Incremental prognostic value of kidney function decline over coronary artery disease for cardiovascular event prediction after coronary computed tomography

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It is unknown whether mild chronic kidney disease (CKD) is associated with adverse cardiovascular (CV) prognosis after accounting for coronary artery disease (CAD). Here we evaluated the interplay between CKD and CAD in predicting CV death or myocardial infarction (MI) and all-cause death. We included 1541 consecutive patients in the Partners registry (mean age 55 years, 43% female) over 18 years old with no known prior CAD who underwent coronary computed tomography angiography (CCTA). The results of CCTA were categorized as normal, nonobstructive (under half), or obstructive (half and over). Overall, 653 of the patients had no CAD, 583 had nonobstructive CAD, and 305 had obstructive CAD, while 1299 had eGFR over 60 ml/min per 1.73 m^2 and 242 had an eGFR under this value. The presence and severity of CAD was significantly associated with an increased rate of CV death or MI and all-cause death, even after adjustment for age, gender, symptoms, and risk factors. Similarly, reduced eGFR was significantly associated with CV death or MI and all-cause death after similar adjustment. The addition of reduced GFR to a model which included both clinical variables and CCTA findings resulted in significant improvement in the prediction of CV death or MI and all-cause death. Thus, among individuals referred for CCTA to evaluate CAD, renal dysfunction is associated with an increased rate of CV events, mainly driven by an increase in the rate of noncoronary CV events. In this group of patients, both eGFR and the presence and severity of CAD together improve the prediction of future CV events and death.

It has been known for decades that individuals with chronic kidney disease (CKD) have accelerated atherosclerosis[1] that leads to a higher incidence of cardiovascular (CV) events and mortality.[2,3] Although most studies have evaluated patients with end-stage renal disease, more recent evidence suggests that even earlier stages of CKD are associated with increased cardiovascular risk.[4]

Robust evidence supports the evaluation of coronary artery disease by coronary computed tomography angiography (CCTA) to predict future cardiovascular events.[5,6] However, CCTA is contraindicated in individuals with advanced renal disease. Thus, literature on the interplay between coronary artery disease (CAD) identified by CCTA and renal dysfunction for the prediction of cardiovascular events is scarce. Such data are needed, as individuals with mild and moderate chronic kidney disease often undergo CCTA. Moreover, recent guidelines propose that absolute cardiovascular risk should be the primary goal of cardiovascular prevention strategies, both in the general population[7] and in individuals with renal disease.[8] Recognizing this need, one recent study evaluated the impact of mild CKD on the incidence of all-cause mortality among patients

undergoing CCTA.[9] However, no data exist with regard to whether mild or moderate CKD is associated with future CV events across the spectrum of CAD detected by CCTA.

Moreover, although individuals with CKD have increased rates of CV mortality, studies have demonstrated that for dialysis patients only 25% of CV events are related to coronary heart disease, whereas the other 75% are related to other causes such as heart failure or arrhythmias.[10] This issue has received even more attention after the AURORA trial, and the 4D study demonstrated no benefit of statins in individuals undergoing hemodialysis.[11,12]

Although data exist relating mild or moderate CKD with future CV events, it is unknown whether the presence or severity of CAD detected on CCTA can be used to further risk stratify such patients, particularly as patients with CKD can experience cardiovascular events other than coronary heart disease events. Therefore, in this study, we specifically aimed to examine the association of renal dysfunction with future CV events across the spectrum of CAD detected by CCTA.

RESULTS
Baseline patient characteristics
Our study included 1541 individuals (55 ± 14 years old, 57% male) (Table 1 and Figure 1). Individuals with an estimated glomerular filtration rate (eGFR) < 60 ml/min per $1.73 \, m^2$ were older, were more likely to be male, and were more likely to have hypertension, diabetes, and dyslipidemia. Consequently, patients with impaired eGFR had a higher pre-test probability of CAD, and had a higher burden of CAD on CCTA. Similarly, a greater burden of CAD was also associated with increased age and with a higher proportion of traditional risk factors (Table 2).

