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# Effects of chronic kidney disease and declining renal function on coronary atherosclerotic plaque progression: a PARADIGM substudy

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## Aims

To investigate the change in atherosclerotic plaque volume in patients with chronic kidney disease (CKD) and declining renal function, using coronary computed tomography angiography (CCTA).

## Methods and results

In total, 891 participants with analysable serial CCTA and available glomerular filtration rate (GFR, derived using Cockcroft–Gault formulae) at baseline (CCTA 1) and follow-up (CCTA 2) were included. CKD was defined as GFR <60 mL/min/1.73 m<sup>2</sup>. Declining renal function was defined as ≥10% drop in GFR from the baseline. Quantitative assessment of plaque volume and composition were performed on both scans. There were 203 participants with CKD and 688 without CKD. CKD was associated with higher baseline total plaque volume, but similar plaque progression, measured by crude (57.5 ± 3.4 vs. 65.9 ± 7.7 mm<sup>3</sup>/year, *P* = 0.28) or annualized (17.3 ± 1.0 vs. 19.9 ± 2.0 mm<sup>3</sup>/year, *P* = 0.25) change in total plaque volume. There were 709 participants with stable GFR and 182 with declining GFR. Declining renal function was independently associated with plaque progression, with higher crude (54.1 ± 3.2 vs. 80.2 ± 9.0 mm<sup>3</sup>/year, *P* < 0.01) or annualized (16.4 ± 0.9 vs. 23.9 ± 2.6 mm<sup>3</sup>/year, *P* < 0.01) increase in total plaque volume. In CKD, plaque progression was driven by calcified plaques whereas in patients with declining renal function, it was driven by non-calcified plaques.

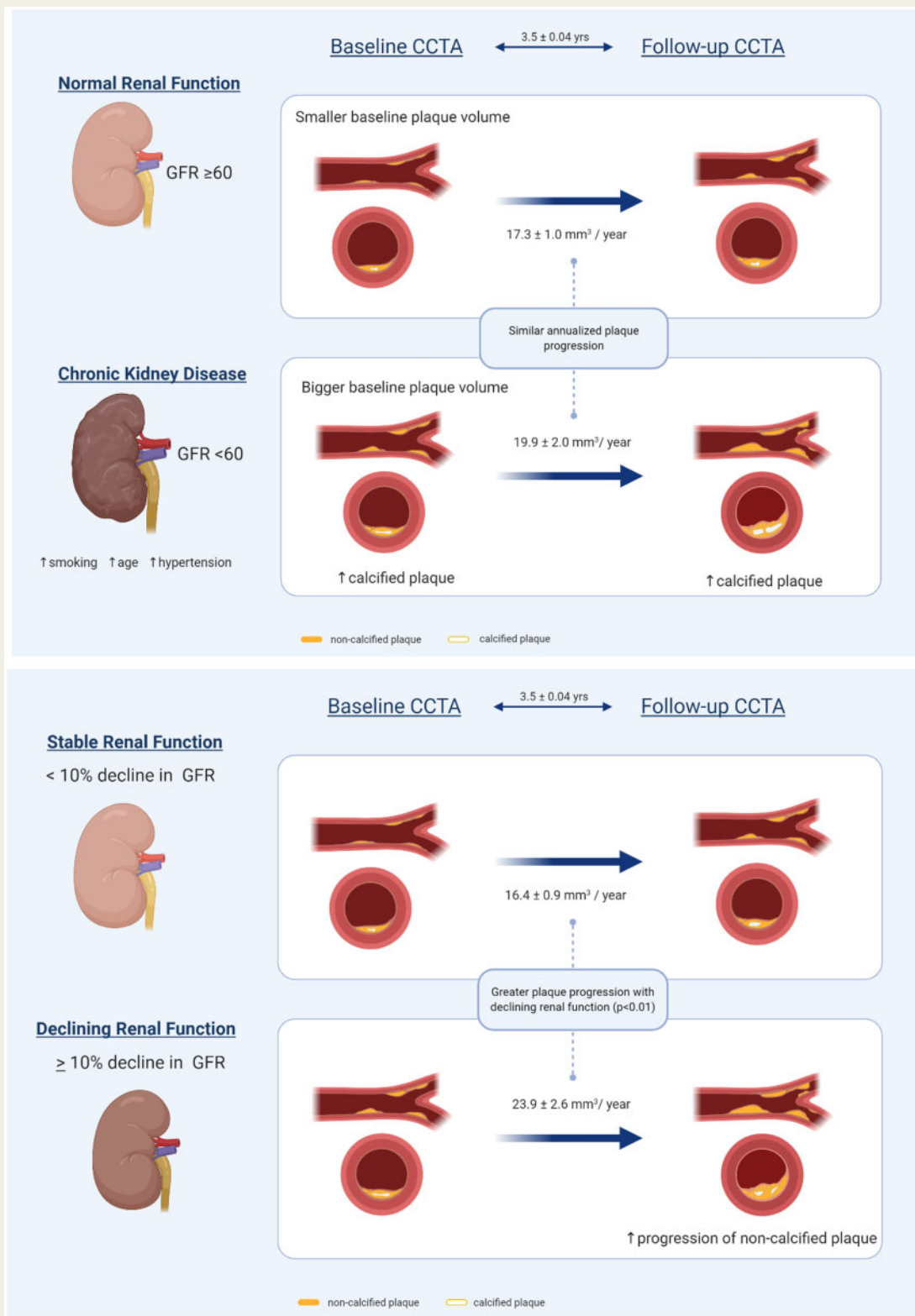
## Conclusion

Decline in renal function was associated with more rapid plaque progression, whereas the presence of CKD was not.

