Published in final edited form as:

Am J Kidney Dis. 2016 December ; 68(6): 873–881. doi:10.1053/j.ajkd.2016.07.022.

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

Finnian R. Mc Causland, MBBCh, MMSc^{1,2}, Brian Claggett, PhD^{2,3}, Emmanuel A. Burdmann, MD, PhD⁴, Kai-Uwe Eckardt, MD⁵, Reshma Kewalramani, MD⁶, Andrew S. Levey, MD⁷, John J.V. McMurray, MD⁸, Patrick Parfrey, MD⁹, Giuseppe Remuzzi, MD^{10,11,12}, Ajay K. Singh, MD^{1,2}, Scott D. Solomon, MD^{2,3}, Robert D. Toto, MD¹³, and Marc A. Pfeffer, MD, PhD^{2,3}

¹Renal Division, Department of Medicine, Brigham and Women's Hospital ²Harvard Medical School, Boston, MA, USA ³Cardiology Division, Department of Medicine, Brigham and Women's Hospital ⁴Division of Nephrology, University of Sao Paulo Medical School, Sao Paulo, Brazil ⁵Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Germany ⁶Global Clinical Development, Amgen, Thousand Oaks, CA ⁷Division of Nephrology, Tufts Medical Center, Boston, MA, USA ⁸Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, Scotland ⁹Health Sciences Centre, Memorial University of Newfoundland, St. John's, Newfoundland, Canada ¹⁰IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Bergamo ¹¹Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo ¹²Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy ¹³Renal Division, University of Texas Southwestern, Dallas, TX

Abstract

Correspondence to: Finnian Mc Causland, MBBCh, MMSc, MRCPI, MRB-4, Brigham and Women's Hospital, Boston, MA, 02115, Phone: 617-732-6432; Fax: 617-732-6392; fmccausland@partners.org.

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Contributions: Research idea and study design: FMC, BC, MAP; data acquisition: EAB, K-UE, RK, ASL, JJVM, PP, GR, AKS, SDS, RDT, MAP; data analysis/interpretation: FMC, BC, MAP; statistical analysis: FMC, BC; supervision or mentorship: MAP. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. FMC, BC and MAP take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Supplementary Material

Table S1: Association of baseline CRP category with ESRD, Scr doubling, composite of ESRD or Scr doubling, composite of ESRD or death, CV composite, and death alone.

Table S2: Association of baseline CRP tertiles with ESRD in patients with baseline CRP above lower limit of detection. Table S3: Difference in eGFR slope according to baseline CRP category.

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Supplementary Material Descriptive Text for Online Delivery

Supplementary Table S1 (PDF). Association of baseline CRP category with ESRD, Scr doubling, composite of ESRD or Scr doubling, composite of ESRD or death, CV composite, and death alone.

Supplementary Table S2 (PDF). Association of baseline CRP tertiles with ESRD in patients with baseline CRP above lower limit of detection.

Supplementary Table S3 (PDF). Difference in eGFR slope according to baseline CRP category.

Background—To better understand a potential association of elevated C-reactive protein (CRP) with progression of chronic kidney disease (CKD), we examined the relationship of CRP 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 the TREAT study.

Predictor—Baseline serum concentrations of CRP.

Outcomes—The primary outcome was development of ESRD; secondary outcomes included doubling of serum creatinine 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 with time to development of the outcomes of interest

Results—Mean age of participants was 67 years, 43% were male and 64% were white. Approximately half of the patients (48%) had a CRP concentration of >3.0 mg/L; 668 patients developed ESRD, while 1270 developed the composite outcome of death or ESRD. Compared to patients with baseline CRP ≤3.0 mg/L, those with moderate-markedly elevated levels of CRP (>3.0–6.9 mg/L; 24% of patients) had a higher adjusted risk of 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 non-diabetic CKD or diabetic CKD in the absence of anemia.

Conclusions—Elevated concentrations of baseline CRP 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.

