C-Reactive Protein and Risk of End-Stage Renal Disease – Results from TREAT (Trial to Reduce cardiovascular Events with Aranesp Therapy)

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Abstract Word Count: 269

Body Word Count: 3,205

Date: July 5th 2016

Running Title: CRP and risk of ESRD

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Keywords: C-Reactive Protein, CRP, ESRD, Type 2 Diabetes Mellitus, Chronic Kidney Disease, Anemia

ABSTRACT

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 and Participants

4,038 patients with type 2 diabetes, CKD and anemia in the TREAT study.

Predictor

Baseline serum concentrations of CRP.

Outcomes

The main outcomes are ESRD, doubling of serum creatinine, composite of ESRD/doubling of serum creatinine and the 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

The 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 mg/L; 668 patients developed ESRD, while 1270 developed the composite outcome of death or ESRD. Compared to patients with baseline CRP ≤3 mg/L, those with moderate-markedly elevated levels of CRP (≥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 non-significant, 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.

Introduction

Chronic kidney disease (CKD) affects approximately 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 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 a prior history of CV disease,[5,6] and in patients with CKD.[7,8] CKD is widely recognized as 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: www.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/1.73m^2 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. 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 endpoint, 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 that developed ESRD. Change in eGFR was calculated as a linear slope in mL/min/1.73m^2/year by plotting a line of best fit for all available eGFR measurements (3,544 individuals had at least two creatinine measurements from which the eGFR slope could be calculated; the mean number of measurements per patient was 5.1). In exploratory analyses, the association of baseline CRP with ESRD was determined for the sub-group of patients with CRP concentrations > 3mg/L.

Statistical Analyses

Continuous variables were examined graphically and recorded as means (± standard deviations) for normally distributed data, or medians (with interquartile ranges) 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, estimated GFR, log-transformed urine protein/creatinine ratio, history of acute renal failure (ARF), duration of T2DM at baseline, HbA1c, retinopathy, insulin use, body mass index, hemoglobin, serum albumin, coronary artery disease (angina, myocardial infarction, 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 concentration (LDL), 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 ≤3 mg/L were assumed to have a CRP=3 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 Gray[22] 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 (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, female, to have a history of ARF, peripheral arterial disease and heart failure, to be a current or former smoker, and to have higher LDL and ferritin concentrations. In addition, those in the higher CRP categories were also more likely to use insulin,

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 ACEi 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).

Association of Baseline CRP with Development of End-Stage Renal Disease

During 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 (HR 1.21; 95%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 [Table 2 and Table 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 (Supplementary Table A). Using a multivariable competing risk model (with death

as the competing outcome) gave similar findings, although the hazard ratio was somewhat attenuated (Table 2).

Similar trends were noted when sub-group analyses of individuals with baseline CRP >3mg/L (n=1,926) were performed (Supplementary Table B). 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 of Baseline CRP with Doubling of Serum Creatinine, and the composite of ESRD or Doubling of Serum Creatinine

During a median follow-up of 2.1 years the endpoint 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 (Supplementary Table A). 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 of Baseline CRP with Development of the Composite of Death or End-Stage Renal Disease, the 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 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 of Baseline CRP with Change in eGFR

The association of baseline categories of CRP with the change in eGFR (mL/min/1.73m^2/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 (-5.9 to 1.4) mL/min/1.73m^2/year. In unadjusted analyses, compared with individuals with normal baseline CRP (≤3 mg/L), there was no evidence for a significant difference in the change in eGFR in either the mildly elevated (difference of -0.3 mL/min/1.73m^2/year; 95%CI -1.1 to 0.5; P=0.50) or moderate-

markedly elevated (difference of 0.4 mL/min/1.73m^2/year; 95%CI -0.4 to 1.2; P=0.30) CRP categories. Similar findings were noted in the adjusted models: difference of -0.2 mL/min/1.73m^2/year (95%CI -1.0 to 0.5; P=0.56) for the mildly elevated CRP category and a difference of 0.5 mL/min/1.73m^2/year (95%CI -0.3 to 1.3; P=0.25) for the moderate-markedly elevated category, compared with individuals with a normal baseline CRP (≤3 mg/L; Supplementary Table C).