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**Graphical Abstract**



**Keywords**

coronary CT angiography • atherosclerosis • chronic kidney disease • coronary artery disease

**Introduction**

Patient with chronic kidney disease (CKD)<sup>1</sup> or deteriorating renal function<sup>2-4</sup> are at increased risks of cardiovascular disease, and their managements pose particular challenges. Patients with CKD often have atypical presentations,<sup>5</sup> and current risk stratification tools have modest accuracy in predicting adverse outcomes.<sup>6</sup> Further, therapeutic strategies shown to reduce cardiovascular risks have diminished or even no benefits when applied to this population.<sup>7,8</sup> It has been postulated CKD patients have accelerated atherosclerosis,<sup>9</sup> though the precise mechanism that CKD contributes to cardiovascular risks remains incompletely understood.

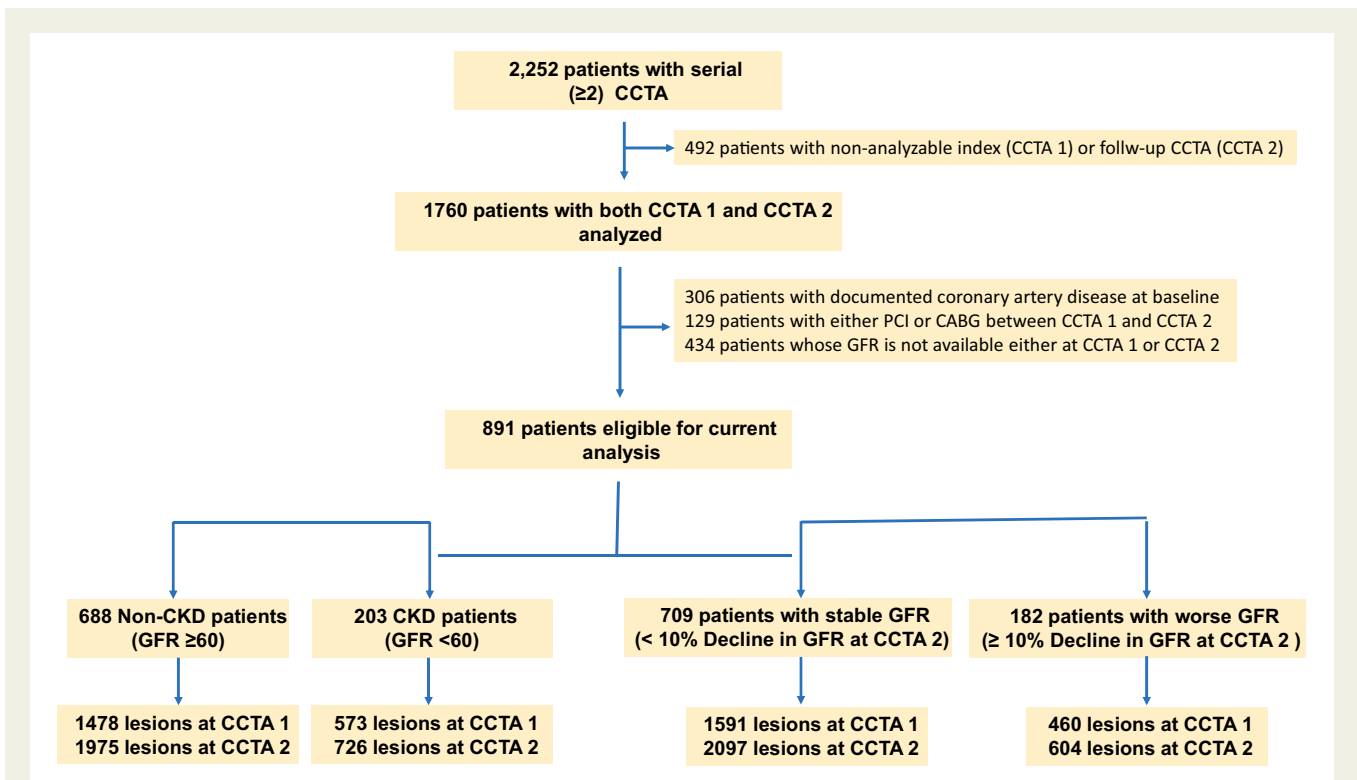
Coronary computed tomography angiography (CCTA) is the preferred modality to diagnose coronary artery disease. In addition to determining luminal stenosis, CCTA can be used to image and quantify plaque burdens, characterize plaque composition, and profile plaques of high-risk morphology.<sup>10</sup> Further, the non-invasive nature allows serial assessment to track plaque progression. Thus, CCTA provides the opportunities to better understand the evolution of atherosclerosis, and more precision in risk prediction so to personalize treatment.

In this study, we aimed to assess if patients of moderate CKD have different plaque features or patterns of progression that could explain more adverse cardiovascular outcomes. In addition, as

deteriorating renal function has also been reported to independently predict worse cardiovascular outcomes,<sup>2-4</sup> we sought to determine if this is mediated through accelerated plaque progression or a more unstable plaque phenotype.

