ORIGINAL RESEARCH

Coronary Artery Disease Is a Predictor of Progression to Dialysis in Patients With Chronic Kidney Disease, Type 2 Diabetes Mellitus, and Anemia: An Analysis of the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT)

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***Background*—**Although clear evidence shows that chronic kidney disease is a predictor of cardiovascular events, death, and accelerated coronary artery disease (CAD) progression, it remains unknown whether CAD is a predictor of progression of chronic kidney disease to end-stage renal disease. We sought to assess whether CAD adds prognostic information to established predictors of progression to dialysis in patients with chronic kidney disease, diabetes, and anemia.

***Methods and Results*—**Using the previously described Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) population, we compared baseline characteristics of patients with and without CAD. Cox proportional hazards models were used to assess the association between CAD and the outcomes of end-stage renal disease and the composite of death or end-stage renal disease. Of the 4038 patients, 1791 had a history of known CAD. These patients were older (mean age 70 versus 65 years, $P<0.001$) and more likely to have other cardiovascular disease. CAD patients were less likely to have marked proteinuria (29% versus 39%, $P<0.001$), but there was no significant difference in estimated glomerular filtration rate between the 2 groups. After adjusting for age, sex, race, estimated glomerular filtration rate, proteinuria, treatment group, and 14 other renal risk factors, patients with CAD were significantly more likely to progress to end-stage renal disease (adjusted hazard ratio 1.20 [95% CI 1.01–1.42], $P=0.04$) and to have the composite of death or end-stage renal disease (adjusted hazard ratio 1.15 [95% CI 1.01–1.30], $P=0.03$).

***Conclusions*—**In patients with chronic kidney disease, diabetes, and anemia, a history of CAD is an independent predictor of progression to dialysis. In patients with diabetic nephropathy, a history of CAD contributes important prognostic information to traditional risk factors for worsening renal disease. **(*J Am Heart Assoc*. 2016;5:e002850 doi: 10.1161/JAHA.115.002850)**

Key Words: coronary disease • diabetes mellitus • kidney

Cardiovascular disease is the leading cause of death in patients with type 2 diabetes mellitus (T2DM)[1,2] and in those with chronic kidney disease (CKD).[3] T2DM and CKD are known independent risk factors for cardiovascular death, and patients with CKD are more likely to die from cardiovascular causes than to progress to end-stage renal disease (ESRD).[3]

The association between kidney disease and poor cardiovascular outcomes has been demonstrated in several populations,[4–6] and a meta-analysis showed that patients with an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m^2 had higher all-cause and cardiovascular mortality compared with patients with an eGFR >90 mL/min per

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1.73 m^2. Furthermore, mortality increased with each incremental decrease in eGFR.[4]

Diabetes increases the risk of cardiovascular disease including coronary artery disease (CAD), stroke, peripheral artery disease, and heart failure (HF).[7] Several studies have demonstrated that having diabetes alone is a cardiovascular risk equivalent in terms of cardiovascular event rates.[8,9] In addition, diabetic patients with evidence of microalbuminuria have a 2-fold increased risk of cardiovascular death, even in the absence of nephropathy.[10] Patients with CKD also have higher rates of stroke, HF, and myocardial infarction[3] as well as cardiovascular death independent of diabetes status.[11] The National Kidney Foundation task force recognizes that patients with both T2DM and CKD are at the highest risk for the development of cardiovascular disease[6] and advocates aggressive cardiovascular risk management of these patients.

Although clear evidence shows that CKD is a predictor of cardiovascular events and death[3,11] and is associated with accelerated CAD progression,[12] the reverse has not been examined. Specifically, it is not known whether CAD is an independent predictor of progression of CKD to ESRD in patients with T2DM. We compared renal outcomes and mortality in patients with diabetic nephropathy in the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) according to history of known CAD.[13]

Methods

TREAT was a randomized placebo-controlled trial of darbepoetin alfa treatment in 4038 patients with CKD (GFR 20–60 mL/min per 1.73 m^2), anemia (hemoglobin ≤11.0 g/dL), and T2DM. Patients were excluded if they had a recent cardiovascular event or a history of renal transplantation. Patients were randomized to placebo or darbepoetin with dose adjusted to a hemoglobin level of 13.0 g/dL. Although there was a significant difference in the secondary outcome of stroke, there were no significant differences between the 2 groups in terms of the primary end points: time to the composite of all-cause mortality, stroke, HF, myocardial infarction, or hospitalization for acute myocardial ischemia or the time to the composite of ESRD or all-cause mortality.[13] This study was approved by an institutional review committee, and the participants gave informed consent to participate in TREAT.