For those that ultimately went on to develop ESRD, the median [25th to 75th percentile] last measured eGFR was lower in patients with lower CRP measurements: 14.9 [11.6 to 20.9] mL/min/1.73m^2 for those with CRP ≤3 mg/L; 16.8 [12.7 to 23.3] mL/min/1.73m^2 for those with CRP >3 to <6.9 mg/L; and 17.1 [12.6 to 22.6] mL/min/1.73m^2 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 mg/L,106 days for those with CRP >3 to <6.9 mg/L and 96 days for those with CRP ≥6.9 mg/L (P for trend=0.89).

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.

CRP (MW ~23 kDa) is a member of the pentraxin protein family, which is intimately involved in the activity of the innate immune system.[23] CRP 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 myocardial infarction 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 renal 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 renal 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 four-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) study: baseline CRP was significantly associated with decline in eGFR using cystatin C, but not when using serum creatinine (using the CKD-EPI equation).[13] Indeed, some have questioned the accuracy of estimating equations for GFR in patients with

T2DM,[26] raising further concerns in relation to 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 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 renal 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 renal replacement therapy. 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 moderate-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 endpoint of death or ESRD.

The major strengths of our study are the large number of independently adjudicated clinical endpoints 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 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 >3mg/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, remains present. 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 death/ESRD 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.

Acknowledgements and Disclosures

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; the authors designed and conducted all analyses described herein and were solely responsible for the drafting and editing of this manuscript.

Contributions: Research idea and study design: FMC, BC, MAP; data acquisition: EAB, KUE, 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 (and, if relevant, registered) have been explained.

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Table 1. Baseline Characteristics of the Cohort According to Categories of C-Reactive Protein

	Baseline CRP			
	Normal (≤3 mg/L)	**Mildly Elevated (>3.0 to <6.9 mg/L)**	**Moderate-markedly Elevated (≥6.9 mg/L)**	**P[a]**
n	2,112	953	973	
CRP	NA	4.5 (3.7-5.4)	13.3 (9.0-23.5)	
Age (years)	67.8 ±10.7	67.1 ±10.6	66.5 ±10.6	0.001
Male (%)	44.6	40.9	40.5	0.02
Race (%)				0.17
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 Pr/Cr ratio	0.4 (0.1-1.8)	0.5 (0.2-1.9)	0.4 (0.1-1.9)	0.11
History of ARF (%)	7.7	10.9	13.2	<0.001
Duration of T2DM (years)	15.5 (8.5-21.6)	15.6 (8.6-21.9)	15.0 (7.5-21.8)	0.24
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	0.23
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	0.15
CVD (%)	17.4	16.5	19.2	0.30
PAD (%)	18.1	20.4	23.3	<0.001
HF (%)	29.7	36.7	38.0	<0.001

SBP (mmHg)	136.0 ±18.7	137.0 ±18.6	134.6 ±18.9	0.13
LDL (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 (mcg/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
Iron therapy (%)	42.9	42.0	48.8	0.01
Treatment (Darbepoetin vs. Placebo, %)	50.0	50.6	48.7	0.58

Values for continuous variables are given as mean ±standard deviation or median (25^{th} – 75^{th} percentile).

Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Pr/Cr, protein to creatinine ratio; ARF, acute renal failure; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin; BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; HF, heart failure; SBP, systolic blood pressure; LDL, low-density lipoprotein; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[a] P values refer to a test for trend across increasing category of CRP concentration.