**Methods****Study design and population**

The Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography IMaging (PARADIGM) is a collaborative, prospective, observational registry with 13 participating clusters from seven countries. The aim of the study is to characterize disease progression using serial CCTA, and to correlate the natural history to clinical and laboratory parameters. The design and the rationale of the study have been described in details previously.<sup>11</sup> Briefly, consecutive patients from participating sites who underwent two clinically indicated CCTA of  $\geq 64$ -detector rows, at least 2 years apart, were enrolled into the study. Patients were excluded if there is complete absence of clinical or laboratory information at within 1 month of either baseline (CCTA 1) or follow-up (CCTA 2) CT. Study protocol was approved by the institutional review boards at all study sites. Of the 2252 participants, 492 were excluded as either CCTA 1 or CCTA 2 and was not analysable (refer to *Figure 1*). A further 306 patients with documented coronary artery disease at baseline, 129 with interscan revascularization (either percutaneous coronary intervention or



**Figure 1** CONSORT flow diagram for the PARADIGM study.

coronary artery bypass graft), and 434 where glomerular filtration rate (GFR) cannot be determined were excluded. GFR was calculated using the Cockcroft–Gault formulae and CKD is defined as  $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ . Decline in renal function is defined as  $\geq 10\%$  drop in GFR from the baseline measurement, regardless of CKD status at baseline. A 10% threshold was chosen based on a prior report that a 2.5% yearly decline in GFR is associated with worse clinical outcomes.<sup>3</sup> As the average study interscan duration is 3.5 years, a  $\sim 10\%$  decline in GFR is expected to be clinically significant. The data underlying this article will be shared on reasonable request to the corresponding author.

## Coronary computed tomography angiography

All CCTA studies were performed using scanners with  $\geq 64$ -detector rows, with all testing, image acquisition, and post-processing conducted following the Society of Cardiac Computed Tomography guidelines.<sup>12,13</sup> The source dataset was transferred to a single core laboratory and analysed by independent level III-experienced readers who were blinded to clinical information. Coronary atherosclerotic plaques were analysed on axial, coronal, sagittal, and multiplanar reformation images, using a semi-automated software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands) with manual corrections. Based on the modified 17-segment American Heart Association model for coronary artery segment classification,<sup>14</sup> segments with diameter  $\geq 2 \text{ mm}$  were evaluated for plaque volume and composition. Quantitative assessment of atherosclerotic plaques was performed at 1-mm cross sectional intervals. Plaque volume from all coronary artery segments was summated to generate total plaque volume at the patient level. Where longitudinal comparisons between baseline and follow-up CCTA were made, coronary segments and plaques were matched-up using anatomical landmarks including distance from the ostia or the bifurcation points. Change in plaque volume was derived by calculating the difference in total, patient-level plaque volume between CCTA 1 and CCTA 2. Change in plaque volume was then annualized to account for the different time intervals between CCTA 1 and CCTA 2. Plaque composition was characterized and categorized into four groups based on their radiodensity, using previously-validated thresholds.<sup>15,16</sup> Specifically, these four groups were, necrotic core ( $-30$  to  $30$  Hounsfield units, HU), fibro-fatty ( $30$  to  $130$  HU), fibrous ( $131$  to  $350$  HU), and calcified ( $>350$  HU) plaques. To control variations in CCTA 1 and CCTA 2 between subjects, total plaque volumes and the four groups of plaque composition were normalized to the duration between CCTA 1 and CCTA 2 in order to compute annualized volume.

In addition, we evaluated the presence of high-risk plaques, which consists of  $\geq 2$  of the following four features shown to be associated with culprit lesions of acute coronary syndrome,<sup>10,17</sup> including (i) positive remodelling, (ii) low attenuation plaques, (iii) napkin ring sign, and (iv) spotty calcifications in both CCTA 1 and CCTA 2. Status in baseline and changing renal function was used to correlate changes in frequency of high-risk plaques and their four components.

## Study endpoints

The primary study endpoint is the rate of plaque progression, calculated by annualized change in plaque volume. Secondary endpoints include plaque composition and the prevalence of high-risk plaques at baseline and follow-up.

## Statistical analysis

Continuous variables were presented as mean  $\pm$  standard error of mean (SEM), and Student's *t*-test was used to compare the difference between

groups. Categorical variables were expressed as absolute count and percentages, and the comparison was made using the  $\chi^2$  test. A general linear model was used to assess independent association between baseline plaque volume and CKD. Clinical variables with significant inter-group difference at baseline (age, sex, and hypertension, where  $P < 0.05$ ), diabetes and statin use were included as covariates, baseline plaque volume as dependent variable, and CKD as the fixed factor in our model. A second general linear model was used to assess independent associations between changing renal function and plaque progression, where the annualized plaque volume was used as the dependent variable, decline in renal function as the fixed factor, and age, gender, hypertension, current cigarette smoking and diabetes, use of statin, baseline heart rate, baseline diastolic blood pressure, body mass index (BMI), baseline triglyceride, baseline GFR and baseline plaque volume, serum calcium, and phosphate levels as co-variables. We repeated this multivariate analysis using CKD as the fixed factor and included the same covariates except baseline GFR.

A *P*-value  $< 0.05$  was considered statistically significant. All analysis was conducted using SPSS (version 26, IBM SPSS, NY, USA).

## Role of funding source

The funding source of this study includes generous grants from the Dalio Foundation, Michael Wolk Foundation, and the Leading Foreign Research Institute Recruitment Program funded by the Ministry of Science, ICT & Future planning, though the National Research Foundation of Korea (grant no. 2012027176).