Keywords

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 approximately 11.5% of the general population¹ 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 top cause of end-stage renal disease (ESRD) in the United States, accounting for approximately 50,000 new cases in 2012 alone.²

Elevated concentration of C-reactive protein (CRP), a biomarker associated with the presence of inflammation, is known to be associated with the development of future cardiovascular (CV) events in patients with^{3,4} and without^{5,6} a prior 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 majority of patients with diabetes and CKD ultimately dying from CV

causes.⁹ In light of these relationships, it has been postulated that chronic inflammation may be a common etiological factor for the progression of both conditions. However, to date, evidence supporting an association of CRP 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} while 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 with the 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 development of ESRD, and death or ESRD.

Methods

Study Design and Population

The design and original results of TREAT (trial registration: [ClinicalTrials.gov](https://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, eGFR of 20–60 mL/min/1.73m² according to the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation, hemoglobin level <11.0 g/dL, and transferrin saturation >15%. Notable exclusion criteria included a recent (within 12 weeks) CV event, grand mal seizure, major surgery, or prior use of an erythropoiesis-stimulating agent (ESA), uncontrolled hypertension, known human immunodeficiency virus 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 the baseline serum concentration of CRP. 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. The CRP was measured using an immuno-turbidimetric 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 was categorized as normal (< 3 mg/L), mildly elevated (>3.0 to <6.9 mg/L) and moderate-markedly elevated (> 6.9 mg/L). The latter two categories were dichotomized at the median for CRP concentrations >3mg/L.

The primary outcome of interest was the time from randomization to 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. The secondary outcomes

were the time to development of 1) doubling of serum creatinine; 2) the composite of ESRD or doubling of serum creatinine; 3) the composite outcome of ESRD or death from any cause; 4) composite CV outcome of death from any cause, nonfatal myocardial infarction (MI), 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 the treatment assignment. Sensitivity analyses were also performed to examine the association of categories of baseline CRP with 1) the change in eGFR from randomization to the development of ESRD or study exit; and 2) the difference in last measured eGFR for those individuals who developed ESRD. Change in eGFR was calculated as a linear slope in mL/min/1.73 m² per year by plotting a line of best fit for all available eGFR values (3,544 individuals had at least two 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 with ESRD was determined for the sub-group of patients with CRP concentrations > 3.0 mg/L.

Statistical Analyses

Continuous variables were examined graphically and recorded as means $\pm$ standard deviations for normally distributed data, or medians (with interquartile ranges [IQRs]) for non-normally distributed data. Categorical variables were examined by frequency distribution and recorded as proportions. Tests for trend across categories of CRP were conducted using linear regression, Cuzick's non-parametric trend test and the Chi-square 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, gender, race, eGFR, log-transformed urine protein-creatinine ratio, history of acute kidney injury, duration of T2DM at baseline, HbA1c, retinopathy, insulin use, body mass index, hemoglobin, serum albumin, coronary artery disease (angina, MI, coronary artery bypass graft, 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 (LDL) cholesterol, statin therapy, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy, smoking status (current, former, never), serum ferritin, 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 where violation of the proportional hazards assumption was evident. Additionally, a Cox regression spline model was fit to examine the continuous association of baseline CRP with the development of ESRD. For the purposes of this analysis, the 2,112 individuals with baseline CRP $\leq$ 3.0 mg/L were assumed to have a CRP=3.0 mg/L, which was taken as the reference value. Subsequently, as mortality may preclude the development of ESRD or doubling of serum creatinine, a multivariable adjusted competing risk model was fit according to the method of Fine and Gray²² in order to estimate the cumulative

incidence function for ESRD, doubling of serum creatinine, and the composite of ESRD/doubling of serum creatinine, where death was considered as the competing risk.

For the sensitivity analyses, unadjusted and adjusted linear regression models were fit to estimate the differences in the slope of eGFR according to baseline CRP categories. For those who went on to develop ESRD, trend tests were used to determine the association of the last measured eGFR with increasing categories of baseline CRP.

Nominal 2-sided p values of <0.05 were considered statistically significant. All analyses were performed using STATA 13.0MP (StataCorp LP, College Station, Tex., USA).

Results

Baseline Characteristics

The primary cohort consisted of 4,038 individuals (57% women) with a median age of 68 years.¹⁸ Just over half of individuals (52.3%) had a baseline CRP concentration at or below the lower limit of detection (3.0 mg/L). Of the remainder, 953 individuals (23.6%) had a mildly elevated CRP (>3.0 to <6.9 mg/L) and 973 (24.1%) had a moderate-markedly elevated level (6.9 mg/L).