A total of 242 individuals (16%) had reduced eGFR, of whom 179 (82%) had an eGFR between 45 and 60 ml/min per $1.73 \, m^2$, 43 had an eGFR between 30 and
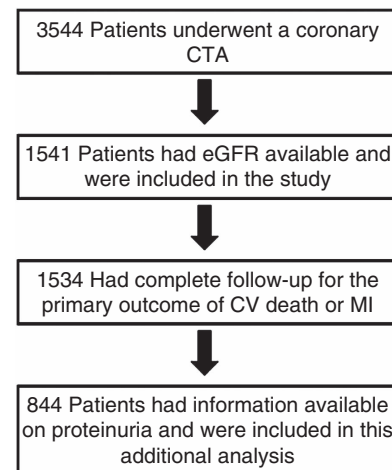

Figure 1 | Study population included in the analysis. CTA, computed tomography angiography; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

Table 1 | Baseline demographic characteristics according to the eGFR

	Total	eGFR <60	eGFR >60	P-value
Number of subjects	1541	242	1299	
Age	55.4 ± 13.7	64.6 ± 12.6	53.7 ± 13.2	<0.001
Male (%)	880 (57%)	100 (41%)	780 (60%)	<0.001
Race				0.39
White	1181 (77%)	191 (79%)	990 (76%)	
Black	111 (7%)	19 (8%)	92 (7%)	
Other	249 (16%)	32 (13%)	217 (17%)	
Hypertension (%)	783 (51%)	175 (72%)	608 (47%)	<0.001
Diabetes mellitus (%)	255 (17%)	61 (25%)	194 (15%)	<0.001
Dyslipidemia (%)	761 (49%)	154 (64%)	607 (47%)	<0.001
Smoking (%)				0.01
Prior smoking	373 (24%)	79 (33%)	294 (23%)	
Current smoking	182 (12%)	22 (9%)	160 (12%)	
Symptoms (%)				0.04
Nonanginal CP	632 (41%)	114 (47%)	518 (40%)	
Atypical CP	607 (39%)	81 (33%)	526 (41%)	
Typical CP	128 (8%)	24 (10%)	104 (8%)	
Asymptomatic	114 (8%)	19 (8%)	95 (7%)	
Unknown	60 (4%)	4 (2%)	56 (4%)	
Pretest probability of >50% CAD	0.45 ± 23	0.58 ± 0.22	0.43 ± 0.22	<0.001
CCTA results				<0.001
Normal	653 (42%)	65 (27%)	588 (45%)	
Nonobstructive CAD	583 (38%)	96 (40%)	487 (37%)	
Obstructive CAD	305 (20%)	81 (33%)	224 (17%)	

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CP, chest pain; eGFR, estimated glomerular filtration rate.
The pretest probability of ≥50% stenosis was calculated using the Morise score[29] that includes age, gender, risk factors, and symptoms according to Diamond and Forrester criteria.[34]

Table 2 | Baseline demographic characteristics according to the presence and severity of CAD detected by CCTA

	Normal	Nonobstructive CAD	Obstructive CAD	P-value
Number of subjects	653 (42%)	583 (38%)	305 (20%)	
Age	47.8 ± 12.5	58.8 ± 11.8	64.7 ± 10.8	<0.001
Male (%)	327 (50%)	345 (59%)	208 (68%)	<0.001
Race				<0.001
White	459 (70%)	459 (80%)	254 (83%)	
Black	79 (12%)	24 (4%)	19 (6%)	
Other	115 (18%)	91 (16%)	32 (11%)	
Hypertension (%)	241 (37%)	317 (54%)	225 (74%)	<0.001
Diabetes mellitus (%)	63 (10%)	99 (17%)	93 (30%)	<0.001
Dyslipidemia (%)	211 (32%)	318 (54%)	232 (76%)	<0.001
Smoking (%)				<0.001
Prior smoking	114 (17%)	153 (26%)	106 (35%)	
Current smoking	75 (11%)	68 (12%)	39 (13%)	
Symptoms (%)				0.25
Nonanginal CP	257 (39%)	239 (41%)	136 (45%)	
Atypical CP	261 (40%)	233 (40%)	113 (37%)	
Typical CP	53 (8%)	43 (7%)	32 (10%)	
Asymptomatic	52 (8%)	43 (7%)	19 (6%)	
Unknown	30 (5%)	25 (4%)	5 (2%)	
Pretest probability of >50% CAD	0.35 ± 0.23	0.50 ± 0.20	0.58 ± 0.18	<0.001
eGFR (ml/min per $1.73 \, m^2$)	80 ± 21	77 ± 22	71 ± 21	<0.001

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CP, chest pain; eGFR, estimated glomerular filtration rate.
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