Statistical Analysis

Our primary predictor was a history of known CAD, defined as a self-reported history of CAD with or without a history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention, as described previously.[14] We assessed whether a history of CAD was associated with the risk of ESRD, as defined in TREAT.[13] Because patients with CAD have a high propensity for death, we also assessed the association of CAD with the composite end point of ESRD or death. In addition, we examined the association of CAD with cardiovascular and noncardiovascular death. A total of 4038 patients were included in this analysis. Variables that were collected in the baseline case report form were used, excluding those with missing data, resulting in 4010 patients in the renal analysis (model 1) and 3877 patients in the death (all-cause, cardiovascular, and noncardiovascular) analysis (model 2).

Baseline characteristics were compared for the groups with known CAD and no known CAD. For continuous variables, a Student *t* test and a Wilcoxon rank sum test were used to compare normal and non-normal variables, respectively. For categorical variables, a chi-square test was used.

Cox proportional hazards models were used to examine the relationship between the predictor of interest and the outcomes. We used previously published models for the prediction of renal outcomes[15] (model 1) and death[16] (model 2), with some revisions. Model 2, which was originally used to predict cardiovascular outcomes and death, included a covariate for coronary heart disease.[16] We excluded this covariate from the current analysis because of overlap with our primary predictor. Treatment group (darbepoetin versus placebo) was included in model 2,[16] as originally described, and added to model 1.[15] CAD was included in all models, and duration of T2DM and systolic blood pressure were added to model 1. The urine protein/creatinine ratio and ferritin were log transformed, and C-reactive protein was included as a categorical variable in the models.[15,16]

Within each model, the statistical strength of the predictive contribution of the covariates to the outcomes of interest was expressed as the chi-square statistic 2-sided *P* value. Stata/SE version 11.1 (StataCorp LP) was used for all analyses.

Results

Of the 4038 patients included in these analyses, 1791 (44%) had known CAD. Baseline characteristics of those with and without known CAD are shown in Table 1. Patients with known CAD were older, more likely to be male, and more likely than the patients without known CAD to be of white race. As expected, patients with known CAD were significantly more likely to have a history of cardiovascular as well as cerebrovascular disease. Patients with known CAD had significantly lower blood pressure (mean systolic blood pressure 134 versus 137 mm Hg; $P<0.001$), lower hemoglobin A1c (7.2 versus 7.4; $P<0.001$), and a lower mean low-density lipoprotein level (86.3 versus

Table 1. Baseline Characteristics of Patients With and Without Known CAD

Variable	Known CAD (n=1791)	No Known CAD (n=2247)	*P* Value
Demographics and exam			
Age (y), mean (SD)	70 (9.0)	65 (11.0)	<0.001
Male sex, n (%)	874 (48.8)	852 (37.9)	<0.001
Race, n (%)			<0.001
White	1301 (72.6)	1269 (56.5)	
Black	292 (16.3)	523 (23.3)	
Other	198 (11.1)	455 (20.3)	
Smoking history			<0.001
Never	901 (50.3)	1366 (60.8)	
Current	79 (4.4)	125 (5.6)	
Past	811 (45.3)	756 (33.6)	
Blood pressure (mm Hg), mean (SD)			
Systolic	134 (19.0)	137 (19.0)	<0.001
Diastolic	71 (11.0)	73 (11.0)	<0.001
BMI (kg/m^2), mean (SD)	31.4 (6.9)	31.6 (7.8)	0.30
Medical history, n (%)			
Cardiovascular disease			
Angina	664 (37.1)	82 (3.7)	<0.001
MI	741 (41.4)	0	N/A
HF	962 (53.7)	385 (17.1)	<0.001
CABG	571 (31.9)	0	N/A
PCI	367 (20.5)	0	N/A
Valvular heart disease	243 (13.6)	105 (4.7)	<0.001
AICD	53 (3.0)	4 (0.2)	<0.001
Atrial fibrillation	309 (17.3)	116 (5.2)	<0.001
Cerebrovascular disease			
Stroke	276 (15.4)	171 (7.6)	<0.001
TIA	162 (9.0)	103 (4.6)	<0.001
Peripheral arterial disease	499 (27.9)	280 (12.5)	<0.001
History of hypertension	1698 (94.8)	2033 (90.5)	<0.001
History of AKI	218 (12.2)	177 (7.9)	<0.001
Duration of diabetes (years), median (IQR)	15.9 (8.6, 22.7)	15.1 (8.1, 21.1)	0.001
Laboratory indices			
Ferritin (μg/L), median (IQR)	132 (68, 253)	134 (66, 261)	0.90
Transferrin saturation, mean (SD)	0.24 (0.10)	0.24 (0.09)	0.35
BUN (mg/dL), mean (SD)	42.9 (17.6)	42.0 (16.6)	0.11
eGFR (/10 mL/min/1.73 m^2), mean (SD)	35.2 (11.7)	35.1 (12.0)	0.93
Protein/creatinine ratio (g/g), median (IQR)	0.3 (0.1, 1.3)	0.5 (0.1, 2.3)	<0.001
Proteinuria (protein/creatinine ratio >1 g/g), n (%)	523 (29.2)	874 (38.9)	<0.001
Albumin (g/dL), mean (SD)	4.0 (0.4)	3.9 (0.5)	<0.001
Hemoglobin (g/dL), mean (SD)	10.4 (1.0)	10.3 (1.0)	0.11
Hemoglobin A1c, mean (SD)	7.2 (1.4)	7.4 (1.6)	<0.001

