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Location of acute coronary artery thromboses in patients with and without chronic kidney disease

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Patients with chronic kidney disease have high rates of myocardial infarction and death following an initial attack. Proximal location of coronary atherosclerotic lesions has been linked to the risk of acute myocardial infarction and to infarction-associated mortality. To examine if the spatial distribution of lesions differs in patients with and without chronic kidney disease, we used quantitative coronary angiography to measure this in patients with acute coronary thromboses who were having angiography following acute myocardial infarction. Multivariable linear regression was used to adjust for differences in baseline characteristics. Among 82 patients with stage 3 or higher chronic kidney disease, 55.6% of lesions were located within 30 mm and 87.7% were within 50 mm of the coronary ostia. This compared to 34.7 and 71.8%, respectively, among 299 patients without significant kidney disease. Chronic kidney disease was independently and significantly associated with a 7.0 mm decrease in the distance from the coronary ostia to the problem lesion. Our study suggests that a causal link between a more proximal culprit lesion location in patients with chronic kidney disease and their high mortality rates after myocardial infarct is possible and may have important implications for interventions to prevent infarction.

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Individuals with chronic kidney disease (CKD) suffer from high rates of myocardial infarction (MI) and cardiovascular death[1] and suffer from high rates of death following MI[2] compared to individuals with normal renal function. Systemic factors such as inflammation and oxidative stress have been implicated in the etiology of this increased risk and have been the focus of numerous investigations,[3–5] but whether patients with CKD have a unique anatomic patters of atherosclerosis and plaque rupture remains undetermined.

In the general population, the location of MI has been measured. Coronary thromboses leading to MI are distributed in a nonuniform manner. They cluster within the proximal one-third of the coronary arteries, and the likelihood of clinically significant plaque rupture decreases by 13–30% for each 10 mm away from the coronary artery ostia.[6,7] Clinical outcomes following plaque rupture are also profoundly influenced by plaque location. In ST elevation MI, for example, the risk of death following acute plaque rupture is low when thromboses are distal, but doubles when thromboses occur proximally.[8–10]

These studies suggest that both the risk of MI and its clinical severity are closely linked to plaque location and vary inversely with distance away from the coronary artery ostium. Differences in the spatial distribution of culprit lesions for MI might partly explain CKD-related differences in both the risk of MI and the risk of death following MI. We sought to identify differences in MI location between patients with and without CKD.

RESULTS

Baseline characteristics

In total, 381 patients, 198 (52.0%) with ST elevation MI (STEMI) and 183 with non-ST elevation MI (NSTEMI) (48.0%) met the inclusion criteria and underwent quantitative angiographic analysis using standardized angiographic views of each coronary segment (Table 1). Mean estimated glomerular filtration rate (eGFR) was 80.0 ± 27.7 ml/min per 1.73 m^2, and 82 (21.5%) patients had an eGFR < 60 ml/min per 1.73 m^2. In all, there were 133 patients with normal renal function/class 1 CKD, 166 patients with class 2 CKD, and 69

Table 1 | Angiographic projections used in individual coronary artery segments

Segment	Projection
Left main artery	Anterior posterior caudal
Ramus intermedius	Left anterior oblique cranial
Right coronary artery	—
Proximal	Straight left anterior oblique
Mid	Straight left anterior oblique
Distal	Straight left anterior oblique
Posterior descending artery	Left anterior oblique cranial
Posterior lateral segment	Left anterior oblique cranial
Left anterior descending artery	—
Proximal	Right anterior oblique caudal
Mid	Right anterior oblique caudal
Distal	Right anterior oblique caudal
First diagonal	Left anterior oblique cranial
Second diagonal	Left anterior oblique cranial
Circumflex artery	—
Proximal	Right anterior oblique caudal
Mid	Right anterior oblique caudal
Distal	Right anterior oblique caudal
First obtuse marginal	Right anterior oblique caudal
Second obtuse marginal	Right anterior oblique caudal

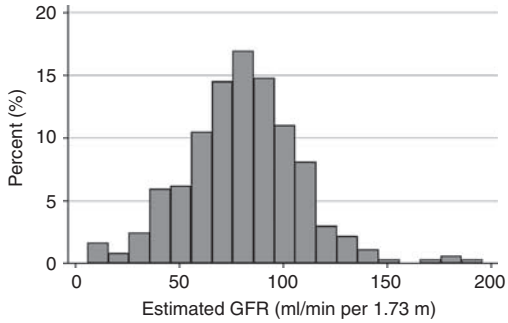

Figure 1 | Distribution of estimated glomerular filtration rate in the study population. CKD was defined as estimated GFR <60 ml/min per 1.72 m^2. Using this definition 82 of the population of 381 (21.5%) had CKD.

patients with class 3 CKD. Of 13 patients with class 4/5 CKD, 3 were on chronic dialysis. Distribution of eGFR is shown in Figure 1.

