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Extrarenal atherosclerotic disease blunts renal recovery in patients with renovascular hypertension

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Abstract

Background—Atherosclerotic renovascular disease (ARVD) is associated with high rates of coronary events and predicts mortality among patients with coronary artery disease (CAD). However, the impact of coronary atherosclerosis on renal outcomes after revascularization of ARVD is unclear. We hypothesized that CAD negatively impacts renal functional outcomes among patients with ARVD undergoing renal artery revascularization.

Methods—Patients with ARVD who underwent echocardiography at Mayo Clinic, Rochester, Minnesota, USA between 2004 and 2012 were identified retrospectively and included if they had ejection fraction more than 50%. Renal and overall outcomes were compared among atherosclerotic renovascular disease patients with coronary artery disease (ARVD-C, $n=75$) and without coronary artery disease (ARVD, $n=56$), within 1 year from initial revascularization and included blood pressure control, renal function, and incident cardiovascular/cerebrovascular events.

Results—Degree of renal artery stenosis was similar in both groups. ARVD-C had higher prevalence of diabetes, peripheral artery disease (PAD), and cerebrovascular disease, and lower baseline renal function. Risk of developing end-stage renal disease was higher in ARVD-C (11 vs. 2%, $P=0.05$). Despite better control of blood pressure and cholesterol levels, renal function postrevascularization worsened in 15% of ARVD-C compared with 2% of ARVD ($P=0.01$). Differences in clinical outcomes remained statistically significant after adjustment for covariables, including sex, baseline blood pressure, renal function, underlying diabetes, cholesterol levels, and medications. Similar differences in clinical outcomes were also associated with PAD and cerebrovascular disease.

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Conflicts of interest

There are no conflicts of interest.

Conclusion—CAD in patients with ARVD is a predictor of worse outcomes after renal revascularization, likely reflecting diffuse atherosclerotic disease. Further studies are needed to develop strategies to manage patients with vascular comorbidities and improve their outcomes.

Keywords

atherosclerosis; coronary artery disease; renal artery revascularization; renal artery stenosis

INTRODUCTION

Atherosclerosis is characterized by chronic inflammation of medium-sized and large-sized blood vessels [1]. Atherosclerotic renovascular disease (ARVD) is frequently observed in conjunction with atherosclerosis in other vascular beds [2,3]. Renal artery stenosis is detectable in 5–20% of patients with coronary artery disease (CAD) undergoing cardiac catheterization [4–8], as both share risk factors and underlying pathogenesis. Complex interactions exist between atherothrombosis at various arterial locations. Experimental evidence has indicated that ischemic injury can accelerate atherosclerosis at remote arterial sites [9], and multivascular atherosclerotic disease (including CAD) independently increases mortality in patients with peripheral arterial [10] and cerebrovascular disease [11,12].

Although overall mortality is increased among ARVD patients with concurrent CAD [13], the impact of CAD on renal outcomes in ARVD patients is unclear. ARVD increases the rates of acute coronary ischemic events, percutaneous and surgical revascularization, and death in patients with CAD [14], implicating ARVD in the complication of cardiovascular events [15]. The mechanism underlying this detrimental effect of ARVD on cardiovascular morbidity and mortality might be related to circulating cytokines [16] and neurohormonal interaction between the kidney and cardiovascular system [8]. Similarly, coexisting CAD might possibly aggravate renal dysfunction or indicate a greater atherosclerotic burden. Indeed, levels of inflammatory markers are elevated in patients with coexistent peripheral arterial disease (PAD) compared with individuals with CAD alone [17].

Recent clinical trials have failed to identify a major clinical benefit for renal revascularization over medical therapy alone in patients with ARVD [18], yet the reasons for these poor outcomes have not been elucidated. Conceivably, the presence of extrarenal and coronary atherosclerosis might be associated with irreversible kidney dysfunction and impede its recovery after renal artery revascularization. However, the association of CAD with renal functional recovery after revascularization of ARVD lesions has not been fully characterized. Therefore, this study was designed to test the hypothesis that coexisting CAD is associated with decreased renal function and attenuated recovery in ARVD patients undergoing revascularization.

