AJKD
Original Investigation

C-Reactive Protein and Risk of ESRD: Results From the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT)

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Background: To better understand a potential association of elevated C-reactive protein (CRP) level with progression of chronic kidney disease (CKD), we examined the relationship of CRP level with the development of end-stage renal disease (ESRD) in the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT).

Study Design: Post hoc analysis of a randomized controlled trial.

Setting & Participants: 4,038 patients with type 2 diabetes, CKD, and anemia in TREAT.

Predictor: Baseline serum CRP concentrations.

Outcomes: The primary outcome was development of ESRD; secondary outcomes included doubling of serum creatinine level, a composite of ESRD/serum creatinine doubling, and a composite of death or ESRD.

Measurements: We fit unadjusted and adjusted Cox regression models to test the association of baseline CRP level with time to the development of the outcomes of interest.

Results: Mean age of participants was 67 years, 43% were men, and 64% were white. Approximately half (48%) the patients had CRP levels $>$ 3.0 mg/L; 668 patients developed ESRD, and 1,270 developed the composite outcome of death or ESRD. Compared with patients with baseline CRP levels $\leq$ 3.0 mg/L, those with moderately/markedly elevated CRP levels ($\geq$6.9 mg/L; 24% of patients) had a higher adjusted risk for ESRD (HR, 1.32; 95% CI, 1.07-1.63) and the composite outcome of death or ESRD (HR, 1.41; 95% CI, 1.21-1.64). Although nonsignificant, similar trends were noted in competing-risk models.

Limitations: Results may not be generalizable to nondiabetic CKD or diabetic CKD in the absence of anemia.

Conclusions: Elevated baseline CRP levels are common in type 2 diabetic patients with anemia and CKD and are associated with the future development of ESRD and the composite of death or ESRD.

Am J Kidney Dis. 68(6):873-881.

INDEX WORDS: C-Reactive protein (CRP); end-stage renal disease (ESRD); risk factor; biomarker; inflammation; disease progression; kidney function trajectory; serum creatinine; mortality; type 2 diabetes mellitus (T2DM); chronic kidney disease (CKD); anemia.

Chronic kidney disease (CKD) affects ~11.5% of the general population[1] and 40% of those with self-reported diabetes mellitus in the United States.[2] Diabetes is a major risk factor for the progression of CKD and is the leading cause of end-stage renal disease (ESRD) in the United States, accounting for approximately 50,000 new cases in 2012 alone.[2]

Elevated concentrations of C-reactive protein (CRP), a biomarker associated with the presence of inflammation, are known to be associated with the development of future cardiovascular (CV) events in patients with[3,4] and without[5,6] a history of CV disease and in patients with CKD.[7,8] It is widely recognized that CKD is a risk factor for CV disease, with the

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Received February 11, 2016. Accepted in revised form July 11, 2016. Originally published online September 16, 2016.

Because an author of this article is an editor for AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Abhijit V. Kshirsagar, MD, MPH) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Journal Policies.

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0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.07.022

majority of patients with diabetes and CKD ultimately dying of CV causes.[9] In light of these relationships, it has been postulated that chronic inflammation may be a common etiologic factor for the progression of both conditions. However, to date, evidence supporting an association of CRP level with kidney function decline (as measured by changes in serum creatinine or estimated glomerular filtration rate [eGFR]) is conflicting, with some studies reporting the presence of a significant association,[10-14] whereas others have not.[15-17]

The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT)[18] provided an opportunity to perform an examination of the association of baseline CRP level with time to the adjudicated outcomes of: (1) ESRD and (2) the composite of death or ESRD in patients with type 2 diabetes (T2DM), CKD, and anemia. We hypothesized that individuals with higher baseline CRP concentrations would be at greater risk for the development of ESRD and death or ESRD.

METHODS

Study Design and Population

The design and original results of TREAT (trial registration: ClinicalTrials.gov; study number: NCT00093015) have been published.[18,19] Briefly, TREAT was a prospective, double-blind, randomized, controlled trial of darbepoetin alfa versus placebo for the treatment of anemia in 4,038 patients with T2DM, eGFRs of 20 to 60 mL/min/1.73 m^2 according to the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation, hemoglobin levels $<$ 11.0 g/dL, and transferrin saturations $>$ 15%. Notable exclusion criteria included a recent (within 12 weeks) CV event, grand mal seizure, major surgery, prior use of an erythropoiesis-stimulating agent, uncontrolled hypertension, known human immunodeficiency virus (HIV) infection, current use of intravenous antibiotics, chemotherapy or radiotherapy, malignancy (except basal cell or squamous cell carcinoma of the skin), active bleeding, hematologic diseases, pregnancy, or kidney transplant recipients. All patients gave written informed consent for participation in the primary trial and the serum samples used in this analysis (Partners IRB 2005P000170).

