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Change in Albuminuria and Risk of Renal and Cardiovascular Outcomes: Natural Variation Should Be Taken into Account

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Introduction: Changes in urinary albumin-to-creatinine ratio (UACR) may affect the risk of advanced chronic kidney disease (CKD). How much the association changes after taking account for natural variation in UACR and the length of time taken to observe changes in UACR is unknown.

Methods: English Clinical Practice Research Datalink records (2000–2015) with linkage to secondary care and death certification were used to identify prospective cohorts with at least 2 measures of UACR within 1, 2, and 3 years. Adjusted Cox regression assessed the separate relevance of the baseline UACR and the UACR change to the risk of developing stages 4 to 5 CKD and end-stage renal disease (ESRD). Associations were compared before and after accounting for the effects of the natural variation in UACR (i.e., regression to the mean).

Results: A total of 212,810 individuals had baseline UACR measurements; 22% had a UACR ≥3.4 mg/mmol, and 3% had UACR ≥33.9 mg/mmol. During a median 4-year follow-up, 5976 developed stage 4 to 5 CKD, and 1076 developed ESRD. There were strong associations between baseline UACR and stage 4 to 5 CKD or ESRD risk, which doubled in strength after accounting for regression to the mean. Over 3 years, the hazard ratios (95% confidence intervals) for stage 4 to 5 CKD, relative to stable UACR, were 0.62 (0.50–0.77) for at least a halving of UACR and 2.68 (2.29–3.14) for at least a doubling of UACR. Associations were weaker for shorter exposure windows (and for cardiovascular disease or death), but strengthened after allowing for regression to the mean.

Conclusion: Baseline values and subsequent medium-term increases in albuminuria are both associated with substantially increased risk of developing advanced CKD. Standard analyses, not allowing for natural variation in UACR, may underestimate these associations.

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In the United Kingdom, the current prevalence of chronic kidney disease (CKD) is approximately 10%,[1] and this is expected to rise as the population ages and diabetes mellitus becomes more common.[2] Progression of CKD to end-stage renal disease (ESRD) usually takes many years, and individuals with CKD often die before any need for renal replacement therapy arises.[3] Nonetheless, avoidance of CKD progression is highly desirable due to the association of CKD with a wide range of health risks[4–6] and substantial health resource use.[7–9]

In 2012, the National Kidney Foundation and the US Food and Drugs Administration sponsored a scientific workshop that concluded that a sustained 30% to 40% decline in the estimated glomerular filtration rate (eGFR) might be an appropriate surrogate for progression to ESRD in certain circumstances.[10,11] This outcome has since been used in a phase III diabetes trial.[12] Albuminuria represents an important independent risk factor for progressive CKD,[6] and international guidelines have incorporated albuminuria levels together with eGFR to subclassify CKD.[13] Findings from previous trials, and particularly studies of

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inhibitors of the renin-angiotensin-aldosterone system (RAAS) in diabetic kidney disease,[14–16] suggest that a sustained reduction in albuminuria may also indicate the nephroprotective potential of intervention. However, it is uncertain whether any drug mechanism that reduces albuminuria also slows the rate of CKD progression,[17] and if this is true for the full range of causes of CKD.[18] In March 2018, a National Kidney Foundation/Food and Drug Administration/European Medical Agency scientific workshop presented such data and discussed whether a change in albuminuria is a reliable surrogate endpoint for CKD progression.[19]

Recently, a 2006 to 2012 observational cohort of nearly 20,000 people from the Stockholm Creatinine Measurements (SCREAM) project who had ≥2 urinary albumin-to-creatinine ratio (UACR) measurements showed that an increase in UACR over 2 years was strongly associated with a future risk of ESRD and death, but this study only considered fatal cardiovascular outcomes.[20] However, UACR can vary considerably within individuals in the short-term,[21,22] representing in part, the natural biological variation rather than pathogenic progression of underlying kidney disease. Such variability is observed by the phenomenon of repeat measures of UACR that tend to regress to the population mean. If this effect is not taken into account, it can result in regression-dilution bias. Furthermore, it is unclear whether changes over 2 years are the most useful measure of a medium-term change in UACR when assessing risk. We therefore aimed to replicate and extend the SCREAM cohort findings and to assess the impact of natural regression to the mean on renal, cardiovascular, and fatal outcomes.

MATERIALS AND METHODS

Data Sources

The Clinical Practice Research Datalink (CPRD) data set is a collection of anonymous primary care records from approximately 700 United Kingdom practices[23] that has been shown to be a useful resource for prospective analyses of continuous exposures, including blood pressure and body mass index.[24–26] Because English primary care physicians were contracted to screen at-risk people for albuminuria and maintain CKD registers,[27] it provides an opportunity to investigate current uncertainties about the relevance of albuminuria to a range of outcomes. This study used data from the three-quarters of CPRD English practices that are linked to the English Hospital Episode Statistics, and used mortality data from the UK Office for National Statistics, as well as patient-level social deprivation indexes.

Study Populations and Exposures

UACR (mg/mmol) was calculated from separate urinary albumin and creatinine results recorded on the same day or from the recorded UACR value if the separate measurements were not available. Patients with at least 1 UACR test result recorded at ages 20 to 79 years, during 2000 to 2015, and with at least 1 year of preceding research quality data were eligible for inclusion in the study population (Supplementary Figure S1). A total of 685,169 eligible UACR tests were identified from 213,120 patients. One data set for analysis of baseline UACR and 3 data sets for analysis of UACR change were then extracted from CPRD based on these UACR tests and their dates.

The first UACR that satisfied the study criteria was selected for analyses of baseline UACR as the exposure. Individuals with at least 2 UACR measurements within a specified baseline exposure window were selected for data sets with UACR change as the exposure (Supplementary Figure S2). Three different data sets were made in which different exposure windows (1 year with a margin of ±4 months; 2 years ± 8 months; and 3 years ± 12 months) were used to define the change. For each data set, the first pair of UACR measurements that fulfilled the relevant criteria was selected for each individual. The UACR value closest to the end of the baseline exposure window was compared with the one at the start of baseline. Change was calculated by dividing the last UACR in the window by the first one, and then annualized. Participants with a baseline UACR (the first UACR in the exposure window for UACR change) >500 mg/mmol or women who were pregnant at the time (identified from the CPRD pregnancy register) were excluded from analyses.

Outcomes

In analyses of baseline UACR, follow-up for each participant began on the date of the baseline UACR test. For studies of UACR change, the start of follow-up was taken as the date of the last UACR value in the baseline exposure window (Supplementary Figure S2). Follow-up continued until the practice stopped providing data to CPRD, the patient died or left the practice, or December 31, 2015 (whichever was earliest). The outcome of incident identified stage 4 to 5 CKD was derived using internationally accepted clinical definitions[28] and an algorithm that incorporated death certificates, inpatient diagnostic or procedural codes, and primary care diagnostic and/or laboratory test results (as used in previous work[26]). When laboratory results were available, eGFR was calculated from creatinine results using the CKD Epidemiology Collaboration formula.[29] Stage 4 to 5 CKD was also accepted if