METHODS

Patient selection and data collection

The study was approved by the Mayo Clinic Institutional Review Board. Study cohort was identified from patients with hemodynamically significant renal artery stenosis, who were

seen and underwent echocardiography at Mayo Clinic, Rochester, Minnesota, USA between 1 January 2004 and 31 August 2012. The inclusion criteria included age above 18 years, significant renal artery stenosis defined by standardized entry criteria analogous to enrollment in Cardiovascular Outcomes for Renal Atherosclerotic Lesions study [19], and consent to have their data used for research purposes. In order to rule out heart failure, which adversely impacts outcomes in patients with ARVD, we excluded patients with left ventricular ejection fraction less than 50% assessed from cardiac echocardiography performed within a 2-year period. A total of 131 patients complied with the inclusion criteria, all of whom subsequently underwent renal artery revascularization. CAD was defined as any evidence of coronary atherosclerotic plaque (obstructive or nonobstructive) on coronary angiography, ischemia on noninvasive cardiac testing, or past history of myocardial infarction/percutaneous coronary intervention/surgical revascularization. Patients with ARVD and CAD (ARVD-C group, $n=75$) were compared with ARVD controls ($n=56$).

Clinical parameters

Baseline clinical and anthropometric variables were recorded at the time of renal imaging. Retrospective review was used to collect recent clinical variables, including laboratory data, medication use, and past medical history from the electronic medical records. For the purpose of the study, cerebrovascular disease was defined by prior history of ischemic stroke and/or asymptomatic carotid artery stenosis ($>60\%$), whereas history of claudication and/or ankle brachial index of less than 0.90 defined PAD. Revascularization outcomes were studied within 1 year from initial revascularization of ARVD, and included blood pressure control, renal function, and incident cardiovascular/cerebrovascular events. Meaningful change in renal function after renal artery revascularization was classified as improved (serum creatinine decreased $>0.5\text{mg/dl}$); worsened (increased $>0.5\text{mg/dl}$); or no change (all others). Follow-up was abstracted from the electronic medical records and censored with the last observed clinical visit at Mayo Clinic; the end of the study period; or death.

Statistical analysis

Statistical analyses were performed using JMP version 8.0 (SAS Institute, Cary, North Carolina, USA). Two-sample- t test was used to compare means of two groups, and paired t -test within groups. For data that did not show a Gaussian distribution, comparisons within and among the groups were performed using nonparametric tests (Wilcoxon and Kruskal–Wallis, respectively). Pearson's chi-squared test was used for categorical data. Outcomes were adjusted for those baseline variables that significantly differed between ARVD and ARVD-C. Kaplan–Meier analysis was used to calculate survival. Alpha was set at 0.05, and $P < 0.05$ was considered statistically significant. The response to revascularization was calculated from the difference between postrevascularization and prevascularization values. Detailed methods are provided in the Online Supplementary Materials, <http://links.lww.com/HJH/A343>, <http://links.lww.com/HJH/A344>.

RESULTS

Patient demographics are provided in Table 1. ARVD patients were likely to have coexistent CAD. Mean age of ARVD-C and ARVD patients was similar, as were BMI and race distribution. CAD was more prevalent among men with ARVD. High-density lipoprotein cholesterol levels were lower, and serum uric acid levels were higher in ARVD-C than in ARVD alone. Overall, hyperlipidemia and blood pressure were better controlled in ARVD-C group, although their glucose levels were higher. C-reactive protein levels were not different between ARVD and ARVD-C.

Diabetes mellitus, cerebrovascular disease, PAD, and family history of cardiovascular disease were more prevalent in ARVD-C patients, whereas smoking status did not differ. The number of antihypertensive drugs and the use of statins were greater in the ARVD-C group. The severity of renal artery stenosis was similar in both groups, but ARVD-C patients had greater renal damage evidenced by elevated serum creatinine and proteinuria. Differences in baseline serum creatinine between the two groups remained statistically significant in a multivariate model after adjustment for significant covariables, including differences in age, sex distribution, blood pressure, cholesterol levels, number of antihypertensive medications, family history of CAD, underlying diabetes mellitus, cerebrovascular disease, PAD, left ventricular ejection fraction, and statin use ($P=0.005$).

Cardiac function

Cardiac catheterization results were available for 55 of 75 patients in the ARVD-C group. Baseline echocardiographic data (Table 1) showed statistically significant elevations in left ventricular end-diastolic diameter, greater proportion of advanced (moderate–severe) diastolic dysfunction in ARVD-C, and while left ventricular ejection fraction declined, it remained within normal limits. Structural cardiac remodeling was similar in both groups.