Continued

Table 1. Continued

Variable	Known CAD (n=1791)	No Known CAD (n=2247)	*P* Value
Total cholesterol (mg/dL), mean (SD)	170.6 (52.2)	182.8 (52.0)	<0.001
LDL (mg/dL), mean (SD)	86.3 (38.2)	95.4 (40.7)	<0.001
HDL (mg/dL), mean (SD)	46.3 (13.8)	49.8 (15.7)	<0.001
Triglycerides (mg/dL), median (IQR)	153 (108, 227)	156 (111, 233)	0.19
CRP category, n (%)			0.02
≤3.0 mg/dL	894 (49.9)	1218 (54.2)	
>3.0 to <6.6 mg/dL	426 (23.8)	480 (21.4)	
≥6.6 mg/dL	471 (26.3)	549 (24.4)	
Medications, n (%)			
Insulin	896 (50.3)	1093 (48.6)	0.38
Oral hypoglycemic (oral antidiabetic agents)	1002 (55.9)	1291 (57.5)	0.34
ACEI or ARB	1388 (77.5)	1835 (81.7)	<0.001
Beta blocker	1131 (63.1)	859 (38.2)	<0.001
Aldosterone receptor antagonist	139 (7.8)	70 (3.1)	<0.001
Statin	1200 (67.0)	1164 (51.8)	<0.001
Aspirin	934 (52.1)	779 (34.7)	<0.001
Oral iron	1211 (67.7)	1388 (61.9)	<0.001
Treatment with darbepoetin, n (%)	870 (48.6)	1142 (50.8)	0.16

ACEI indicates angiotensin converting enzyme inhibitor; AICD, automatic implantable cardioverter defibrillator; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; IQR, interquartile range; LDL, low-density lipoprotein; MI, myocardial infarction; N/A, not available; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

95.4 mg/dL; $P<0.001$) than the patients without known CAD. They were more likely to be taking an aldosterone receptor antagonist, β-blocker, or statin but less likely to be on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patients with known CAD were less likely to have marked proteinuria, defined as a urine protein/creatinine ratio >1 (29% versus 39%; $P<0.001$), but there was no significant difference in eGFR between the 2 groups ($P=0.93$). The 2 groups did not differ in terms of treatment with the original study drug, darbepoetin ($P=0.16$).

Renal Outcomes

Of the 4038 patients analyzed, 668 (17%) developed ESRD and 1270 (31%) had the composite of death or ESRD. Overall, 293 (16.4%) of the patients with known CAD and 375 (16.7%) of those without known CAD developed ESRD. CAD was not significantly associated with progression to ESRD (unadjusted hazard ratio [HR] 1.03, 95% CI 0.89–1.21) on univariate analysis; however, after adjusting for the covariates in model 1, a history of known CAD was significantly associated with progression to ESRD (adjusted HR 1.20, 95% CI 1.01–1.42) (Table 2). A strong confounder in model 1 was the log urine protein/creatinine ratio, which was significantly higher in the patients without known CAD (Table 1). After adjustment for this covariate alone, CAD emerged as a significant predictor of ESRD (adjusted HR 1.34, $P<0.001$).

ESRD or death occurred in 634 (35%) of patients with known CAD and 636 (28%) of those without known CAD, corresponding to a significant increase in risk for the CAD patients of either progressing to ESRD or dying (unadjusted HR 1.32, 95% CI 1.18–1.47) (Figure). After adjusting for the covariates in model 1, a history of known CAD remained a significant predictor of the composite renal outcome (adjusted HR 1.15, 95% CI 1.01–1.30) (Table 3).