Exposures and Outcomes

The primary exposure of interest was baseline serum CRP level. All baseline samples were stored locally by individual sites at −20°C before shipment on dry ice for long-term storage at −70°C in a central tissue repository. CRP was measured using an immunoturbidimetric assay. This was a standard-sensitivity assay with a lower limit of detection of 3 mg/L. Therefore, for the purposes of these analyses, CRP level was categorized as normal (≤3 mg/L), mildly elevated (>3.0-<6.9 mg/L), and moderately/markedly elevated (≥6.9 mg/L). The latter 2 categories were dichotomized at the median for CRP concentrations $>$ 3 mg/L.

The primary outcome of interest was the development of ESRD, defined as the initiation of renal replacement therapy (RRT; sustained for at least 30 days), initiation of RRT with death within 30 days, a physician recommendation to initiate RRT with documented patient refusal, or receipt of a kidney transplant. Secondary outcomes were the development of: (1) doubling of serum creatinine level; (2) the composite of ESRD or doubling of serum creatinine level; (3) the composite outcome of ESRD or death from any cause; (4) composite CV outcome of death from any cause, nonfatal myocardial infarction, stroke, heart failure, or hospitalization for myocardial ischemia; and (5) death from any cause.[18] The CV components of the composite end point, ESRD and death were adjudicated by a clinical end points committee blinded to treatment assignment. Sensitivity analyses were also performed to examine the association of categories of baseline CRP levels with: (1) change in eGFR from randomization to the development of ESRD or study exit, and (2) the difference in the last measured eGFR for individuals who developed ESRD. Change in eGFR was calculated as a linear slope in mL/min/1.73 m^2 per year by plotting a line of best fit for all available eGFR values (3,544 individuals had at least 2 creatinine measurements from which the eGFR slope could be calculated; mean number of measurements per patient, 5.1). In exploratory analyses, the association of baseline CRP level with ESRD was determined for the subgroup of patients with CRP concentrations $>$ 3.0 mg/L.

Statistical Analyses

Continuous variables were examined graphically and recorded as mean ± standard deviation for normally distributed data or median (with interquartile range [IQR]) for non-normally distributed data. Categorical variables were examined by frequency distribution and recorded as proportion. Tests for trend across categories of CRP were conducted using linear regression, Cuzick nonparametric trend test, and χ^2 test for trend for continuous normal, continuous non-normal, and categorical data, respectively.

The relationship between categories of CRP with time to the events of interest was examined by proportional hazards regression. Initially, an unadjusted model (model 1) was fit. Subsequently, a multivariable-adjusted model (model 2) was fit; this model included terms for potential confounding variables that were measured at baseline[20,21]: age, sex, race, eGFR, log-transformed urine protein-creatinine ratio, history of acute kidney injury, duration of T2DM at baseline, hemoglobin A_{1c} level, retinopathy, insulin use, body mass index, hemoglobin level, serum albumin level, coronary artery disease (angina, myocardial infarction, coronary artery bypass graft, and percutaneous coronary intervention), cerebrovascular disease (including transient ischemic attack and carotid artery disease), peripheral arterial disease (including peripheral artery stenosis and aortic aneurysm repair), heart failure, systolic blood pressure, low-density lipoprotein cholesterol level, statin therapy, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, smoking status (current, former, and never), serum ferritin level, transferrin saturation, iron therapy, and randomized treatment assignment. The proportionality assumption was assessed on the basis of Schoenfeld residual testing. Additional models were created that included the corresponding predictor-time interaction variables in situations in which violation of the proportional hazards assumption was evident. Additionally, a Cox regression spline model was fit to examine the continuous association of baseline CRP level with the development of ESRD. For purposes of this analysis, the 2,112 individuals with baseline CRP levels ≤ 3.0 mg/L were assumed to have a CRP level of 3.0 mg/L, which was taken as the reference value. Subsequently, because mortality may preclude the development of ESRD or doubling of serum creatinine level, a multivariable-adjusted competing-risk model was fit according to the method of Fine and Gray[22] in order to estimate the cumulative incidence function for ESRD, doubling of serum creatinine level, and the composite of ESRD/doubling of serum creatinine level, where death was considered as the competing risk.

For sensitivity analyses, unadjusted and adjusted linear regression models were fit to estimate differences in the slope of eGFR according to baseline CRP categories. For those who went on to