Revascularization outcomes

Outcomes after revascularization are presented in Table 2. DBPs fell in both groups, whereas a significant decline in SBP was observed only in ARVD. The fall in both was attenuated in ARVD-C compared with ARVD, indicated by smaller delta () change. Serum creatinine remained higher in ARV0044-C compared with the ARVD, and this difference remained statistically significant after adjustment for multiple covariables (including underlying diabetes mellitus) in a multivariate model. The changes in serum creatinine and estimated glomerular filtration rate (eGFR) were small in both groups, yet a fall in eGFR was significantly greater in ARVD-C compared with ARVD group ($P=0.04$).

Meaningful improvement (serum creatinine decrease >0.5 mg/dl postrevascularization) was recorded in 4% of ARVD-C vs. 2% of ARVD patients ($P=0.48$). However, renal function worsened (serum creatinine increased >0.5 mg/dl) in 15% of ARVD-C and 2% of ARVD patients ($P=0.01$), and remained unchanged in 81 and 94% of the ARVD-C and ARVD groups, respectively ($P=0.02$, Fig. 1).

Given their strong associations, we also compared the independent effects of diabetes mellitus, cerebrovascular, and PAD on revascularization outcomes in patients with ARVD.

DBPs fell after revascularization in all groups, except for patients with PAD, whereas a significant decline in SBP was observed in ARVD patients with diabetes mellitus and those without cerebrovascular or PAD (Tables 1s–3s). The drop in SBP was attenuated in ARVD patients with cerebrovascular or PAD, and in ARVD patients without diabetes mellitus. The change in renal function (serum creatinine and eGFR) after revascularization was small in all the groups. A rise in serum creatinine and a fall in eGFR were significantly greater in ARVD patients with cerebrovascular disease or PAD, but not in ARVD patients with diabetes, compared with their respective control-ARVD groups. Details are provided in Supplementary Material, <http://links.lww.com/HJH/A343>, <http://links.lww.com/HJH/A344>.

Follow-up survival data

Mean duration of follow-up was similar between the ARVD and ARVD-C groups (Table 1). Despite a similar degree of renal artery stenosis before the procedure, patients in the ARVD-C group were more likely to develop end-stage renal disease (11 vs. 2%, $P=0.05$), and 35% of them died during the course of follow-up, compared with 20% in ARVD ($P=0.05$). Figure 2 displays the survival curves of the patients in ARVD and ARVD-C group (log rank test, $P=0.05$). In a multivariate Cox regression model, age and postrevascularization eGFR levels were independent predictors of mortality for the entire population (Table 3).

DISCUSSION

The major finding of this study is that despite similar degree of renal artery stenosis, ARVD patients with coexisting CAD had greater degree of renal dysfunction and worse outcomes after revascularization, including increased mortality. Basal renal function was lower in ARVD-C patients, and remained lower in 1-year postrenal revascularization after adjustment for multiple covariables (including baseline renal function and diabetes mellitus). Similarly, coexisting diseases in the cerebral or peripheral vascular beds aggravated outcomes of renal artery revascularization in ARVD patients, but not coexisting diabetes. Therefore, these worse outcomes can likely be attributed to a diffuse atherothrombotic process.

To date, randomized trials have failed to show measurable benefit of renal artery revascularization in terms of improvement in renal function [18]. Previous studies have reported the association of basal renal dysfunction with increased long-term mortality in ARVD patients treated with stenting [20], but baseline rate of CAD was not different among these patients [21]. In our study, meaningful improvement in serum creatinine was noted in a small proportion of patients in both groups, and proteinuria remained unchanged. Lack of improvement in the remaining patients could be related to parenchymal disease, damage to intrarenal microvasculature [13], or coexisting chronic kidney disease, all of which would have limited responses to renal revascularization. Moreover, worsening of renal function after revascularization was noted in a higher proportion of patients with ARVD-C, suggesting that these poststenotic kidneys might be more susceptible to insults such as reperfusion injury or restenosis.

The incidence of atherosclerotic heart disease may quadruple in patients with ARVD relative to the general population [22], and strong correlations exist between renovascular, cerebrovascular disease, and PAD [22–25]. Indeed, we observed a high prevalence of

coexisting cerebrovascular and PAD in ARVD-C. An adverse impact of ARVD on other organ systems has been consistently observed, implicating renal artery stenosis as a predictor of increased mortality and adverse cardiovascular and cerebrovascular outcomes [20,21,26,27]. Similarly, coexisting atherosclerosis in other organ systems may well worsen outcomes in patients with ARVD.