Individuals with stage 3 or higher CKD were older (72.5 years vs 60.7 years) more likely to be women (52.2 vs 27.4%), and they were more likely to have diabetes (41.5 vs 22.4%), dyslipidemia (72.0 vs 55.2%), or a prior history of MI (31.7 vs 14.7%). STEMI was less common in individuals with stage 3 or higher CKD (30.5 vs 58.9%) and left main artery infarct location was more common (6.1 vs 1.0%). Other MI characteristics did not differ by CKD class. Patient characteristics are summarized in Table 2.

Overall lesion characteristics

Median distance to lesion (DTL) for the entire cohort was 35.3 mm. Lesions were more frequently located in the left anterior descending (LAD) or diagonal vessels ($N=140$) and the right coronary (RCA; $N=145$) than in other vessels. Left main ($N=8$) and ramus intermedius vessels ($N=5$) were infrequent sites of acute thrombosis. Thromboses in the RCA were more distal than lesions in other coronary arteries ($P<0.001$) whereas left main lesions were significantly more proximal ($P<0.002$). Distribution of lesions according to vessel and CKD status is shown in Table 3.

Lesion location

On univariate analysis (Table 4), male patients ($\beta=8.18$, $P<0.001$), patients with STEMI ($\beta=8.58$, $P<0.001$), and patients with an RCA infarct ($\beta=11.78$, $P<0.001$) had more distal lesions. Patients with diabetes ($\beta=-5.78$, $P<0.001$), stage 3 or higher CKD ($\beta=-10.21$, $P<0.001$), left main infarct or LAD infarcts had more proximal lesions. Lesion location was not associated with peak CK or ejection fraction, but patients with congestive heart failure did have more proximal lesions ($\beta=-7.11$, $P=0.05$) than patients without heart failure. Overall DTL was closely related to the stage of CKD with lower distances observed in more advanced stages of CKD (P for trend <0.001). Mean (s.d.) DTL was 43.3 (25.1) in patients with no CKD/class 1 CKD, 41.3 (24.0) in class 2 CKD, 32.5 (24.0) in class 3 CKD, and 29.7 (15.6) in class 4/5 CKD.

When the major vessels were examined individually (vessel analysis), patients with stage 3 or higher CKD had more proximal lesions in the left circumflex (LCX; 19.6 vs 27.6, $P=0.06$) and the RCA (34.5 vs 50.2, $P=0.02$), but not in the LAD (19.4 mm vs 21.5, $P=0.43$). In patients with CKD, 55.6% of lesions were located within 30 mm and 87.7% were located within 50 mm of the coronary ostia (left main analysis). Conversely, in patients without stage 3 or higher CKD, only 34.7% of lesions were located within 30 mm and only 71.8% were located within 50 mm of the coronary ostia. Unadjusted associations of CKD with lesion location are shown in Figures 2 and 3.

Chronic kidney disease remained a significant predictor of DTL after adjustment for age, sex, race, diabetes, hypertension, smoking, hyperlipidemia, infarct vessel, and family history of coronary artery disease (Table 5). Stage 3 or higher CKD was independently associated with a 7.0 mm more proximal MI location (95% confidence interval (CI): 13.39–0.61, $P=0.03$) compared to patients without CKD. Conversely RCA lesions and male sex were associated with adjusted increases of 10.54 mm (95% CI: 5.14–15.94, $P<0.001$) and 7.31 mm (95% CI: 2.05–12.58, $P=0.01$), respectively. The association of CKD with DTL was similar in diabetics vs nondiabetics (P for interaction 0.18), STEMI vs NSTEMI (P for interaction 0.23) and men vs women (P for interaction 0.30). The adjusted association of CKD with DTL was not significantly different in patients with LAD infarcts compared to those with infarcts in other vessels (P for interaction 0.18).

Secondary analyses using the stages of CKD in place of the binary definition of CKD revealed a trend toward shorter DTL in patients with more advanced stages of CKD. Results were qualitatively similar regardless of the serum creatinine used to estimate eGFR (Table 6).

Table 2 | Baseline characteristics of the study population

Characteristic	Chronic kidney disease (*N*=82)	Normal kidney function (*N*=299)	*P*-value
Demographics			
Age, mean ± s.d.	72.5 ± 11.3	60.7 ± 12.0	<0.001
Male sex	40 (48.8)	215 (72.6)	<0.001
Race			
White	70 (85.4)	249 (83.3)	0.65
Black	6 (7.3)	24 (8.0)	0.83
Medical history			
Diabetes	34 (41.5)	67 (22.4)	0.001
Dyslipidemia	59 (72.0)	165 (55.2)	0.01
Hypertension	73 (89.0)	197 (65.9)	<0.001
Present smoking	6 (7.3)	97 (32.4)	<0.001
Past smoking	24 (29.3)	78 (26.1)	0.56
Prior MI	26 (31.7)	44 (14.7)	<0.001
Family history of coronary artery disease	20 (24.4)	116 (38.8)	0.02
Laboratory data			
Creatinine, median (IQR), (mg per 100 ml)	1.4 (1.3–1.7)	0.90 (0.8–1.0)	<0.001
Estimated GFR, median (IQR), (ml/min per 1.73 m^2)	44.8 (37.2–53.3)	87.2 (75.0–102.8)	<0.001
Ejection fraction, mean ± s.d., (%)	46.3 ± 12.2	47.6 ± 11.8	0.45
Peak CK, median (IQR), (IU/l)	395 (142–1360)	492 (175–1128)	0.57
Infarct characteristics			
ST elevation MI	25 (30.5)	173 (58.9)	<0.001
Infarct location			0.04
Left main	5 (6.1)	3 (1.0)	—
LAD	29 (35.4)	111 (37.1)	—
LCX	19 (23.2)	64 (21.4)	—
RCA	27 (32.9)	118 (39.5)	—
Ramus	2 (2.4)	3 (1.0)	—
CHF on presentation	13 (15.9)	36 (12.0)	0.12