All-Cause, Cardiovascular, and Noncardiovascular Death

CAD was found to be a significant predictor of all-cause death (unadjusted HR 1.61, 95% CI 1.40–1.85), which occurred in 444 (25%) of the patients with known CAD and 363 (16%) of those without known CAD. After adjusting for the variables in model 2, CAD was no longer a significant independent predictor of mortality (adjusted HR 1.02, 95% CI 0.87–1.20). A history of HF appeared to be a strong confounder in this model. With exclusion of this single covariate from the model, CAD remained a significant predictor of all-cause death

Table 2. Multivariable Models for Renal Outcomes

	ESRD		ESRD or Death	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Known CAD	1.20 (1.01–1.42)	0.041	1.15 (1.01–1.30)	0.031
Age	1.00 (0.99–1.00)	0.432	1.02 (1.01–1.02)	<0.001
Male sex	1.69 (1.44–1.99)	<0.001	1.42 (1.26–1.59)	<0.001
Race (referent: white)				
Black	1.72 (1.43–2.08)	<0.001	1.27 (1.10–1.47)	0.001
Other	1.00 (0.81–1.25)	0.966	0.92 (0.77–1.08)	0.312
BMI, per 10 kg/m^2	0.81 (0.71–0.92)	0.001	0.80 (0.74–0.88)	<0.001
Insulin use	1.15 (0.97–1.36)	0.112	1.14 (1.00–1.29)	0.042
eGFR, per 10 mL/min/1.73 m^2	0.52 (0.47–0.58)	<0.001	0.77 (0.71–0.82)	<0.001
BUN, per 10 mg/dL	1.12 (1.06–1.17)	<0.001	1.08 (1.04–1.13)	<0.001
Log (UPCR)	1.87 (1.73–2.02)	<0.001	1.42 (1.35–1.49)	<0.001
Albumin, per 1 g/dL	0.70 (0.58–0.84)	<0.001	0.61 (0.53–0.70)	<0.001
Prior stroke	1.17 (0.91–1.50)	0.211	1.30 (1.11–1.53)	0.002
Prior PAD	1.10 (0.90–1.35)	0.355	1.13 (0.98–1.30)	0.084
Prior HF	1.30 (1.09–1.56)	0.004	1.49 (1.31–1.69)	<0.001
History of arrhythmia	1.17 (0.93–1.48)	0.189	1.27 (1.09–1.48)	0.002
Hemoglobin, per 1 g/dL	0.95 (0.88–1.03)	0.188	0.95 (0.90–1.00)	0.073
Log (ferritin)	1.10 (1.01–1.19)	0.030	1.04 (0.98–1.11)	0.202
CRP (referent: ≤3.0 mg/L)				
CRP 3.1–6.5 mg/L	1.13 (0.93–1.37)	0.229	1.16 (1.00–1.34)	0.044
CRP ≥6.6 mg/L	1.31 (1.08–1.58)	0.006	1.42 (1.24–1.63)	<0.001
History of acute kidney injury	1.32 (1.05–1.66)	0.019	1.22 (1.03–1.45)	0.023
Systolic blood pressure	1.00 (1.00–1.01)	0.248	1.00 (1.00–1.00)	0.763
Duration of T2DM	1.00 (1.00–1.00)	0.109	1.00 (1.00–1.00)	0.835
Treatment with darbepoetin	1.08 (0.93–1.26)	0.321	1.12 (1.00–1.25)	0.044

BMI indicates body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus; UPCR, urine protein/creatinine ratio.

(adjusted HR 1.18, *P*=0.035). Similarly, CAD was a significant predictor of cardiovascular death (unadjusted HR 1.91, 95% CI 1.60–2.28); however, it became nonsignificant after adjustment using model 2 (adjusted HR 1.21, 95% CI 0.99–1.48). Again, a history of HF was a strong confounder in this model.

Sensitivity Analysis: Angina

To assess whether our results changed significantly with inclusion of these patients, we reanalyzed the models after including 82 patients from TREAT who gave a self-reported history of angina without a history of CAD, myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. Inclusion of these patients slightly strengthened the relationship between CAD and progression to ESRD (adjusted HR 1.22, 95% CI 1.03–1.45) and the renal composite outcome (adjusted HR 1.17, 95% CI 1.03–1.32) (Tables 4 and 5).

Discussion

We found that in patients with CKD, T2DM, and anemia, the presence of known CAD was independently predictive of progression of CKD to ESRD. Contrary to previous studies which suggest an association between proteinuria and CAD,[17,18] in our study patients with CAD had significantly less proteinuria than those without CAD. It is not clear why these patients had less proteinuria despite taking fewer angiotensin receptor blockers or angiotensin-converting enzyme inhibitors. One possibility is that the patients with CAD were more likely to