Table 2. Association of Category of Baseline C-Reactive Protein with Time to ESRD, Doubling of Serum Creatinine, Composite of ESRD of Doubling of Serum Creatinine, Composite of ESRD or Death, CV Composite, and Death alone

	Hazard Ratio (95% CI) for ESRD			**P for trend**
Events/Total	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (668/4,038)	Ref	1.21 (1.01 - 1.46)	1.37 (1.14 – 1.64)	P=0.001
Adjusted (598/3,642)	Ref	1.08 (0.88 – 1.33)	1.32 (1.07 – 1.63)	P=0.01
Competing Risk (598/3,642)	Ref	1.01 (0.81-1.25)	1.23 (0.99-1.53)	P=0.09
	Hazard Ratio (95% CI) for Doubling of Serum Creatinine			
Events/Total	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (428/3,654)	Ref	0.96 (0.76 - 1.22)	1.06 (0.84 – 1.35)	P=0.72
Adjusted (367/3,305)	Ref	0.90 (0.69 – 1.18)	0.94 (0.71 – 1.25)	P=0.59
Competing Risk (367/3,305)	Ref	0.86 (0.65-1.14)	0.93 (0.69-1.25)	P=0.51
	Hazard Ratio (95% CI) for Composite of ESRD/Doubling of Serum Creatinine			
Events/Total	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (871/4,038)	Ref	1.16 (0.99 - 1.37)	1.28 (1.09 – 1.51)	P=0.002
Adjusted (769/3,642)	Ref	1.05 (0.87 – 1.26)	1.17 (0.97 – 1.42)	P=0.11
Competing Risk (769/3,642)	Ref	0.99 (0.82-1.20)	1.12 (0.92-1.36)	P=0.32

	Hazard Ratio (95% CI) for Death or ESRD			
	CRP ≤3.0 mg/L	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (n=1,270/ 4,038)	Ref	1.21 (1.05 - 1.39)	1.57 (1.38 – 1.79)	P<0.001
Adjusted (n=1,139/ 3,642)	Ref	1.11 (0.96 – 1.29)	1.41 (1.21 – 1.64)	P<0.001
	Hazard Ratio (95% CI) for CV Composite Outcome*			
	CRP ≤3.0 mg/L	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (n=1,234/ 4,038)	Ref	1.26 (1.09 - 1.45)	1.77 (1.55 – 2.02)	P<0.001
Adjusted (n=1,111/ 3,642)	Ref	1.16 (0.99 – 1.35)	1.55 (1.34 – 1.81)	P<0.001
	Hazard Ratio (95% CI) for Death From Any Cause			
	CRP ≤3.0 mg/L	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (n=807/ 4,038)	Ref	1.20 (1.00 – 1.43)	1.85 (1.57 – 2.16)	P<0.001
Adjusted (n=734/ 3,642)	Ref	1.15 (0.95 – 1.39)	1.59 (1.32 – 1.91)	P<0.001

The multivariable models were adjusted for age, gender, race, estimated GFR, log-transformed urine protein/creatinine ratio, history of acute renal failure, 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. Multivariable adjusted competing risk models were fit, with death as

the competing outcome, for the endpoints of ESRD, doubling of serum creatinine and the composite of ESRD/doubling of serum creatinine.

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

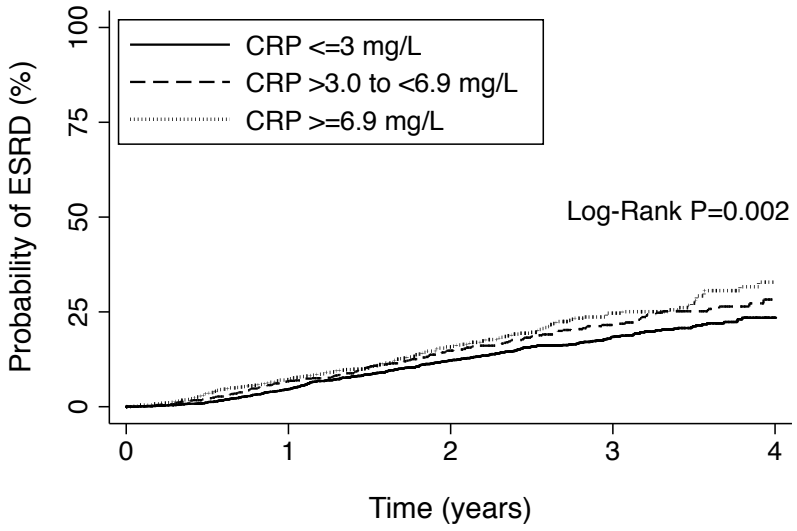
Table 3. Unadjusted and Multivariable adjusted associations of Baseline Factors with Development of End-Stage Renal Disease.