Individuals in the higher CRP categories were more likely to be younger and female; to have a history of acute kidney injury, peripheral arterial disease and heart failure; to be a current or former smoker; and to have higher LDL cholesterol and ferritin concentrations. In addition, those in the higher CRP categories were also more likely to use insulin and have a higher BMI and higher glycated hemoglobin, but to have lower hemoglobin and transferrin saturations, and were less likely to have retinopathy or to be taking a statin or an ACE inhibitor or ARB. Although serum creatinine concentration was statistically significantly higher (and eGFR lower) in the patients in the higher CRP categories, the absolute differences were very small and unlikely to be of clinical importance. No significant trend was noted in relation to baseline proteinuria (Table 1).

Associations of Baseline CRP With Various Outcomes

Association With Development of ESRD—During a median follow-up time of 2.2 years, a total of 668 adjudicated ESRD events were recorded. In unadjusted analyses, compared with individuals with CRP 3.0 mg/L, those in the mildly elevated category had a 21% greater risk of developing ESRD (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.01–1.46; p=0.04), while those in the moderate-markedly elevated category had 37% greater risk (HR, 1.37; 95% CI, 1.14–1.64; p=0.001 [Figure 1]). In the fully adjusted analyses (Model 2), compared with individuals with CRP 3.0 mg/L, those in the moderate-markedly elevated category of baseline CRP had 32% greater risk of developing ESRD (HR, 1.32; 95% CI, 1.07–1.63; p=0.01; Tables 2 and 3). Effect estimates were essentially unchanged when time-varying coefficients were added to the model to address concerns of potential violation of the proportional hazards assumption (Table S1, available as online supplementary material). Using a multivariable competing risk model (with death as the competing outcome) gave similar findings, although the HR was somewhat attenuated (Table 2).

Similar trends were noted when sub-group analyses of individuals with baseline CRP >3.0 mg/L (n=1,926) were performed (Table S2). When CRP was examined as a continuous variable there was evidence for a monotonic association of higher CRP with increasing risk of ESRD (Figure 2).

Association With Serum Creatinine Doubling and Composite of ESRD or Serum Creatinine Doubling—During a median follow-up of 2.1 years, the end point of doubling of serum creatinine occurred in 428 individuals. There was no significant association of elevated categories of baseline CRP with the risk of development of doubling of serum creatinine, or with the development of the composite outcome of ESRD or doubling of serum creatinine (Table 2). Effect estimates were essentially unchanged when time-varying coefficients were added to the model to address concerns of potential violation of the proportional hazards assumption (Table S1). Using a multivariable competing risk model (with death as the competing outcome) higher baseline CRP was not associated with either doubling of serum creatinine or the composite of ESRD/doubling of serum creatinine (Table 2)."

Association With Development of Composite of Death or ESRD, CV Composite Outcome, and Death From Any Cause—During a median follow-up period of 2.3 years, a total of 1,270 adjudicated composite events of death or ESRD were recorded. In unadjusted models, compared with CRP ≤3.0 mg/L, there was a 21% (HR, 1.21; 95% CI, 1.05–1.39; P=0.01) and 57% (HR, 1.57; 95% CI, 1.38–1.79; P<0.001) greater risk, respectively, of the combined end point with increasing categories of baseline CRP (Tables 2 and 3). In the fully adjusted model (Model 2), the effects estimates were attenuated, but remained significant for the moderate-markedly elevated CRP category (HR, 1.41; 95% CI, 1.21–1.64; p<0.001). Similar patterns of association were noted for the CV composite end point and all-cause death (Table 2).