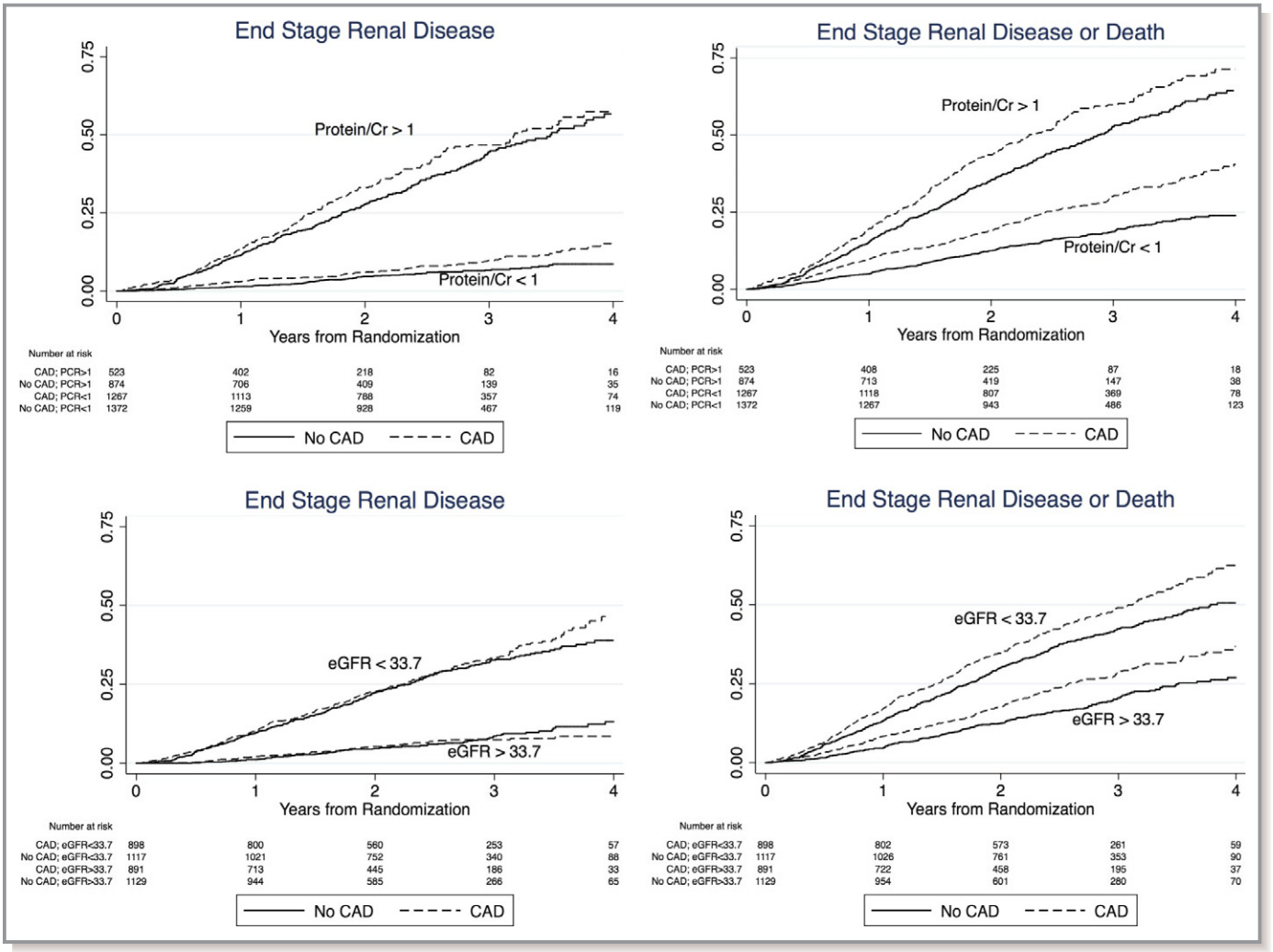

Figure. The association between CAD, proteinuria, eGFR and renal outcomes. A history of known CAD contributes to proteinuria and eGFR as a risk factor for progression to ESRD and ESRD or death. Proteinuria is represented as a categorical variable divided at a PCR of 1. eGFR is represented as a categorical variable divided at the median, 33.8 mL/min per 1.73 m^2. An interaction term for CAD and proteinuria was added to the final renal multivariable model and found to be nonsignificant for the outcomes of ESRD (P=0.23) and ESRD or death (P=0.10). Similarly, the interaction terms for eGFR and CAD were found to be nonsignificant in the final multivariable model for both outcomes (ESRD, P=0.44; ESRD or death, P=0.59). CAD indicates coronary artery disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PCR, protein/creatinine ratio.

be of white race, and proteinuria occurs more frequently in non-whites.[19,20] Another reason may be that the patients with CAD were on more aldosterone receptor antagonists, which have been shown to be associated with a decrease in proteinuria.[21] Despite having less proteinuria, the patients with CAD had a higher propensity for progression to dialysis after adjusting for risk factors for dialysis including proteinuria and eGFR. These results suggest that in patients with CKD, a history of CAD can augment the prognostic information provided by traditional risk factors for renal disease progression.