## Results

### Baseline clinical and plaque characteristics

This study included 891 eligible patients, with a mean age of  $60.0 \pm 0.3$  (mean  $\pm$  standard error of mean) years old, and 480 (53.9%) were man. The average duration between CCTA1 and CCTA2 was  $3.5 \pm 0.04$  years. Baseline mean creatinine was  $1.0 \pm 0.02 \text{ mg/dL}$ , and GFR was  $77.4 \pm 0.8 \text{ mL/min/1.73 m}^2$  for the whole cohort. The plaque volume for the whole study cohort was  $107.2 \pm 5.8 \text{ mm}^3$ . Per lesion analysis found the mean area stenosis to be  $32.4 \pm 0.4\%$ , and the lesion length to be  $22.1 \pm 0.3 \text{ mm}$ . Baseline clinical characteristics between patients with and without CKD are presented in *Table 1*. There were 688 (77%) patients in the no CKD group, and 203 (23%) in the CKD group. CKD patients were older (no CKD vs. CKD,  $57.9 \pm 0.3$  vs.  $67.4 \pm 0.6$ ,  $P < 0.001$ ) and more likely to be female (39% vs. 71%,  $P < 0.001$ ). As expected, CKD patients had a higher serum creatinine ( $0.9 \pm 0.0$  vs.  $1.2 \pm 0.1 \text{ mg/dL}$ ,  $P < 0.001$ ) and lower GFR ( $85.1 \pm 0.8$  vs.  $51.3 \pm 0.6 \text{ mL/min/1.73 m}^2$ ,  $P < 0.001$ ), but the proportion of patients with significant decline in renal function were comparable between CKD and no CKD groups (22% vs. 16%,  $P = 0.06$ ). CKD patients were more likely to have hypertension and to be current smokers, but the prevalence of other atherosclerotic risk factors including diabetes were similar. CKD patients had lower BMI, and they also differed from non-CKD patients in heart rate and diastolic blood pressure. In addition, CKD patients had a higher level of serum calcium. Cholesterol profile was comparable between non-CKD and CKD patients, except for triglyceride, which was lower in the CKD group. CKD patients were more likely to receive aspirin and diuretics, but the frequencies of statin use, either at baseline (36% vs. 41%,  $P = 0.19$ ) or follow-up (47% vs. 42%,  $P = 0.27$ ),



**Table 1** Baseline characteristics

	No CKD N = 688	CKD N = 203	P-value
Age, years	57.9 ± 0.3	67.4 ± 0.6	<0.001
Sex (female)	267 (39%)	144 (71%)	<0.001
Renal function			
Serum creatinine (mg/dL)	0.9 ± 0.0	1.2 ± 0.1	<0.001
GFR (mL/min/1.73 m <sup>2</sup> )	85.1 ± 0.8	51.3 ± 0.6	<0.001
Hypertension	346 (50%)	136 (67%)	<0.001
Hyperlipidaemia	221 (32%)	66 (33%)	0.95
Diabetes	140 (20%)	45 (22%)	0.59
Family history of CVD	183 (27%)	41 (20%)	0.07
Current smoker	141 (21%)	29 (14%)	0.05
Declining GFR (≥10% drop)	150 (22%)	32 (16%)	0.06
HR (bpm)	59.5 ± 0.3	57.6 ± 0.6	<0.01
SBP (mmHg)	128.2 ± 0.7	128.2 ± 1.3	0.99
DBP (mmHg)	78.3 ± 0.4	76.2 ± 0.8	<0.05
Body mass index	25.6 ± 0.1	23.5 ± 0.2	<0.001
Cholesterol profile (mg/dL)			
Total cholesterol	189.1 ± 1.5	187.4 ± 2.5	0.59
HDL cholesterol	50.2 ± 0.5	52.4 ± 1.1	0.06
Triglyceride	147.8 ± 3.5	128.7 ± 4.7	<0.01
LDL cholesterol	116.0 ± 1.3	113.2 ± 2.3	0.32
Serum calcium	8.6 ± 0.1	9.0 ± 0.1	<0.05
Serum phosphate	3.6 ± 0.6	3.7 ± 0.6	0.20
Interscan duration (years)	3.6 ± 0.0	3.3 ± 0.1	<0.01
Medications			
Aspirin	248 (36%)	90 (45%)	<0.05
Beta-blocker	168 (25%)	52 (26%)	0.71
Diuretics	49 (7%)	27 (13%)	<0.01
ACEi/ARB	187 (28%)	65 (32%)	0.18
Statin	145 (36%)	198 (41%)	0.19
Plaque Characteristics (mm <sup>3</sup> )			
Total plaque volume	96.0 ± 5.5	145.4 ± 16.6	<0.01
Fibrous plaque volume	44.0 ± 2.7	58.3 ± 6.6	0.05
Fibrofatty plaque volume	21.0 ± 1.4	18.9 ± 2.5	0.21
Necrotic core volume	2.7 ± 0.3	2.3 ± 0.5	0.42
Dense calcification	28.3 ± 2.4	65.9 ± 10.1	<0.001

were similar between the two groups. At baseline, CKD patients had a higher mean total plaque volume ( $96.0 \pm 5.5$  vs.  $145.4 \pm 16.6$  mm<sup>3</sup>,  $P < 0.01$ ) and a higher mean volume of calcified plaques ( $28.3 \pm 2.4$  vs.  $65.9 \pm 10.1$  mm<sup>3</sup>,  $P < 0.001$ ). Similarly, compared to non-CKD patients, CKD patients had higher mean plaque burden (plaque volume normalized to vessel volume,  $35.3 \pm 1.7\%$  vs.  $51.9 \pm 4.6\%$ ,  $P < 0.01$ ). Multivariate analysis using the general linear model confirmed the independent association between CKD and baseline plaque volume ( $P = 0.03$ ), and other significant clinical variables include age ( $P < 0.001$ ), sex ( $P < 0.001$ ), hypertension ( $P < 0.001$ ), and statin use ( $P < 0.001$ ). Moreover, atherosclerotic plaques in CKD patients were more calcified (calcified plaque volume as a percentage of total plaque volume,  $27.4 \pm 1.1\%$  vs.  $40.2 \pm 2.1\%$ ,  $P < 0.001$ ).