Association With Change in eGFR—The association of baseline categories of CRP with the change in eGFR (mL/min/1.73 m² per year) from randomization to development of ESRD or study exit was then assessed. The median change in eGFR in the whole cohort was −1.8 (95% CI, −5.9 to 1.4) mL/min/1.73m² per year. In unadjusted analyses, compared with individuals with normal baseline CRP (≤3.0 mg/L), there was no evidence for a significant difference in the change in eGFR in either the mildly elevated (difference of −0.3 [95% CI, −1.1 to 0.5] mL/min/1.73 m² per year; P=0.5) or moderate-markedly elevated (difference of 0.4 [95% CI, −0.4 to 1.2] mL/min/1.73 m² per year; P=0.3) CRP categories. Similar findings were noted in the adjusted models: difference of −0.2 (95% CI, −1.0 to 0.5) mL/min/1.73 m² per year (P=0.6) for the mildly elevated CRP category and a difference of 0.5 (95% CI, −0.3 to 1.3) mL/min/1.73 m² per year (P=0.3) for the moderate-markedly elevated category, compared with individuals with a normal baseline CRP (≤3.0 mg/L; Table S3).

For those who ultimately went on to develop ESRD, the median last eGFR value was lower in patients with lower CRP measurements: 14.9 (IQR, 11.6–20.9) mL/min/1.73 m² for those with CRP ≤3.0 mg/L; 16.8 (IQR, 12.7–23.3) mL/min/1.73 m² for those with CRP >3.0 to <6.9 mg/L; and 17.1 (IQR, 12.6–22.6) mL/min/1.73 m² for those with CRP ≥6.9 mg/L (P for trend=0.02). The median time that these measurements were collected prior to the

declaration of ESRD was 88 days for those with CRP ≤ 3.0 mg/L; 106 days, CRP >3.0 to <6.9 mg/L; and 96 days, CRP ≥ 6.9 mg/L (P for trend=0.9).

Discussion

In this post-hoc analysis of the TREAT study we found that higher baseline concentrations of CRP were associated with greater risk of the adjudicated outcomes of ESRD and the composite of death or ESRD, but not with changes in eGFR or doubling of serum creatinine.

C-reactive protein (molecular weight, ~ 23 kDa) is a member of the pentraxin protein family, which is intimately involved in the activity of the innate immune system.²³ It is primarily produced by hepatocytes, and its synthesis can be markedly up-regulated as part of the acute phase response.²⁴ Although cause and effect has not been proven, prior epidemiological studies have demonstrated a clear association of higher CRP concentrations with the future development of MI and ischemic stroke.^{5,6,25} The association of higher levels of CRP with greater risk of CV disease also appears to be consistent in patients with a history of CKD.^{7,8}

The presence of inflammation has been proposed as a common etiological pathway in the pathogenesis and progression of both CV and CKD. However, to date, the prior evidence linking CRP with progressive decline in kidney function is conflicting, with some studies reporting no association,^{7,15–17} while others have reported a positive association.^{11,14} Importantly, the ascertainment of the kidney outcome appears to play an important role in the heterogeneity of prior reports. For example, Fried et al. reported a significant association of baseline CRP with greater decline in eGFR (using the 4-variable MDRD Study equation) in 4,620 community-based individuals aged <65 years in the CV Health Study (25% had diabetes).¹⁰ However, an analysis of the same study by Keller et al. failed to find such an association when decline in eGFR was assessed using cystatin C.¹² In another report, Hiramoto et al. found discrepant results in their analyses of 4,966 participants of the Multi-Ethnic Study of Atherosclerosis (MESA): baseline CRP was significantly associated with decline in eGFR using the CKD-EPI cystatin C equation, but not when using CKD-EPI creatinine equation.¹³ Indeed, some have questioned the accuracy of estimating equations for GFR in patients with T2DM,²⁶ raising further concerns regarding the use of changes in such parameters over time.

Our analyses were performed in individuals with the triad of T2DM, anemia and CKD. We did not find a significant association of baseline CRP with changes in eGFR (calculated using serum creatinine) or doubling of serum creatinine during the study period, but we did report an association with development of the clinically important adjudicated end point of ESRD. While we recognize that the use of a linear slope to describe progression of CKD in a group of patients does not accurately reflect individual rates and patterns of progressive kidney function decline, it is also noteworthy that the last available eGFR prior to the development of ESRD was higher across increasing CRP categories.