	Unadjusted			Adjusted	
	Hazard Ratio (95% CI)	**P**		**Hazard Ratio (95% CI)**	**P**
CRP (mg/L)					
≤3.0	Ref	-		Ref	-
>3.0 to <6.9	1.21 (1.01-1.46)	0.04		1.08 (0.88-1.33)	0.45
≥6.9	1.37 (1.14-1.64)	0.001		1.32 (1.07-1.63)	0.01
Age (/10 years)	0.71 (0.67-0.77)	<0.001		0.91 (0.83-1.00)	0.04
Male (vs. female)	1.75 (1.51-2.04)	<0.001		1.84 (1.53-2.20)	<0.001
Race					
White	Ref	-		Ref	-
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)	0.29
Other	1.13 (0.71-1.82)	0.71		0.93 (0.57-1.53)	0.77
eGFR (/10mL/min/1.73m^2 increase)	0.40 (0.36-0.44)	<0.001		0.46 (0.41-0.50)	<0.001
Log Urine Pr/Cr ratio (/unit)	2.04 (1.93-2.15)	<0.001		1.77 (1.63-1.92)	<0.001
History of ARF (vs. none)	1.63 (1.30-2.03)	<0.001		1.42 (1.12-1.81)	0.004
Duration of T2DM (/12 months)	1.01 (1.01-1.02)	0.001		1.01 (1.00-1.02)	0.03
HbA1c (/%)	1.10 (1.05-1.15)	<0.001		0.98 (0.93-1.04)	0.50
Retinopathy (vs. none)	1.83 (1.56-2.13)	<0.001		1.05 (0.87-1.26)	0.61
Insulin use (vs none)	1.55 (1.33-1.81)	<0.001		1.11 (0.92-1.33)	0.27
BMI (/10kg/m2)	0.85 (0.77-0.95)	0.01		0.84 (0.73-0.95)	0.01
Hemoglobin (/g/dL)	0.78 (0.73-0.84)	<0.001		0.95 (0.88-1.03)	0.25

Albumin (/g/dL)	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)	0.42		1.10 (0.91-1.32)	0.34
CVD (vs. none)	0.94 (0.77-1.16)	0.59		1.13 (0.90-1.42)	0.28
PAD (vs. none)	1.09 (0.90-1.32)	0.38		1.00 (0.81-1.25)	0.98
HF (vs. none)	1.33 (1.13-1.55)	<0.001		1.46 (1.22-1.75)	<0.001
SBP (/10 mmHg)	1.16 (1.12-1.21)	<0.001		1.01 (0.96-1.05)	0.73
Statin (vs. none)	0.85 (0.73-1.00)	0.04		0.94 (0.79-1.12)	0.46
ACEi/ARB (vs. none)	0.86 (0.71-1.03)	0.10		0.97 (0.79-1.19)	0.80
LDL (/10mg/dL)	1.06 (1.04-1.08)	<0.001		1.01 (0.99-1.02)	0.61
Smoking					
Current	Ref	-		Ref	-
Former	0.64 (0.48-0.86)	0.004		0.84 (0.60-1.18)	0.31
Never	0.56 (0.41-0.75)	<0.001		0.83 (0.59-1.15)	0.26
Ferritin (/100mcg/L)	1.04 (1.03-1.06)	<0.001		1.01 (0.99-1.03)	0.27
Iron Saturation (/%)	1.02 (1.01-1.02)	<0.001		1.00 (1.00-1.01)	0.33
Iron therapy (vs. none)	1.08 (0.93-1.26)	0.33		1.07 (0.91-1.26)	0.42
Darbepoetin (vs. placebo)	1.01 (0.87-1.18)	0.90		1.08 (0.92-1.27)	0.36