According to the US Renal Data System 2013 Annual Data Report, the incidence of ESRD in 2011 was 357 per 1 million population, and >100 000 patients started therapy for ESRD in 2011 alone, representing a 1.5% increase from the previous year.[22] Patients on hemodialysis have twice the mortality rate of the general population with diabetes, CAD, cancer, HF, or stroke and 10 times the mortality rate of similarly aged patients without CKD.[22] Overall, 40% of patients with T2DM develop CKD, and T2DM is the most frequent cause of ESRD.[23] In addition, evidence shows that anemia is a risk factor that may contribute to the progression of diabetic nephropathy to ESRD.[24] Because progression of renal injury in patients with CKD with or without diabetes is quite variable, early identification of risk factors that contribute to renal loss can be important for risk stratification and treatment.[23,25]

Table 3. Association Between Known CAD and Outcomes

Outcome	Participants With Event, n (%), Incidence Rate Per 100 Person-Years		Unadjusted HR (95% CI) *P* Value	Adjusted HR (95% CI) *P* Value
	Known CAD (n=1791)	No Known CAD (n=2247)		
Model 1*				
ESRD	293 (16.4%) 7.5/100	375 (16.7%) 7.3/100	1.03 (0.89–1.21) 0.66	1.20 (1.01–1.42) 0.04
Death or ESRD	634 (35.4%) 15.9/100	636 (28.3%) 12.1/100	1.32 (1.18–1.47) <0.001	1.15 (1.01–1.30) 0.03
Model 2†				
All-cause death	444 (24.8%) 10.3/100	363 (16.2%) 6.4/100	1.61 (1.40–1.85) 0.001	1.02 (0.87–1.20) 0.78
Noncardiovascular death	143 (8.0%) 3.3/100	155 (6.9%) 2.7/100	1.21 (0.96–1.52) 0.10	0.77 (0.60–1.00) 0.046
Cardiovascular death	301 (16.8%) 7.0/100	208 (9.3%) 3.7/100	1.91 (1.60–2.28) <0.001	1.21 (0.99–1.48) 0.06

CAD indicates coronary artery disease; ESRD, end-stage renal disease; HR, hazard ratio.
*Model 1 covariates: age, sex, race, body mass index, insulin use, estimated glomerular filtration rate, blood urea nitrogen, log urine protein/creatinine ratio, albumin, history of stroke, history of peripheral artery disease, history of heart failure, arrhythmia, hemoglobin, log ferritin, C-reactive protein, history of acute renal failure, duration of diabetes, systolic blood pressure, and treatment with darbepoetin (renal model,[15] plus duration of type 2 diabetes mellitus, systolic blood pressure, and treatment with darbepoetin).
†Model 2 covariates: age, race, sex, history of heart failure, log urine protein/creatinine ratio, C-reactive protein, abnormal ECG, serum albumin, arrhythmia, hemoglobin A1c, reticulocytes, blood urea nitrogen, insulin use, cerebrovascular disease, loop diuretics, hemoglobin level, and treatment with darbepoetin (cardiovascular model).[14]

Vascular calcification has been implicated as the pathophysiological link between CKD and CAD,[26] and some studies have suggested that coronary artery calcium scores are associated with increasing severity of kidney disease. The Chronic Renal Insufficiency Cohort study demonstrated a graded association between coronary artery calcium and the severity of CKD after adjusting for traditional risk factors.[27] Furthermore, coronary artery calcium scores >100 were significantly more common in patients with CKD and diabetes than in those with CKD alone.[27] Garland et al prospectively followed 125 predialysis patients for decline in kidney function and found that, compared with a score of 0, a coronary artery calcium score of 100 to 399 was associated with 7.4 increased odds of a decline in kidney function, and a score >400 was associated with 8.8 increased odds of kidney function decline at 1 year of follow-up.[28] Nevertheless, it is not clear whether vascular calcification is a cause of worsening renal function.

There are a few possible explanations for the observed association between baseline CAD and subsequently worsening renal disease in patients with diabetes. The progression of diabetic nephropathy is marked by accumulation of extracellular matrix, tubulointersitial fibrosis, tubular arteriosclerosis, and abnormal podocyte morphology,[29] and inflammation may play an important role. Sun et al found in an animal model that coronary artery stenosis increased renal oxidative stress, fibrosis, inflammation, tubular injury, and microvasculature remodeling.[30] Circulating matrix metalloproteinases, which may contribute to renal fibrosis, are elevated in CAD and have been implicated as a poor prognostic indicator in these patients.[31,32] Hsu et al showed that in patients with CAD, circulating matrix metalloproteinases are independently associated with renal disease progression.[33] This association was seen in nondiabetic patients but also may be an important link in the diabetic population. Bleyer et al suggested an association between atherosclerosis and progression of renal disease using carotid intimal thickness.[34] It is possible that patients with extrarenal atherosclerosis may have renal vasculature arteriosclerosis causing worsening renal disease.