As higher baseline CRP was *not* associated with progression of CKD as measured by a decline in eGFR (but *was* associated with progression to clinical ESRD), a tentative hypothesis might be that higher CRP identifies individuals with a greater burden of

comorbidities who may be more likely to require earlier initiation of RRT. Alternatively, higher CRP may identify individuals with a greater burden of comorbid conditions leading to overestimation of measured GFR due to lower creatinine generation.²⁷ Our finding that the risk of developing the CV composite outcome during the trial was higher in those with higher baseline CRP provides supportive evidence for both possibilities.

It is worth noting that moderately/markedly elevated CRP is associated with significantly greater risk of death and with a greater risk of ESRD. In the competing risk model, the association of elevated CRP with ESRD becomes attenuated and of borderline significance. However, in this model death precludes progression to ESRD, and so we may interpret this constellation of findings to indicate that, among those who have not died, higher CRP is a risk factor for ESRD. This interpretation is supported by the finding that higher CRP is associated with a greater risk of developing the composite end point of ESRD or death.

The major strengths of our study are the large number of independently adjudicated clinical end points and detailed data collection that occurred in the setting of a double-blind randomized controlled trial. However, there are limitations. The first relates to the use of standard sensitivity measurements of CRP with a lower limit of measurement of 3.0 mg/L, thereby restricting our ability to examine CRP as a continuous variable. On the other hand, despite the lack of high-sensitivity measurements, 48% of these patients with T2DM, CKD and anemia had baseline CRP measurements >3.0 mg/L, which highlights the prevalence of underlying inflammation in this important patient population. Another limitation is that only one baseline measurement of CRP was available. However, the stability of CRP in individual patients has been demonstrated previously (albeit in non-CKD patients),²⁸ while the clinical relevance of our findings remains applicable, such that those with moderate-markedly elevated CRP measurements (≥ 6.9 mg/L) were significantly more likely to develop ESRD. That the direction of association was similar in the analyses of the composite outcome of ESRD or death, the CV composite outcome and the outcome of death from any cause provides additional reassurance of the clinical relevance of our findings. In the setting of a secondary analysis of a randomized trial, several potential confounding variables had to be considered in the model building process. In this regard it is possible that residual confounding based on variables not considered, or due to incomplete adjustment of those that were considered, still exists. This post-hoc study was not powered to assess the influence of anti-inflammatory therapies or other factors that could potentially modify the relationship between CRP and ESRD. Finally, the sample in this study consisted of patients with T2DM, CKD and anemia in the setting of a randomized controlled trial, limiting the generalizability to individuals without this comorbid disease pattern.

In conclusion, we found that higher baseline CRP was associated with a greater risk of developing ESRD and the composite of ESRD or death in patients with the triad of T2DM, CKD and anemia. When reviewing a patient with these comorbidities, the presence of an elevated CRP may prompt the clinician to explore for potentially modifiable sources of inflammation, such as infection. Whether interventions that lower CRP will result in a reduced risk of ESRD is unknown, but may provide opportunities for future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: Dr. Mc Causland is supported by the National Institute of Diabetes and Digestive and Kidney Diseases grant K23DK102511.

Financial Disclosure: TREAT was funded by Amgen. This analysis was conducted independently by the authors and used the data set held at the Brigham & Women's Hospital.

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	Number at risk				
CRP ≤ 3 mg/L	2112	1873	1283	584	142
CRP > 3.0 to < 6.9 mg/L	953	814	549	248	58
CKD ≥ 6.9 mg/L	973	794	512	214	44

Figure 1.
Kaplan-Meier failure probabilities of the association of baseline categories of CRP with risk of ESRD.

Figure 2. Spline analysis of the association of CRP with ESRD

Hazard ratios (HR; continuous line) and 95% Upper and Lower Confidence Intervals (UCI and LCI; dashed lines) for the association of CRP as a continuous variable with the risk of ESRD. For the purposes of this analysis, the 2,112 individuals with baseline CRP ≤ 3.0 mg/L were assumed to have a CRP=3 mg/L, which was taken as the reference value (large bar at the extreme left of the x-axis). Effect estimates were adjusted for age, gender, race, estimated GFR, log-transformed urine protein-creatinine ratio, history of acute kidney injury, duration of T2DM, HbA1c, retinopathy, insulin use, body mass index, hemoglobin, serum albumin, coronary artery disease, cerebrovascular disease, peripheral arterial disease, heart failure, systolic blood pressure, low-density lipoprotein concentration, statin therapy, ACE inhibitor or ARB therapy, smoking status, ferritin, transferrin saturation, iron therapy and randomized treatment assignment. Estimates are presented for CRP values between up to the 95th percentile of recorded values.