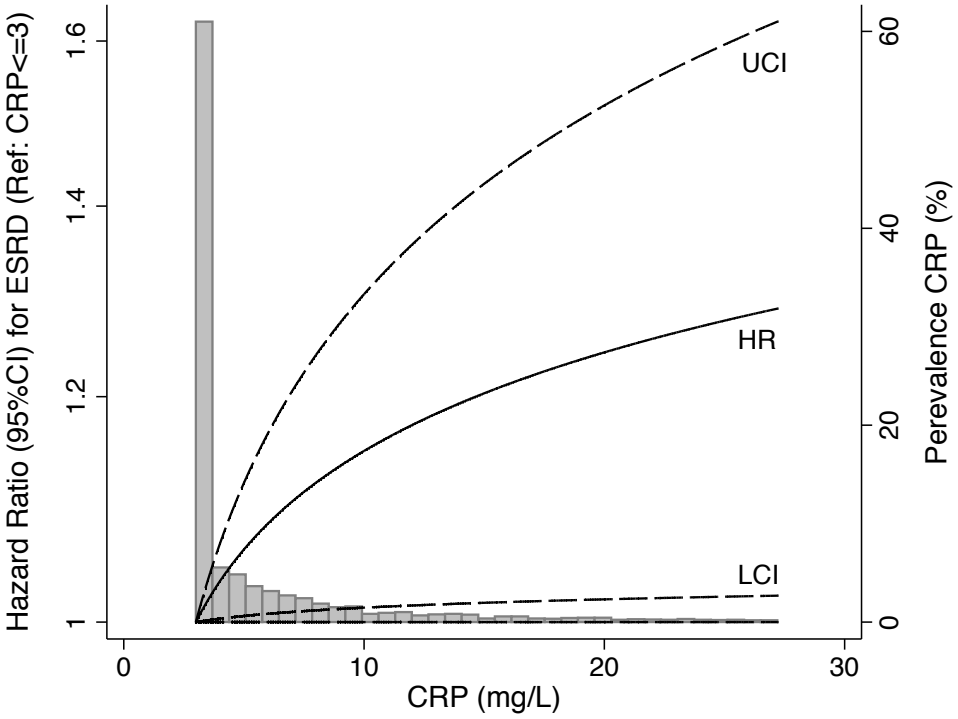
The multivariable models were adjusted for age, gender, race, estimated GFR, log-transformed urine protein/creatinine ratio, history of acute renal failure, duration of T2DM, HbA1c, retinopathy, insulin use, body mass index, hemoglobin, serum albumin, coronary artery disease, cerebrovascular disease, 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.

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



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 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 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 renal failure, 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.



Supplementary Table A. Association of Category of Baseline C-Reactive Protein with Time to ESRD, Doubling of Serum Creatinine, Composite of ESRD of Doubling of Serum Creatinine, Composite of ESRD or Death, CV Composite, and Death alone

	Hazard Ratio (95% CI) for ESRD			**P for trend**
Model (Events/Total)	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (668/4,038)	Ref	1.21 (1.01 - 1.46)	1.37 (1.14 – 1.64)	P=0.001
Adjusted (598/3,642)	Ref	1.08 (0.88 – 1.33)	1.32 (1.07 – 1.63)	P=0.01
Adjusted non-PH[a] (598/3,642)	Ref	1.09 (0.89-1.34)	1.31 (1.06-1.63)	P=0.01
	Hazard Ratio (95% CI) for Doubling of Serum Creatinine			
Model (Events/Total)	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (428/3,654)	Ref	0.96 (0.76 - 1.22)	1.06 (0.84 – 1.35)	P=0.72
Adjusted (367/3,305)	Ref	0.90 (0.69 – 1.18)	0.94 (0.71 – 1.25)	P=0.84
Adjusted non-PH[b] (367/3,305)	Ref	0.91 (0.69-1.19)	0.95 (0.71-1.26)	P=0.62
	Hazard Ratio (95% CI) for ESRD/Doubling of Serum Creatinine			
Model (Events/Total)	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (871/4,038)	Ref	1.16 (0.99 - 1.37)	1.28 (1.09 – 1.51)	P=0.002
Adjusted (769/3,642)	Ref	1.05 (0.87 – 1.26)	1.17 (0.97 – 1.42)	P=0.11
Adjusted non-PH[c] (769/3,642)	Ref	1.04 (0.87-1.25)	1.18 (0.97-1.42)	P=0.10