Interestingly, despite better control of hypertension and hyperlipidemia, the risk for progressive worsening of renal function and development of end-stage renal disease remained magnified in the presence of CAD, even after adjustment for covariables such as underlying diabetes mellitus and baseline blood pressure. Indeed, the relationship between blood pressure control and clinical outcomes in patients with ARVD is not as clear as in patients with essential hypertension [28–30]. Although we excluded patients with left ventricular ejection fraction less than 50%, systolic function was still lower in ARVD-C, likely related to underlying ischemic cardiomyopathy.

ARVD is a common manifestation of diffuse systemic atherosclerosis [15], characterized by chronic inflammatory plaques in the vessel wall, involving many components of the vascular, metabolic, and immune systems [1]. In addition to the traditional cardiovascular risk factors, elevated levels of circulating inflammatory markers have been observed in patients with ARVD [16,31,32] or CAD [33–35]. Possibly, coexistence of atherosclerosis in the renal and other vascular beds may interact synergistically to accelerate the chronic inflammatory process. In experimental models, ischemic injury increases inflammation in remote atherosclerotic plaques [9], and autoimmune conditions accelerate atherosclerosis [1] linking underlying pathways to fostering the disease process. Furthermore, circulating levels of inflammatory and prothrombotic biomarkers are elevated when PAD and CAD coexist [17], suggesting that multivessel atherothrombosis, such as concurrent ARVD, CAD, cerebrovascular disease, and PAD might reflect a more advanced or aggressive disease. The relatively minor incremental effect of diabetes on revascularization outcomes in our ARVD patient population may underscore the specific impact of atherogenic factors on the poststenotic kidney. Conversely, protective mechanisms may also be activated in response to remote ischemic injury [36–40], but may be more conspicuous in response to acute injury than during a chronic process.

Being a retrospective study, our study has several limitations. First, our sample was small in size and obtained from a single institution with primarily white patients, both of which limited the generalizability of the results. Including ARVD patients who underwent echocardiography also introduced selection bias to favor the presence of CAD and other vascular diseases, and may account for the noteworthy mortality observed in our cohort. Further studies are needed to explore the disease responsible for this increased mortality in patients with multivascular disease. Secondly, all patients had hemodynamically significant renal artery stenosis (>60%) suggesting advanced atherosclerosis, thereby limiting extrapolation of the results in patients with early atherosclerosis. Yet, the latter are also unlikely to undergo revascularization. Finally, we did not have a record of specific invasive/noninvasive cardiac testing in 43% of the ARVD patients, some of whom might have had clinically silent CAD, although some patients with ARVD-C had non-obstructive plaques as well.

In conclusion, overall clinical outcomes were worse in patients with coexisting ARVD and CAD, likely due to the effects of atherosclerotic burden and diffuse disease. Underlying diabetes, male sex, and to a lesser degree family history of CAD were the significant predictors of CAD in patients with ARVD. ARVD patients with coexisting disease in other vascular beds had attenuated response to revascularization, evidenced by elevated serum creatinine and lower eGFR 1 year later. Further studies are needed to develop aggressive management strategies to reduce the burden of atherosclerosis and improve renal viability in this high-risk group of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ARVD	atherosclerotic renovascular disease
CAD	coronary artery disease
E	peak mitral inflow velocity
e'	medial mitral annulus peak diastolic velocity
eGFR	estimated glomerular filtration rate
HDL	high-density lipoprotein
LDL	low-density lipoprotein
LVEDD	left ventricular end-diastolic diameter
LVH	left ventricular hypertrophy
PAD	peripheral arterial disease
	delta change or difference between postrevascularization and prerevascularization values

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Reviewer's Summary Evaluation**Referee 1**

The predictive effect of atherosclerotic renovascular disease for coronary events and mortality in patients with coronary artery disease (CAD) is well established. The novel finding in the present study is that CAD also negatively impacts renal functional outcomes in patients with atherosclerotic renovascular disease undergoing renal artery revascularization. A shortcoming of this study is that there is a higher proportion of comorbidities in the patients with coronary disease, and the outcome increase may be due to these comorbidities rather than 'CAD' itself. In addition, the patient number is not high. However, the finding is novel and deserves further study.

FIGURE 1.

Distribution of changes in serum creatinine after revascularization in ARVD and ARVD-C, presented as percentage of patients ($\% \pm$ standard errors). Meaningful decrease in serum creatinine is defined as a fall >0.5 mg/dl after renal artery revascularization, no change as ≤ 0.5 mg/dl change, and worsening as increase >0.5 mg/dl. * $P < 0.05$ for ARVD-C vs. ARVD. ARVD, atherosclerotic renovascular disease.

Figure 2.