## Association between CKD and plaque progression

The details of interscan changes in atherosclerotic plaques are presented in *Table 2* and *Figure 2*. The change in total plaque volume between CCTA 1 and CCTA 2 was  $57.5 \pm 3.4$  mm<sup>3</sup> in the non-CKD and  $65.9 \pm 7.7$  mm<sup>3</sup> in CKD patients, indicating similar plaque progression between both groups ( $P = 0.28$ , *Figure 2*). Annualized change in plaque volume was also similar between the two groups ( $17.3 \pm 1.0$  vs.  $19.9 \pm 2.0$  mm<sup>3</sup>/year,  $P = 0.25$ ). In our multivariate analysis, we did not find independent association between CKD and plaque progression ( $P = 0.31$ ).

## Association between CKD and changes in plaque composition

The details of changes in plaque composition are presented in *Table 2* and *Figure 3*. Compared to patients with no CKD, CKD patients had a significantly higher increase in both crude ( $28.9 \pm 2.1$  vs.  $50.3 \pm 5.8$  mm<sup>3</sup>/year,  $P < 0.01$ ) and annualized calcified plaque volume ( $8.4 \pm 0.6$  vs.  $15.0 \pm 1.6$  mm<sup>3</sup>/year,  $P < 0.001$ ). On the other hand, patients with no CKD had more crude ( $28.7 \pm 2.9$  vs.  $15.7 \pm 4.8$  mm<sup>3</sup>/year,  $P = 0.03$ ) and annualized increase in non-calcified plaque volume ( $8.9 \pm 0.9$  vs.  $4.9 \pm 1.4$  mm<sup>3</sup>/year,  $P = 0.02$ ). These results indicate that atherosclerotic plaques in CKD patients become progressively calcified over time.

## Association between changes in renal function and plaque progression

We examined changes in total plaque volume in patients whose renal function had significantly deteriorated during the study, between CCTA1 and CCTA2 (refer to *Table 3* and *Figure 2*). We found both crude (stable GFR vs. declining GFR,  $54.1 \pm 3.2$  vs.  $80.2 \pm 9.0$  mm<sup>3</sup>,  $P < 0.01$ ) and the annualized changes in total plaque volume ( $16.4 \pm 0.9$  vs.  $23.9 \pm 2.6$  mm<sup>3</sup>/year,  $P < 0.01$ ) were higher in patients with declining renal function. We further examined the pattern of plaque progression and found that in patients with declining renal function, in total, there were 460 lesions at CCTA 1, which had increased to 604 lesions at CCTA 2. In addition, plaque length had increased from  $22.8 \pm 0.7$  mm<sup>3</sup> at baseline to  $26.4 \pm 0.8$  mm<sup>3</sup> at follow-up ( $P < 0.001$ ). Similarly, in patients with stable GFR, both total plaque numbers (1591 lesions in CCTA 1 and 2097 in CCTA 2) and mean plaque length ( $21.9 \pm 0.4$  vs.  $25.2 \pm 0.4$  mm<sup>3</sup>,  $P < 0.001$ ) had increased between CCTA1 and CCTA 2. Collectively, they indicate both development of new lesions and extension of existing plaques contribute to plaque progression.

## Association between changes in renal function and changes in plaque composition

As shown in *Table 2* and *Figure 3*, Patients with declining renal function had a significant increase in both crude (stable GFR vs. declining GFR,  $22.4 \pm 2.6$  vs.  $38.8 \pm 6.5$  mm<sup>3</sup>,  $P = 0.02$ ) and annualized change in non-calcified plaque volume ( $7.1 \pm 0.8$  vs.  $11.6 \pm 1.8$  mm<sup>3</sup>/year,  $P = 0.02$ ). On the other hand, no significant difference in interval increase in calcified plaques was noted between the two groups.

**Table 2** Plaque progression by CKD status

	No CKD N = 688	CKD N = 203	P-value
Change in plaque volume (mm <sup>3</sup> )			
Total plaque volume	57.5 ± 3.4	65.9 ± 7.7	0.28
Fibrous plaque volume	23.1 ± 1.9	16.3 ± 3.5	0.09
Fibrofatty plaque volume	5.1 ± 1.4	-0.2 ± 0.02	<0.05
Necrotic core volume	0.5 ± 0.3	-0.3 ± 0.5	0.16
Calcified plaque volume	28.9 ± 2.1	50.3 ± 5.8	<0.01
Annualized change in plaque volume (mm <sup>3</sup> /year)			
Total plaque volume	17.3 ± 1.0	19.9 ± 2.0	0.25
Fibrous plaque volume	7.0 ± 0.6	5.2 ± 1.1	0.13
Fibrofatty plaque volume	1.7 ± 0.4	-1.0 ± 0.6	<0.05
Necrotic core volume	0.1 ± 0.1	-0.2 ± 0.2	0.10
Calcified plaque volume	8.4 ± 0.6	15.0 ± 1.6	<0.001

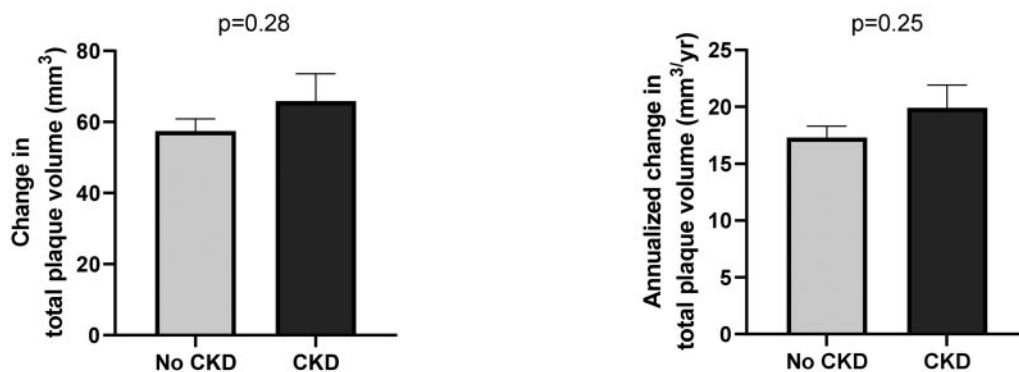
### Multivariate analysis for association between changing renal function and plaque progression