Clinical factors should also be considered in the observed relationship between CAD and renal decline. HF may contribute to renal progression in patients with CAD, and although we found that CAD was independently associated with worsening renal function independent of a history of HF, it is not known whether these patients had subsequent episodes of HF after the baseline assessment. Another consideration is that patients with CAD may have a greater risk of progressive renal injury related to contrast administration from invasive angiography; however, we tested this hypothesis by including a time-varying covariate for coronary revascularization in the models and found that coronary revascularization was not significantly associated with renal disease progression and had a negligible effect on the relationship between known CAD and renal disease progression.

In terms of mortality, we found that known CAD was not associated with all-cause or cardiovascular death independent of a history of HF, suggesting that death caused by CAD in patients with CKD may be predominantly influenced by a

Table 4. Multivariable Model for Renal Outcomes After Including Patients With Angina

	ESRD Model		ESRD or Death	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Known CAD	1.22 (1.03–1.45)	0.023	1.17 (1.03–1.32)	0.017
Age	1.00 (0.99–1.00)	0.411	1.02 (1.01–1.02)	<0.001
Male sex	1.69 (1.44–1.99)	<0.001	1.41 (1.26–1.59)	<0.001
Race (referent: white)				
Black	1.72 (1.43–2.08)	<0.001	1.27 (1.10–1.47)	0.001
Other	1.01 (0.81–1.25)	0.0	0.92 (0.78–1.09)	0.318
BMI, per 10 kg/m^2	0.81 (0.71–0.92)	0.001	0.80 (0.74–0.88)	<0.001
Insulin use	1.15 (0.97–1.36)	0.117	1.14 (1.00–1.29)	0.043
eGFR, per 10 mL/min/1.73 m^2	0.52 (0.47–0.59)	<0.001	0.77 (0.71–0.82)	<0.001
BUN, per 10 mg/dL	1.12 (1.06–1.17)	<0.001	1.09 (1.05–1.13)	<0.001
Log (UPCR)	1.87 (1.73–2.02)	<0.001	1.42 (1.35–1.49)	<0.001
Albumin, per 1 g/dL	0.70 (0.58–0.84)	<0.001	0.61 (0.53–0.70)	<0.001
Prior stroke	1.16 (0.91–1.49)	0.231	1.30 (1.10–1.53)	0.002
Prior PAD	1.10 (0.90–1.34)	0.368	1.13 (0.98–1.30)	0.085
Prior HF	1.29 (1.08–1.54)	0.005	1.48 (1.30–1.68)	<0.001
History of arrhythmia	1.17 (0.92–1.47)	0.198	1.27 (1.09–1.47)	0.002
Hemoglobin, per 1 g/dL	0.95 (0.88–1.03)	0.190	0.95 (0.9–1.01)	0.074
Log (ferritin)	1.10 (1.01–1.20)	0.029	1.04 (0.98–1.11)	0.195
C-reactive protein (referent: ≤3.0 mg/L)				
CRP 3.1–6.5 mg/L	1.13 (0.93–1.37)	0.232	1.16 (1.00–1.34)	0.044
CRP ≥6.6 mg/L	1.31 (1.08–1.59)	0.006	1.42 (1.24–1.63)	<0.001
History of AKI	1.31 (1.04–1.65)	0.021	1.22 (1.03–1.44)	0.024
Systolic blood pressure	1.00 (1.00–1.01)	0.252	1.00 (1.00–1.00)	0.758
Duration of T2DM	1.00 (1.00–1.00)	0.113	1.00 (1.00–1.00)	0.855
Treatment with darbepoetin	1.08 (0.92–1.26)	0.340	1.12 (1.00–1.25)	0.048

AKI indicates acute kidney injury; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; PAD, peripheral artery disease; T2DM, type 2 diabetes mellitus; UPCR, urine protein/creatinine ratio.

history of HF. In contrast, CAD is predictive of noncardiovascular death after adjustment for HF. Bauters et al corroborated the importance of HF by showing that the strongest predictor of mortality in patients with stable CAD is a history of HF hospitalization.[35] Furthermore, Parfrey et al found that ischemic heart disease was not a predictor of mortality in dialysis patients independent of HF.[36]

This study has some limitations. This is a secondary analysis of TREAT, a randomized controlled trial of darbepoetin treatment in patients with anemia, T2DM, and CKD that included patients with eGFR of 20 to 60 mL/min per 1.73 m^2. It is possible that our results would change if we included patients with a broader range of eGFRs. In addition, we found known CAD to be predictive of renal events in patients with T2DM, CKD, and anemia, but these findings may not be generalizable to CKD patients without T2DM and anemia. Furthermore, the definition of ESRD in this study was based on the subjective decision of the clinician and not necessarily on the eGFR or rate of deterioration of eGFR.