Survival plots of atherosclerotic renal artery disease patients with (ARVD-C) or without (ARVD) coronary artery disease. Events were recorded in 27 and 12 patients in the ARVD-C and ARVD groups, respectively, Log-Rank test, $P=0.05$. $*P<0.001$ after adjustment for age, sex, LDL, HDL cholesterol, personal and family history of CAD, diabetes mellitus, cerebrovascular disease, peripheral artery disease, smoking, ejection fraction, statins, blood pressure, and eGFR after revascularization, in a cox regression analysis model. ARVD, atherosclerotic renovascular disease; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TABLE 1

Clinical characteristics of patients with atherosclerotic renovascular disease subdivided according to presence (ARVD-C) or absence (atherosclerotic renovascular disease) of coronary artery disease

Variables	ARVD-C	ARVD	P
N	75 (57%)	56 (43%)	<0.001
Duration of follow-up (years)	3.9 (0.01–8.4)	4.6 (0.05–8.5)	0.45
Age (years)	76 (51–91)	75 (53–91)	0.74
Sex (male/female)	43/32	14/42	0.0002
BMI (kg/m ²)	28 (21–48)	28 (19–47)	0.46
Race (white/other/unknown)	67/1/6	54/0/2	0.38
SBP (mmHg)	144 ± 25	150 ± 24	0.15
DBP (mmHg)	70 ± 14	76 ± 13	0.01
Total cholesterol (mg/dl)	153 (93–382)	187 (88–329)	0.0001
LDL cholesterol (mg/dl)	81 (40–176)	107 (42–225)	<0.001
HDL cholesterol (mg/dl)	45 (24–84)	56 (28–103)	0.0001
Triglycerides (mg/dl)	142 (48–494)	132 (52–335)	0.67
Glucose (mg/dl)	112 (87–275)	105 (68–189)	0.02
C-reactive protein [†] (mg/l)	2.15 (0–11.7)	1.6 (0.3–44.7)	0.53
Uric acid (mg/dl)	7 (4–14)	7 (5–13)	0.03
Comorbidities			
Diabetes mellitus	28 (37%)	8 (14%)	0.003
Cerebrovascular disease	46 (61%)	22 (39%)	0.01
Peripheral artery disease	33 (44%)	12 (21%)	0.007
Family history of CAD	49 (66%)	26 (46%)	0.02
Smoking status			0.42
Current smoker	5 (7%)	4 (7%)	
Former smoker	44 (59%)	27 (48%)	
Nonsmoker	25 (34%)	25 (45%)	
Recent myocardial infarction/stroke	10 (13%)	1 (2%)	0.02
Hospitalization for pulmonary edema	11 (15%)	2 (3%)	0.03
Coronary artery bypass grafting	41 (55%)	0	<0.001
Atrial fibrillation	24 (32%)	13 (23%)	0.27
Sleep apnea	21 (28%)	12 (21%)	0.39
Cardiovascular medications			

Variables	ARVD-C	ARVD	P
Antihypertensive (number of drugs)	3 (1–7)	3 (0–7)	0.009
Statins	61 (81%)	31 (55%)	0.001
Severity of RAS			
Bilateral RAS	21 (30%)	9 (19%)	0.21
Ultrasound-Doppler peak systolic velocity*	322 ± 64	310 ± 121	0.78
Grading as per CT/MRA**			0.88
Moderate (60–70%)	15 (23%)	11 (21%)	
High grade (70–90%)	42 (65%)	33 (63%)	
Severe (>90%)	8 (12%)	8 (15%)	
Renal function			
Serum creatinine (mg/dl)	1.4 (0.6–3.7)	1.1 (0.7–2.9)	0.003
eGFR-MDRD (ml/min per 1.73m ²)	45 (16–101)	48 (16–85)	0.14
Proteinuria(mg/24 h)	204 (25–3168)	106 (17–1127)	0.007
Echocardiographic parameters			
LV mass index (g/m ²)	111 (57–237)	100 (71–150)	0.11
Left atrial volume index (ml/m ²)	43 (15–106)	38 (18–69)	0.09
LVEDD (mm)	48 ± 5	47 ± 4	0.03
E/e' ratio	16 (1–46.7)	14 (7–33)	0.06
LV geometry			0.9
Normal	13 (20%)	10 (19%)	
Concentric remodeling	19 (29%)	17 (32%)	
Eccentric LVH	8 (12%)	6 (11%)	
Concentric LVH	26 (40%)	20 (38%)	
Ejection fraction (%)	62 ± 7	67 ± 6	0.0001
Cardiac index (l/min/m ²)	3 (2–4.6)	3 (2–4.5)	0.9
Diastolic function			0.06
Normal	6 (8%)	4 (7%)	
Mild (grade I, Ia)	15 (20%)	20 (36%)	
Moderate (grade II)	25 (33%)	16 (28%)	
Severe (grade III)	16 (21%)	4 (7%)	