To further evaluate if declining renal function is independently associated with plaque progression, we performed a multivariate analysis, the result was presented in *Table 4*. Three clinical variables were independently associated with plaque progression (annualized change in plaque volume), including baseline plaque volume ( $P < 0.001$ ), serum calcium ( $P = 0.044$ ), and declining GFR ( $P = 0.046$ ).

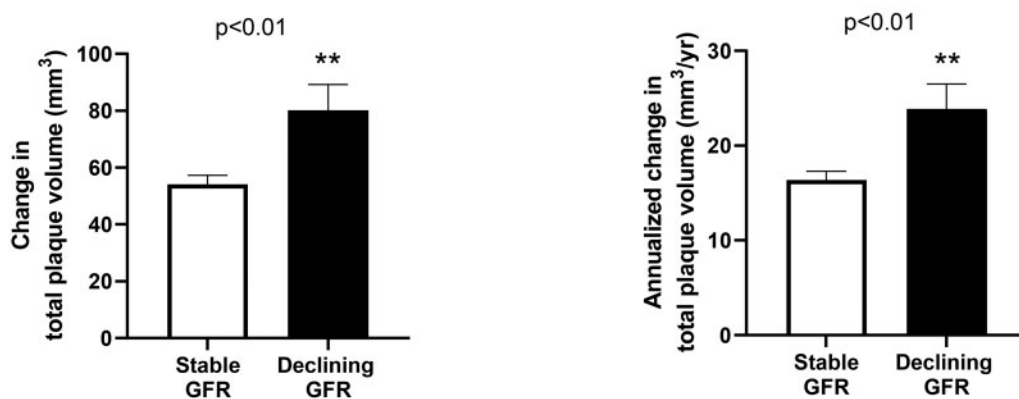
### Association between CKD, changing renal function, and high-risk plaques

We performed per-lesion analysis to examine the frequency of high-risk plaques and its four constituent features in patients with and without CKD (refer to *Table 5*). No significant between-group difference in high-risk plaques was found either at baseline or at follow-up. Of the four constituent high-risk features, low attenuation plaques were more prevalent at baseline in the patients with no CKD ( $P = 0.03$ ) and napkin ring sign was more prevalent in CKD patients at

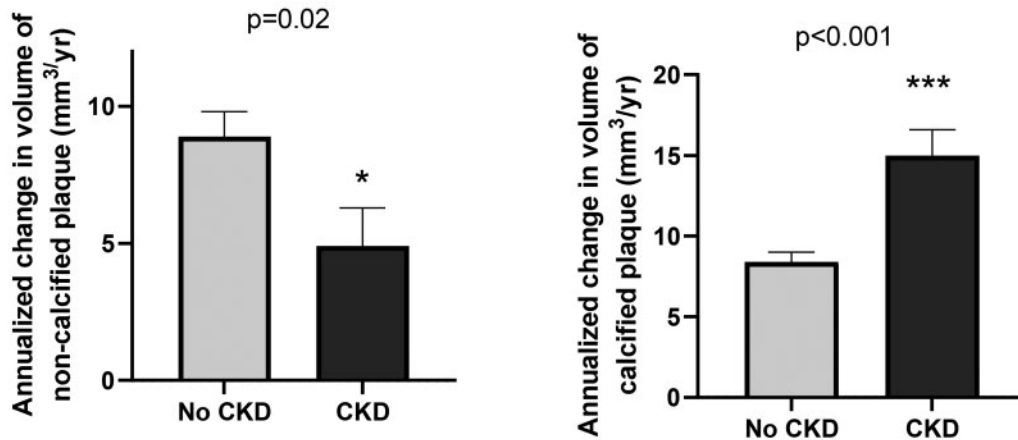
#### Plaque progression by CKD status



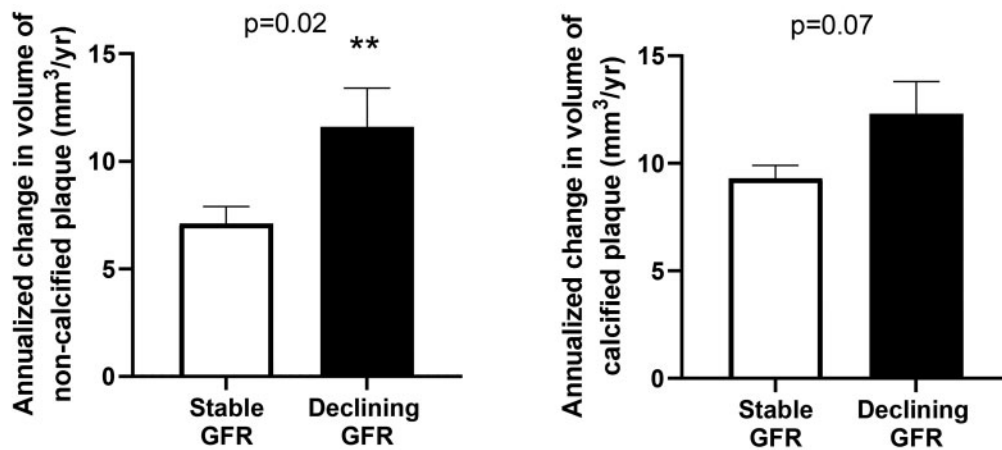
#### Plaque progression by Changes in GFR

