockade was discontinued (5,6).

Overall, after 4 years of follow-up, 18 (18%) developed ESRD, of whom 8 died, 2 received kidney grafts, 6 continue on hemodialysis, and 2 were lost to follow-up. Most of the ESRD occurred earlier during follow-up. In the last 24 months, only 2 patients newly reached ESRD, and in both circumstances, ESRD developed following cardiothoracic thoracotomy operations. Age did not predict ESRD. Of the 13 (13%) deaths that occurred, 8 involved ESRD patients, with 5 of those either refusing or stopping hemodialysis before death. The remaining 5 deaths occurred in patients with stable and improved eGFR (24 – 47 mL/min per 1.73 m^2 BSA) from non-renal causes including septicemia and cancer. One death occurred after a motor vehicle accident. Reduced left ventricular ejection fraction (LVEF: 30% – 40% or lower) predicted death among ESRD patients. Excluding ESRD, deaths, and loss to follow-up, and

also excluding 2 subjects with incomplete data sets, the final eGFR in 70 patients was 38 mL/min per 1.73 m^2 BSA (range: 7 – 90 mL/min) after 43 months (range: 4 – 69 months). In 35 of those 70 patients (50%), improvement by at least one CKD stage was demonstrated after 45 months (range: 4 – 69 months), and in another 28 patients (40%), CKD stage remained the same after 40 months (range: 5 – 63 months), including 16 patients who remained at stage IV. Of these 70 patients, 7 (10%) showed progression of CKD stage after 43 months (range: 16 – 63 months).

Discussion and conclusions

This article describes death and ESRD outcomes over a mean follow-up of 4 years, in a high-risk elderly cohort of 100 CKD patients. The high risk is a result of advanced age and presentation with significant acute kidney injury (AKI) at enrollment into the study. In 2009, Ishani *et al.* studied a Medicare beneficiary database of 233,803 patients 67 years of age or older after hospital discharge and demonstrated that AKI in elderly patients with CKD portend increased risk of ESRD (7). The 4-year ESRD rate of only 18% and death rate of only 13% reported here contrast very sharply with the results reported by Keith *et al.* and Menon *et al.* (3,4), despite a significantly greater age than that seen in both of those cohorts and a clearly higher risk of development of ESRD, because, at enrollment, all were experiencing AKI (5–7).

Given the prospective nature of the present study and a robust network of interconnected EMR systems in the PBRN, it was possible to follow nearly every event experienced by the cohort members in real time. In their retrospective report, Keith *et al.* clearly showed that the rate of renal replacement therapy over a 5-year observation period increased with increasing CKD stage: 1.1%, 1.3%, and 19.9% for CKD stages II, III, and IV respectively (3). Similarly, those authors revealed increased 5-year mortality rates for increasing CKD stage: 19.5%, 24.3%, and 45.7% for stages II, III, and IV respectively (3). Of interest, very significant age differences were observed for the patients reported by Keith *et al.,* because patient age also increased with CKD staging (3). That finding is not necessarily applicable to all CKD populations. Furthermore, the contribution of selection biases—with respect to whether study patients are in primary care compared with tertiary care, managed care compared with others, age,

prospective compared with retrospective study, sex, anemia level, proteinuria level, presence of diabetes mellitus or other medical comorbidities, exposure to potential nephrotoxins, and so on—remain unknown and only conjectural at this point.

In an attempt to establish an algorithm to predict CKD progression, Kshirsagar *et al.* recently used a combined cohort ($n = 14,155$) of two community-based studies, the Atherosclerosis Risk in Communities Study and the cardiovascular Health Study, to complete an assessment of the contribution of various concurrent risk factors (8). Despite efforts at developing such algorithms, the fact that no exact understanding has been reached concerning the factors and mechanisms that determine these outcomes raises significant doubts as to the usefulness of the algorithms. Also, the presence and effects of confounding variables, some of which remain unknown, further aggravate these concerns. Notably, in 2008, several reports from the Midelfort clinic, Mayo Health System, Eau Claire, Wisconsin, established the occurrence of significant renal failure, including acute renal failure and ESRD in older CKD patients, associated with RAAS blockade (5,6,9–11). It is acknowledged, however, that the contribution of late-onset renal failure from angiotensin blockade and its variants to ESRD progression in CKD patients remains to be confirmed by larger multicentric controlled studies (5,6,9–11).

Finally, a recent commentary by Bansal and Hsu reiterated the fact that the disparate ESRD and mortality rates in various CKD populations as reported by various studies in the literature only emphasize the heterogeneity of CKD populations (12). The same authors had concluded that nephrologists should not rely on CKD staging alone to direct management or risk stratification for CKD patients, and that nephrologists must consider several factors for CKD prognostication, with a need to *individualize* CKD management (12). This author cannot agree more with that analysis. I had, in the past, called attention to the misgivings and pitfalls of the "one size fits all" approach to CKD management in general and to diabetic nephropathy in particular (13). Further research is clearly needed in these areas, because several questions remain unanswered.

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