ARVD, atherosclerotic renovascular disease; ARVD-C, ARVD with coronary artery disease; E, peak mitral inflow velocity; e', medial mitral annulus peak diastolic velocity; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEDD-LV end-diastolic diameter; LVH, left ventricular (LV) hypertrophy.

[†] C-reactive protein levels measured within 2 years, were available for 20 ARVD-C and 17 ARVD patients.

* In 23 ARVD-C and nine ARVD patients.

** In 65 ARVD-C and 52 ARVD patients. Data are presented as median (range), N (%), or mean ± SD; as appropriate.

TABLE 2

One-year outcomes postrevascularization of atherosclerotic renovascular disease based on presence (ARVD-C) or absence (atherosclerotic renovascular disease) of coronary artery disease

Outcomes	ARVD-C	ARVD	Unadjusted <i>P</i> value	Adjusted* <i>P</i> value
SBP (mmHg)	139 ± 17	143 ± 17**	0.25	0.03
Change (mmHg)	-5.6 ± 25	-7 ± 24	0.71	0.002
DBP (mmHg)	66 ± 12**	67 ± 12**	0.85	0.002
Change (mmHg)	-3.9 ± 15	-9 ± 14	0.04	<0.001
Serum creatinine (mg/dl)	1.4 (0.7–8.6)**	1.2 (0.7–3.5)	0.01	<0.001
Change (mg/dl)	0.1 (-1–+7.1)	0 (-1.2–+1.9)	0.21	0.05
eGFR (ml/min/1.73m ²)	43 (4.5–83)	46 (12–85)	0.20	<0.001
Change (ml/min per 1.73m ²)	-2.9 (-35–+47)	-0.6 (-38–+38)	0.89	0.04
Proteinuria (mg/dl)	158 (28–3707)	102 (21–978)	0.12	0.01
Change (mg/dl)	-12 (-1880–+2962)	21 (-407–+249)	0.09	0.20

ARVD, atherosclerotic renovascular disease; ARVD-C, ARVD with coronary artery disease; eGFR, estimated glomerular filtration rate.

* Outcomes adjusted for sex, baseline DBP, HDL, LDL cholesterol levels, diabetes mellitus, peripheral artery disease, cerebrovascular disease, family history of CAD, statin use, number of antihypertensive medications, baseline serum creatinine, baseline proteinuria, and left ventricular ejection fraction in a multivariate model.

** *P*<0.05 vs. prerevascularization. Data are presented as median (range), *N* (%), or mean ± SD; as appropriate.

TABLE 3

Predictors of mortality based on univariate and multivariate cox regression model with hazard ratio and 95% confidence intervals

	Univariate predictors of mortality		Multivariate cox regression model*	
	HR (95% CI)	P	HR (95% CI)*	P*
Age	1.1 (1.04–1.1)	<0.001	1.08 (1.02–1.16)	0.004
Female sex	0.92 (0.48–1.8)	0.81		
Blood pressure [†]	0.99 (0.97–1.01)	0.50		
eGFR [†]	0.95 (0.93–0.98)	<0.001	0.94 (0.91–0.97)	<0.001
Diabetes mellitus	1.4 (0.7–2.7)	0.35		
Cerebrovascular disease	0.9 (0.5–1.8)	0.81		
Peripheral artery disease	1.6 (0.8–3.0)	0.17		
LDL cholesterol	0.98 (0.97–1.0)	0.03		
HDL cholesterol	1.01 (0.99–1.03)	0.34		
Statins	1.8 (0.8–4.6)	0.12		
Personal history of CAD	1.9 (1.0–4.2)	0.05		
Family history of CAD	1.1 (0.6–2.1)	0.85		
Smoking	1.2 (0.3–3.4)	0.74		
Ejection fraction	0.94 (0.89–0.99)	0.02		

CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

* Adjusted for age, sex, LDL, HDL cholesterol, personal and family history of CAD, diabetes mellitus, cerebrovascular disease, peripheral artery disease, smoking, ejection fraction, statins, blood pressure, and eGFR postrevascularization.

[†] Post revascularization levels.