**Figure 2** Plaque progression by CKD and changing renal function status.

### Change in plaque composition by CKD status



### Change in plaque composition by change in GFR



**Figure 3** Change in plaque composition by CKD and changing renal function status.

follow-up ( $P=0.05$ ). Similarly, stratified by changing renal functions, we did not see significant differences in the prevalence of high-risk plaques between patients with stable and declining GFR in CCTA 2 to indicate evolution into a more unstable plaque phenotype. Additionally, we examined the number of lesions that has destabilized over time, i.e. lesions with  $<2$  high-risk features at CCTA 1 but evolved to become a high-risk plaque in CCTA 2. In CKD patients,  $0.4 \pm 0.2$  lesions in each patient turned into high-risk plaques, compared to  $0.5 \pm 0.2$  lesions in non-CKD patients ( $P=0.78$ ). Similarly, the number of lesions that became high-risk over the study period were not different between patients with stable and declining GFR ( $0.4 \pm 0.2$  vs.  $0.4 \pm 0.2$ ,  $P=0.98$ ) (Table 6).

## Discussion

The principal findings of this study are (i) declining renal function, but not CKD, is independently associated with plaque progression. (ii) Compared with no CKD, plaques in CKD patients have more calcified plaque and further progression in calcified components of plaques over time. (iii) Neither CKD nor declining renal function is associated with higher prevalence of high-risk plaque features.

Using both intravascular ultrasound and CCTA, investigators have established that plaque progression, defined as an increase in total plaque volume over time, is a strong independent prognosticator of worse outcomes.<sup>10,18</sup> This observation has been validated in both the



**Table 3** Plaque progression according to change in renal function

	Stable GFR N = 709	Declining GFR N = 182	P- value
Change in plaque volume (mm <sup>3</sup> )			
Total plaque volume	54.1 ± 3.2	80.2 ± 9.0	<0.01
Fibrous plaque volume	18.7 ± 1.7	32.4 ± 4.6	<0.01
Fibrofatty plaque volume	3.2 ± 1.3	6.6 ± 2.5	0.25
Necrotic core volume	0.4 ± 0.3	-0.2 ± 0.5	0.29
Calcified plaque volume	31.8 ± 2.4	41.7 ± 4.9	0.07
Annualized change in plaque volume (mm <sup>3</sup> )			
Total plaque volume	16.4 ± 0.9	23.9 ± 2.6	<0.01
Fibrous plaque volume	5.8 ± 0.5	9.8 ± 1.3	<0.01
Fibrofatty plaque volume	1.1 ± 0.4	2.0 ± 0.7	0.30
Necrotic core volume	0.1 ± 0.1	-0.2 ± 0.2	0.07
Calcified plaque volume	9.3 ± 0.6	12.3 ± 1.5	0.07

**Table 4** Generalized linear model for the association between clinical variables and plaque progression

	F-value	P-value
Age	0.012	0.91
Sex	0.397	0.53
BMI	3.844	0.05
Triglyceride	0.128	0.72
Diastolic blood pressure	0.736	0.39
Heart rate	2.079	0.15
Hypertension	1.640	0.20
Current smoker	2.580	0.11
Statin at baseline	1.735	0.19
Diabetes	0.226	0.64
Baseline plaque volume	178.169	<0.001
Baseline GFR	2.737	0.10
Serum calcium	4.068	<0.05
Serum phosphate	0.137	0.71
Decline in renal function	3.992	<0.05

general and CKD populations.<sup>19</sup> In this study, patients with CKD had similar plaque progression compared to those without CKD. This is consistent with a prior meta-analysis of 989 patients that showed plaque progression, assessed by an intravascular ultrasound, is similar between CKD (GFR < 60 mL/min/1.73 m<sup>2</sup>) and non-CKD patients.<sup>20</sup> On the other hand, we found that deteriorating renal function over time is independently associated with plaque progression, which could provide a mechanistic explanation to the epidemiological observation that longitudinal decline in renal function, independent of baseline status, is associated with total and cardiovascular

mortality.<sup>2-4</sup> In the National Observatory of Atherosclerosis in Nephrology (NEPHRONA) study, investigators prospectively followed 1553 CKD patients over 24 months and found that declining renal function is associated with progression of atherosclerosis, measured by the number of femoral or carotid territory affected by atheroma, as determined by vascular ultrasound.<sup>21</sup> This study extended these observations to the coronary circulation, the vasculature most relevant to clinical events and most important in prognosis,<sup>22</sup> and lends support to the notion declining renal function is associated with accelerated atherosclerosis. This may be, in part, related to the progression in atherosclerotic plaques in abdominal aorta and renal artery. From a mechanistic perspective, the parallel progression between CKD and coronary atherosclerosis may be explained by shared pathogenesis processes that drive both diseases. Traditional risk factors, most notably, hypertension and diabetes, are commonly present in and contribute to both disease states. In this study, we have adjusted for traditional risk factors and statin use, thus differences in risk profile, co-morbidities, and treatment have been accounted for. However, emerging risk factors including endothelial dysfunction, inflammation, and oxidative stress also play significant roles in both disease processes.<sup>23</sup> As these variables were not measured in clinical practice, it was not possible to adjust for them to determine the magnitude of their contribution and interaction with declining renal function, CKD, and atherosclerosis. We suspect there were residual confounding from these important factors. Simply put, plaque and renal disease progression could be different manifestations of the same underlying pathological process. From a clinical standpoint, given plaque progression is a well-recognized marker of future risk, one implication of our finding is that deteriorating renal function may serve as a marker of underlying vascular risks, and more intensive medical therapy should be considered. Our finding also suggests better control and halting worsening of renal impairment may slow down plaque progression thus improves cardiovascular outcomes, though this needs to be validated by future clinical studies. On one hand, CKD is associated with higher baseline plaque volume, a powerful prognosticator. On the other hand, this study found that CKD is not associated with more rapid progression or a high-risk plaque phenotype. These findings implicate that cardiovascular risks associated with CKD are likely mediated through plaque activity and other plaque-independent processes including platelet dysfunction, hypercoagulability, and inflammation.