	Hazard Ratio (95% CI) for Death or ESRD			
Model (Events/Total)	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (1,270/ 4,038)	Ref	1.21 (1.05 - 1.39)	1.57 (1.38 – 1.79)	P<0.001
Adjusted (1,139/ 3,642)	Ref	1.11 (0.96 – 1.29)	1.41 (1.21 – 1.64)	P<0.001
Adjusted non-PH[d] (1,139/ 3,642)	Ref	1.12 (0.96-1.30)	1.40 (1.20-1.63)	P<0.001
	Hazard Ratio (95% CI) for CV Composite Outcome*			
Model (Events/Total)	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (1,234/ 4,038)	Ref	1.26 (1.09 - 1.45)	1.77 (1.55 – 2.02)	P<0.001
Adjusted (1,111/ 3,642)	Ref	1.16 (0.99 – 1.35)	1.55 (1.34 – 1.81)	P<0.001
Adjusted non-PH[e] (1,111/ 3,642)	Ref	1.16 (0.99-1.35)	1.54 (1.33-1.80)	P<0.001
	Hazard Ratio (95% CI) for Death From Any Cause			
Model (Events/Total)	**CRP ≤3.0 mg/L**	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (807/ 4,038)	Ref	1.20 (1.00 – 1.43)	1.85 (1.57 – 2.16)	P<0.001
Adjusted (734/ 3,642)	Ref	1.15 (0.95 – 1.39)	1.59 (1.32 – 1.91)	P<0.001
Adjusted non-PH[f]	Ref	1.15 (0.95-1.39)	1.58 (1.32-1.90)	P<0.001

(734/ 3,642)				

The multivariable models were adjusted for age, gender, race, estimated GFR, log-transformed urine protein/creatinine ratio, history of acute renal failure, 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.
*CV composite included death from any cause, nonfatal MI, stroke, heart failure or hospitalization for myocardial ischemia

In the case of violations of the proportional hazards assumption, time varying coefficients were included in the corresponding multivariable models as follows: [a] race, duration of T2DM, HbA1c, retinopathy, body mass index, estimated GFR, log-transformed urine protein/creatinine ratio, albumin, peripheral arterial disease and low-density lipoprotein; [b] HbA1c and estimated GFR; [c] HbA1c, insulin use, body mass index, albumin and low density lipoprotein; [d] race, log-transformed urine protein/creatinine ratio, albumin, peripheral arterial disease and low-density lipoprotein; [e] age, race, treatment assignment, log-transformed urine protein/creatinine ratio, albumin and ACEi/ARB use; [f] log-transformed urine protein/creatinine ratio and albumin.

Supplementary Table B. Association of Tertiles of Baseline C-Reactive Protein with Time to ESRD in Patients with Baseline CRP Above the Lower Limit of Detection (>3 mg/L)

	Hazard Ratio (95% CI) for ESRD			**P for trend**
Model (Events/Total)	**Lowest Tertile**	**Middle Tertile**	**Highest Tertile**	
Adjusted (308/1,710)	Ref	0.99 (0.73 - 1.33)	1.32 (0.98 – 1.77)	P=0.07

For the purposes of this exploratory analysis only patients with baseline CRP concentrations above the lower limit of detection were included (>3 mg/L). The multivariable model was adjusted for age, gender, race, estimated GFR, log-transformed urine protein/creatinine ratio, history of acute renal failure, 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.

Supplementary Table C. Difference in eGFR slope according to category of baseline C-Reactive Protein

	Difference in eGFR (95% CI) in mL/min/1.73m^2/year			**P for trend**
	CRP ≤3.0 mg/L	**CRP >3.0 to <6.9 mg/L**	**CRP ≥6.9 mg/L**	
Unadjusted (n=3,544)	Ref	-0.3 (-1.1 to 0.5)	0.4 (-0.4 to 1.2)	P=0.42
Adjusted (n=3,228)	Ref	-0.2 (-1.0 to 0.5)	0.5 (-0.3 to 1.3)	P=0.36

The multivariable models were adjusted for age, gender, race, baseline estimated GFR, log-transformed urine protein/creatinine ratio, history of acute renal failure, 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.