Table 1

Baseline Characteristics of Cohort According to Baseline CRP Categories

	Normal: 3.0 mg/L	Mildly Elevated: >3.0–<6.9 mg/L	Moderately/markedly Elevated: 6.9 mg/L	p^a
No. of Participants	2,112	953	973	
CRP	NA	4.5 (3.7–5.4)	13.3 (9.0–23.5)	
Age (y)	67.8 ±10.7	67.1 ±10.6	66.5 ±10.6	0.001
Male sex	44.6	40.9	40.5	0.02
Race				0.2
Black	18.6	20.4	23.5	
Hispanic	16.3	11.0	9.1	
Other	4.0	2.1	1.0	
White	61.1	66.5	66.3	
Creatinine (mg/dL)	1.8 (1.5–2.3)	1.9 (1.5–2.4)	1.9 (1.5–2.4)	0.04
eGFR (mL/min/1.73m ²)	32 (25–40)	31 (24–39)	31 (24–41)	0.05
Urine PCR	0.4 (0.1–1.8)	0.5 (0.2–1.9)	0.4 (0.1–1.9)	0.1
History of AKI	7.7	10.9	13.2	<0.001
Duration of T2DM (y)	15.5 (8.5–21.6)	15.6 (8.6–21.9)	15.0 (7.5–21.8)	0.2
HbA1c	6.9 (6.2–7.8)	7.1 (6.3–8.2)	7.1 (6.3–8.1)	<0.001
Neuropathy	47.3	47.0	49.8	0.2
Retinopathy	50.5	46.1	40.1	<0.001
Insulin use	44.4	55.1	54.2	<0.001
BMI (kg/m ²)	29.1 (25.7–33.5)	31.2 (26.9–36.1)	32.1 (27.4–38.5)	<0.001
Hemoglobin (g/dL)	10.4 ±1.0	10.4 ±1.0	10.3 ±1.0	0.01
Albumin (g/dL)	4.0 ±0.4	4.0 ±0.4	3.9 ±0.4	<0.001
CAD	35.1	38.7	37.3	0.2
Cerebrovascular disease	17.4	16.5	19.2	0.3
PAD	18.1	20.4	23.3	<0.001
Heart Failure	29.7	36.7	38.0	<0.001
SBP (mmHg)	136.0 ±18.7	137.0 ±18.6	134.6 ±18.9	0.1
LDL cholesterol (mg/dL)	89 ±39	94 ±42	93 ±40	0.01
Statin	61.7	57.0	53.2	<0.001
ACEi or ARB	82.1%	77.4%	77.2%	<0.001
Smoking				0.01
Current	4.5	4.7	6.5	
Former	38.0	38.7	40.7	
Never	57.5	56.6	52.8	
Ferritin (µg/L)	120 (60–240)	133 (66–256)	161 (90–299)	<0.001
Transferrin Saturation (%)	25.6±9.4	24.1±9.6	21.2±8.4	<0.001

	Normal: 3.0 mg/L	Mildly Elevated: >3.0–<6.9 mg/L	Moderately/markedly Elevated: 6.9 mg/L	p^a
Iron therapy	42.9	42.0	48.8	0.01
Treatment: Darbepoetin vs Placebo	50.0	50.6	48.7	0.6

Note: Values for categorical variables are given as percentage; values for continuous variables, as mean $\pm$ standard deviation or median [interquartile range].

Abbreviations: AKI, acute kidney injury; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; PCR, protein-creatinine ratio; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin; BMI, body mass index; CAD, coronary artery disease; PAD, peripheral arterial disease; SBP, systolic blood pressure; LDL, low-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

^aP values refer to a test for trend across increasing category of CRP concentration.