This study also found that CKD and declining renal function have different effects on plaque composition. Atherosclerotic plaques in CKD patients were more calcified at baseline and became progressively more calcified over time. This is consistent with previous studies showing positive correlation between CKD and coronary calcification, measured by coronary calcium score.<sup>24-26</sup> It is important to note that, CKD patients commonly have vascular calcification both in the intima, the location of atherosclerotic lesion, as well as the media.<sup>27</sup> Since coronary calcium score cannot distinguish these two, previous studies may over-estimate the volume of calcified plaques. One strength of this study is that we used a semi-automated software that quantified both calcified and non-calcified constituents of atherosclerotic plaques, thus providing a more accurate measure of calcific components of atherosclerotic plaques. In contrast, compared to patients with stable GFR, declining renal function is associated with more rapid progression in non-calcified plaques. The

**Table 6** Per lesion analysis of high-risk plaque features according to change in renal function

	CCTA 1			CCTA 2		
	Stable GFR N = 1591	Declining GFR N = 460	P-value	Stable GFR N = 2097	Declining GFR N = 604	P-value
High-risk plaques	287 (18%)	73 (16%)	0.28	391 (19%)	101 (17%)	0.28
Positive remodelling	1140 (72%)	341 (74%)	0.30	1575 (75%)	455 (75%)	0.91
Napkin ring sign	5 (0.3%)	5 (1%)	0.04	6 (0.3%)	3 (0.5%)	0.43
Spotty calcification	190 (12%)	57 (12%)	0.81	273 (13%)	79 (13%)	0.97
Low attenuation plaques	214 (13%)	48 (10%)	0.09	239 (11%)	57 (9%)	0.17

**Table 5** Per lesion analysis of high-risk plaque features according to CKD status

	CCTA 1			CCTA 2		
	No CKD N = 1478	CKD N = 573	P-value	No CKD N = 1975	CKD N = 726	P-value
High-risk plaques <sup>a</sup>	272 (18%)	88 (15%)	0.10	373 (19%)	119 (16%)	0.14
Positive remodelling	1068 (72%)	413 (72%)	0.93	1476 (75%)	554 (76%)	0.40
Napkin ring sign	6 (0.4%)	4 (0.7%)	0.40	4 (0.2%)	5 (0.7%)	0.05
Spotty calcification	180 (12%)	67 (12%)	0.72	269 (14%)	83 (11%)	0.13
Low attenuation plaques	203 (14%)	59 (10%)	0.03	228 (12%)	68 (9%)	0.11

<sup>a</sup>High-risk plaques defined as having  $\geq 2$  of the following: positive remodelling, napkin ring sign, spotty calcification, and low attenuation plaques.

prognostic implication of different plaque compositions, in particular, given its dynamic nature, is complex and remains an area of active investigations. For example, the Coronary CT Angiography Evaluation For clinical Outcomes: An International Multicenter (CONFIRM) registry demonstrated that in CKD patients, a higher coronary calcium score is associated with worse outcomes.<sup>28</sup> On the other hand, a recent post-hoc analysis from the Scottish Computed Tomography of the HEART (SCOT-Heart) trial showed that calcified plaques do not independently predict adverse clinical events.<sup>29</sup> These seemingly conflicting results highlight current knowledge gaps and calls for novel imaging markers of high specificity to improve risk stratification. In this study, we have not found any between-group differences in high-risk plaques or its constituent features that could account for excessive risks in patients with CKD and declining renal function.

There are a number of limitations to this study. Firstly, inherent to the registry studies are selection bias, and patients with severe CKD or on dialysis are likely deliberately excluded in clinical practice to avoid contrast nephropathy. Secondly, CKD in this study is defined solely on GFR and did not include patients with microalbuminuria, which has been implicated in atherogenesis and vascular risks.<sup>26</sup> Thirdly, CKD plaques are more calcified, which could compromise

image quality and potentially affect analysis. Fourthly, while all studies were performed using CT scanners of at least 64 detectors, CCTA 1 and CCTA 2 may be performed on CT scanners with different CT technology and image reconstruction techniques. This can potentially affect image quality and plaque analysis, though we believe the potential impact is limited. Balancing these are the large sample size drawing from multiple sites and the robust methodology that comprehensively profile atherosclerotic plaques.

## Conclusion

Deteriorating renal function, but not CKD, is associated with progression of atherosclerotic plaques but not high-risk plaque morphology. This suggests deteriorating renal function is associated with an accelerated atherosclerosis and may serve as marker for future risks, where more intensive medical therapy should be considered. This hypothesis needs to be further evaluated in future clinical studies. Atherosclerotic plaques in CKD patients become progressively calcified whereas in patients with declining GFR, there is a significant interval increase in non-calcified plaques. The clinical significance of these disparate changes in plaque composition is unclear and warrants further investigations.

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## Data availability

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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