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Clinical Nephrology 2018: Chronic Kidney Disease and Mortality Risk: A Systematic Review

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Current guidelines identify people with chronic kidney disease (CKD) as being at high risk for cardiovascular and all-cause mortality. Because as many as 19 million Americans may have CKD, a comprehensive summary of this risk would be potentially useful for planning public health policy. A systematic review of the association between non–dialysis-dependent CKD and the risk for all-cause and cardiovascular mortality was conducted. Patient- and study-related characteristics that influenced the magnitude of these associations also were investigated. MEDLINE and EMBASE databases were searched, and reference lists through December 2004 were consulted. Authors of 10 primary studies provided additional data. Cohort studies or cohort analyses of randomized, controlled trials that compared mortality between those with and without chronically reduced kidney function were included. Studies were excluded from review when participants were followed for <1 yr or had ESRD. Two reviewers independently extracted data on study setting, quality, participant and renal function characteristics, and outcomes. Thirty-nine studies that followed a total of 1,371,990 participants were reviewed. The unadjusted relative risk for mortality in participants with reduced kidney function compared with those without ranged from 0.94 to 5.0 and was significantly more than 1.0 in 93% of cohorts. Among the 16 studies that provided suitable data, the absolute risk for death increased exponentially with decreasing renal function. Fourteen cohorts described the risk for mortality from reduced kidney function, after adjustment for other established risk factors. Although adjusted relative hazards were consistently lower than unadjusted relative risks (median reduction 17%), they remained significantly more than 1.0 in 71% of cohorts. This review supports current guidelines that identify individuals with CKD as being at high risk for cardiovascular mortality. Determining which interventions best offset this risk remains a health priority.

It has been known for many years that ESRD is associated with very high mortality and accelerated cardiovascular disease (1). Several recent studies suggest that the risk for death is increased independently in individuals who have less severe impairment of kidney function and are not dialysis dependent, compared with those who have preserved kidney function (2,3). However, other rigorously conducted studies have found little or no significant increase in all-cause or cardiovascular mortality in the setting of mild to moderate chronic kidney disease (CKD) (4,5). Even among studies that have demonstrated higher mortality rates in people with CKD, the magnitude of the increased risk has varied substantially for reasons that are unclear.

Current guidelines identify individuals with CKD as being at high risk for cardiovascular disease and other adverse outcomes (6). Because non–dialysis-dependent CKD may affect as many as 19 million Americans (7), a summary of the risk for all-cause and cardiovascular mortality associated with this condition potentially would be useful to decision-makers and researchers. In addition, identification of factors that modify the strength of the relation between CKD and adverse outcomes may help to improve the current understanding of how impaired kidney function leads to higher risk.

Despite considerable interest in this topic, previous summaries of the available evidence have been presented predominantly as narrative reviews, which have widely known limitations (8,9). Therefore, we conducted a systematic review to evaluate the association between non–dialysis-dependent CKD and

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the risk for all-cause and cardiovascular mortality. We also sought to determine patient- and study-related characteristics that influenced the magnitude of these associations.

Materials and Methods

Search Strategy

Two reviewers searched Medline (1969 to 2004) and EMBASE (1988 to 2004) and the reference lists of primary studies, review articles, and clinical practice guidelines independently and in duplicate. The search strategies were created with the assistance of a research librarian and were not restricted to the English language (Appendixes A and B). Any study that was deemed potentially relevant by one or more reviewers was retrieved for inspection.

Study Selection: The search strategy and data extraction were defined by a prospective protocol. Studies were eligible for inclusion when they studied adults and contained data that permitted comparison of long-term (>1 yr) cardiovascular mortality or all-cause mortality between those with and without kidney disease (defined by abnormal GFR, creatinine clearance [CrCl], or serum creatinine [SCr] levels). Studies were excluded when they were published in abstract only, included data from patients with acute renal failure (or included people who were at high risk for acute renal failure, e.g., those with acute myocardial infarction), or included patients who had ESRD and were on dialysis or received a renal transplant. Finally, meta-analyses, case-control studies, studies with <100 subjects, studies without a contemporaneous control group drawn from the same population, and studies that did not report the outcomes of interest were excluded.

Conclusion: Non–dialysis-dependent CKD was associated with an increased risk for all-cause and cardiovascular death in the majority of studies. This finding remained after within-study adjustment for potential confounders and was consistent across studies despite variations in design, study populations, event rates in control subjects, and definitions of CKD. This review supports current guidelines that identify individuals with CKD as being at high risk for cardiovascular disease and other adverse outcomes and supports calls for more intensive intervention in patients with CKD to prevent adverse outcomes (78). Therapeutic strategies that have been shown to prevent cardiovascular events in patients with CKD include aggressive BP control, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (79). The first step in addressing any care gap is identifying and quantifying the magnitude of the problem; our systematic review achieves this goal by highlighting the consistency of the evidence about the hazards that are associated with CKD. The challenge that clinicians now face is to search for CKD and manage it aggressively. The challenge that researchers now face is to evaluate novel means of detecting CKD (80) and to expand the therapeutic armamentarium for patients with CKD.