Table 2

Association of Baseline CRP Category with ESRD, Doubling of Scr, Composite of ESRD or Doubling of Scr, Composite of ESRD or Death, CV Composite, and Death alone

Model: Events/Total	HR (95% CI)		P for trend
	CRP >3.0–<6.9 mg/L	CRP ≥ 6.9 mg/L	
Development of ESRD			
Unadjusted: 668/4,038	1.21 (1.01 – 1.46)	1.37 (1.14 – 1.64)	0.001
Adjusted: 598/3,642	1.08 (0.88 – 1.33)	1.32 (1.07 – 1.63)	0.01
Competing Risk: 598/3,642	1.01 (0.81–1.25)	1.23 (0.99–1.53)	0.09
Doubling of Scr			
Unadjusted: 428/3,654	0.96 (0.76 – 1.22)	1.06 (0.84 – 1.35)	0.7
Adjusted: 367/3,305	0.90 (0.69 – 1.18)	0.94 (0.71 – 1.25)	0.6
Competing Risk: 367/3,305	0.86 (0.65–1.14)	0.93 (0.69–1.25)	0.5
Composite of ESRD/Scr Doubling			
Unadjusted: 871/4,038	1.16 (0.99 – 1.37)	1.28 (1.09 – 1.51)	0.002
Adjusted: 769/3,642	1.05 (0.87 – 1.26)	1.17 (0.97 – 1.42)	0.1
Competing Risk: 769/3,642	0.99 (0.82–1.20)	1.12 (0.92–1.36)	0.3
Death or ESRD			
Unadjusted: n=1,270/4,038	1.21 (1.05 – 1.39)	1.57 (1.38 – 1.79)	<0.001
Adjusted: n=1,139/3,642	1.11 (0.96 – 1.29)	1.41 (1.21 – 1.64)	<0.001
CV Composite Outcome *			
Unadjusted: n=1,234/4,038	1.26 (1.09 – 1.45)	1.77 (1.55 – 2.02)	<0.001
Adjusted: n=1,111/3,642	1.16 (0.99 – 1.35)	1.55 (1.34 – 1.81)	<0.001
Association With Death From Any Cause			
Unadjusted: n=807/4,038	1.20 (1.00 – 1.43)	1.85 (1.57 – 2.16)	<0.001
Adjusted: n=734/3,642	1.15 (0.95 – 1.39)	1.59 (1.32 – 1.91)	<0.001

Note: CRP ≥ 3.0 mg/L was reference category for all. The multivariable models were adjusted for age, gender, race, estimated glomerular filtration rate, log-transformed urine protein-creatinine ratio, history of acute kidney injury, duration of type 2 diabetes mellitus, glycated hemoglobin, retinopathy, insulin use, body mass index, hemoglobin, serum albumin, coronary artery disease, cerebrovascular disease, peripheral arterial disease, heart failure, systolic blood pressure, low-density lipoprotein cholesterol concentration, statin therapy, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, smoking status, ferritin, transferrin saturation, iron therapy and randomized treatment assignment. Multivariable adjusted competing risk models were fit, with death as the competing outcome, for the end points of ESRD, doubling of Scr and the composite of ESRD/doubling of Scr.

CI, confidence interval; CRP, C-reactive protein; CV, cardiovascular; ESRD, end-stage renal disease; HR, hazard ratio; Scr, serum creatinine

* CV composite included death from any cause, nonfatal MI, stroke, heart failure or hospitalization for myocardial ischemia

Table 3

Unadjusted and Multivariable adjusted associations of Baseline Factors with Development of ESRD

	Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P
CRP category				
3.0 mg/L	1.00 (reference)	-	1.00 (reference)	-
>3.0 – <6.9 mg/L	1.21 (1.01–1.46)	0.04	1.08 (0.88–1.33)	0.4
6.9 mg/L	1.37 (1.14–1.64)	0.001	1.32 (1.07–1.63)	0.01
Age, per 10 y older	0.71 (0.67–0.77)	<0.001	0.91 (0.83–1.00)	0.04
Male sex, vs female	1.75 (1.51–2.04)	<0.001	1.84 (1.53–2.20)	<0.001
Race				
White	1.00 (reference)	–	1.00 (reference)	-
Black	1.65 (1.38–1.97)	<0.001	1.44 (1.18–1.77)	<0.001
Hispanic	1.53 (1.23–1.90)	<0.001	0.87 (0.67–1.13)	0.3
Other	1.13 (0.71–1.82)	0.7	0.93 (0.57–1.53)	0.8
eGFR, per 10–mL/min/1.73 m ² increase	0.40 (0.36–0.44)	<0.001	0.46 (0.41–0.50)	<0.001
Log Urine PCR, per 1-unit greater	2.04 (1.93–2.15)	<0.001	1.77 (1.63–1.92)	<0.001
History of AKI, vs none	1.63 (1.30–2.03)	<0.001	1.42 (1.12–1.81)	0.004
Duration of T2DM, per 12 mo longer	1.01 (1.01–1.02)	0.001	1.01 (1.00–1.02)	0.03
HbA1c, per 1% greater	1.10 (1.05–1.15)	<0.001	0.98 (0.93–1.04)	0.5
Retinopathy, vs none	1.83 (1.56–2.13)	<0.001	1.05 (0.87–1.26)	0.6
Insulin use, vs none	1.55 (1.33–1.81)	<0.001	1.11 (0.92–1.33)	0.3
BMI, per 10–kg/m ² greater	0.85 (0.77–0.95)	0.01	0.84 (0.73–0.95)	0.01
Hemoglobin, per 1–g/dL greater	0.78 (0.73–0.84)	<0.001	0.95 (0.88–1.03)	0.3
Albumin, per 1–g/dL greater	0.24 (0.21–0.27)	<0.001	0.58 (0.47–0.72)	<0.001
CAD, vs none	0.94 (0.80–1.10)	0.4	1.10 (0.91–1.32)	0.3
CVD, vs none	0.94 (0.77–1.16)	0.6	1.13 (0.90–1.42)	0.3
PAD, vs none	1.09 (0.90–1.32)	0.4	1.00 (0.81–1.25)	0.9
Heart failure, vs none	1.33 (1.13–1.55)	<0.001	1.46 (1.22–1.75)	<0.001
SBP, per 10–mm Hg greater	1.16 (1.12–1.21)	<0.001	1.01 (0.96–1.05)	0.7
Statin, vs none	0.85 (0.73–1.00)	0.04	0.94 (0.79–1.12)	0.5
ACEi/ARB, vs none	0.86 (0.71–1.03)	0.1	0.97 (0.79–1.19)	0.8
LDL cholesterol, per 10–mg/dL greater	1.06 (1.04–1.08)	<0.001	1.01 (0.99–1.02)	0.6
Smoking				
Current	1.00 (reference)	–	1.00 (reference)	-
Former	0.64 (0.48–0.86)	0.004	0.84 (0.60–1.18)	0.3
Never	0.56 (0.41–0.75)	<0.001	0.83 (0.59–1.15)	0.3
Ferritin, per 100–µg/L greater	1.04 (1.03–1.06)	<0.001	1.01 (0.99–1.03)	0.3

	Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P
Iron Saturation, per 1% greater	1.02 (1.01–1.02)	<0.001	1.00 (1.00–1.01)	0.3
Iron therapy, vs none	1.08 (0.93–1.26)	0.3	1.07 (0.91–1.26)	0.4
Darbepoetin, vs placebo	1.01 (0.87–1.18)	0.9	1.08 (0.92–1.27)	0.4

Note: The multivariable models were adjusted for age, gender, race, eGFR, log-transformed urine PCR, history of acute kidney injury, duration of T2DM, HbA1c, retinopathy, insulin use, BMI, hemoglobin, serum albumin, coronary artery disease, cerebrovascular disease, peripheral arterial disease, heart failure, systolic blood pressure, low-density lipoprotein cholesterol concentration, statin therapy, ACEi or ARB therapy, smoking status, ferritin, transferrin saturation, iron therapy and randomized treatment assignment.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; PCR, protein-creatinine ratio; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin; HR, hazard ratio; BMI, body mass index; CAD, coronary artery disease; PAD, peripheral arterial disease; SBP, systolic blood pressure; LDL, low-density lipoprotein; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.