Another potential limitation is that because CAD was self-reported, there may be patients with underlying CAD (eg, asymptomatic myocardial ischemia) who were misclassified as having no CAD. This issue of possible misclassification was partially addressed in TREAT because the investigators individually reviewed all forms and patients were reclassified if discrepancies were found, such as a patient reporting a history of coronary artery bypass grafting but no history of CAD. Nevertheless, 3% of patients without self-reported CAD underwent cardiac revascularization during the follow-up period of TREAT. Although this finding may suggest misclassification of some of the non-CAD patients, it may also be consistent with previous data showing that even CKD patients

Table 5. Association Between Known CAD and Outcomes After Including Patients With Angina

Outcome	Participants With Event, n (%), Incidence Rate Per 100 Person-Years		Unadjusted Model HR (CAD vs No CVD), 95% CI, *P* Value	Adjusted Model HR (CAD vs No CVD), 95% CI, *P* Value
	Known CAD (n=1873)	No Known CAD (n=2165)		
Model 1*				
ESRD	308 (16.4%) 7.5/100	360 (16.6%) 7.3/100	1.03 (0.89–1.20) 0.67	1.22 (1.03–1.45) 0.02
Renal composite	662 (35.3%) 15.8/100	608 (28.1%) 12.1/100	1.31 (1.17–1.46) <0.001	1.17 (1.03–1.32) 0.02
Model 2†				
All-cause death	466 (24.9%) 10.3/100	341 (15.8%) 6.3/100	1.65 (1.43–1.89) 0.001	1.07 (0.92–1.26) 0.38
Noncardiovascular death	150 (8.0%) 3.3/100	148 (6.8%) 2.7/100	1.22 (0.97–1.53) 0.09	0.79 (0.62–1.02) 0.08
Cardiovascular death	316 (16.9%) 7.0/100	193 (8.9%) 3.6/100	1.98 (1.65–2.36) <0.001	1.29 (1.06–1.59) 0.01

With inclusion of these 82 patients, CAD was no longer significantly associated with a decreased risk of noncardiovascular death (adjusted HR 0.79, 95% CI 0.62–1.02); however, addition of these patients strengthened the relationship between CAD and cardiovascular death, ESRD, and the composite renal outcome. CAD indicates coronary artery disease; ESRD, end-stage renal disease; HR, hazard ratio.

*Model 1 covariates: age, sex, race, body mass index, insulin use, estimated glomerular filtration rate, blood urea nitrogen, log urine protein/creatinine ratio, albumin, history of stroke, history of peripheral artery disease, history of heart failure, arrhythmia, hemoglobin, log ferritin, C-reactive protein, history of acute renal failure, duration of diabetes, systolic blood pressure, and treatment with darbepoetin (renal model,[15] plus duration of type 2 diabetes mellitus, systolic blood pressure, and treatment with darbepoetin).

†Model 2 covariates: age, race, sex, history of heart failure, log urine protein/creatinine ratio, C-reactive protein, abnormal ECG, serum albumin, arrhythmia, hemoglobin A1c, reticulocytes, blood urea nitrogen, insulin use, cerebrovascular disease, loop diuretics, hemoglobin level, and treatment with darbepoetin (cardiovascular model).[14]

with normal initial coronary angiography might have higher rates of acute myocardial infarction during 3-year follow-up, suggesting accelerated coronary atherosclerosis in these patients.[37] Patients who reported angina but not CAD were not included as CAD patients in TREAT; therefore, we conducted a sensitivity analysis of our results by including those patients who reported angina without CAD and found that the association between CAD and renal outcomes and cardiovascular death was actually strengthened by including these patients. Another important limitation of this study is that patients were censored at the time of death, which is a competing risk, in the model assessing the outcome of ESRD alone. Finally, although an association between peripheral artery disease and worsening renal function was demonstrated previously,[38] we did not find peripheral artery disease to be an independent predictor of ESRD. Since less than 25% of the TREAT cohort had a history of peripheral artery disease, this study may not have been powered to detect a significant association.

In this study of patients with CKD and T2DM, we found that a history of known CAD was an independent predictor of ESRD and the composite of death or ESRD. Because CAD is a known predictor of death, we also assessed the association between CAD and ESRD alone and found that known CAD was an independent risk factor for the progression of CKD to ESRD in this study population. Consequently, patients with diabetic nephropathy and CAD may be a particularly high-risk group not only in terms of cardiovascular disease but also in terms of renal disease progression. Consequently, CAD should be considered an important factor in the risk stratification of these patients. A continued cooperative effort among cardiologists and nephrologists will be necessary to prevent further disease progression of these interrelated organ systems and, ultimately, to optimize the care of these complicated patients.

Disclosures

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