MI, myocardial infarction; IQR, interquartile range; GFR, glomerular filtration rate; CK, chronic kidney; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary; CHF, congestive heart failure.

Table 3 | Distance to lesion in millimeters from coronary ostia

Location of occlusion	CKD (*N*=81)	No CKD (*N*=299)	*P*-value
Overall[a], median (IQR)	28.4 (12.0–41.0)	37.2 (12.7–51.6)	<0.001
Left main, median (IQR)	13.6 (12.0–24.7)	7.3 (6.8–28.0)	0.46
Left anterior descending, median (IQR)	19.4 (11.7–28.7)	21.5 (14.1–32.7)	0.43
Left circumflex, mean ± s.d.	19.6 ± 14.9	27.6 ± 17.0	0.06
Right coronary artery, mean ± s.d.	34.5 ± 19.3	50.2 ± 31.4	0.02
Ramus, mean ± s.d.	7.0 ± 3.6	12.0 ± 5.6	0.31

CKD, chronic kidney disease; IQR, interquartile range.
[a]Overall distance to lesion is measured in millimeters from the ostium of the right coronary artery for right coronary lesions and from the ostium of the left main for all other lesions. In the individual coronary arteries distance to lesion is measured from the ostium of each artery.

DISCUSSION

Patients with CKD suffer from both a high incidence of MI and a high risk of death following initial MI,[1,2] but the etiology of this remains incompletely understood. Differences in the distribution and location of coronary artery plaque ruptures in individuals with CKD compared to those without CKD could partly explain this increased risk, but has not been previously examined. We therefore compared the distribution of acute coronary thromboses in patients with and without CKD who were undergoing angiography for acute MI. We found that the lesions accounting for acute MI were, on average, significantly more proximally distributed in patients with stage 3 or higher CKD than in patients without CKD and that this difference was independent of comorbid conditions such as diabetes and hypertension.

Proximal culprit lesions are known to be significantly associated with an increased risk of death or major complications following an MI. In an analysis of STEMI patients undergoing thrombolysis, Karha *et al.*[9] found that the risks of in-hospital death or recurrent MI were twofold higher when the culprit lesion was located proximal to the first major branch vessel of an epicardial artery. Within the LAD, the odds ratio of 30-day death or MI decreased by 0.79 for each 1 cm increase in distance down the artery. In a similar analysis of patients undergoing primary percutaneous intervention for acute MI, the adjusted odds of in-hospital

mortality was more than 1.5-fold higher in patients with proximal lesions compared to those with more distal lesions. The presence of proximal culprit lesions was independently associated with the risk of ventricular arrhythmias or sustained hypotension during the initial hospitalization and demonstrated a strong trend toward an increased risk of major adverse cardiovascular events during the first year following MI.[10]

Table 4 | Crude associations with distance to lesion

Variable	β	*P*-value
Demographics	—	—
Age	—	—
<40	9.17	0.22
40–59	−1.57	0.54
60–79	Referent	Referent
⩾80	−3.85	0.39
Male sex	8.18	0.001
Race	—	—
White	Referent	Referent
Black	4.35	0.33
Other	−0.95	0.83
Medical history		
Diabetes	−5.78	0.03
Dyslipidemia	−3.61	0.17
Hypertension	−1.58	0.55
Present smoking	4.82	0.08
Past smoking	1.25	0.65
Prior MI	2.30	0.46
Family history of CAD	4.64	0.06
CKD	−10.21	<0.001
Laboratory data	—	—
Estimated GFR (per 10 ml/min per 1.73 m^2)	1.20	0.01
Ejection fraction, (per 10%)	1.45	0.21
Peak CK, (per 1 U/l)	0.00	0.67
Infarct characteristics		
ST elevation MI	8.58	<0.001
Infarct vessel		
Left main	−25.53	0.002
Left anterior descending	−7.22	0.004
left circumflex	−2.33	0.43
Right coronary artery	11.78	<0.001
Ramus	−14.85	0.16
CHF on presentation	−7.11	0.05

MI, myocardial infarction; CAD, coronary artery disease; CK, chronic kidney; GFR, glomerular filtration rate; CHF, congestive heart failure.

Within the context of this strong association between the risk of death or recurrent MI and the location of the culprit lesion responsible for acute MI, our findings of a significant difference in the spatial distribution of culprit lesions in individuals with and without CKD suggests that spatial distribution of coronary lesions may be an important determinant of the high risk of death following MI in patients with CKD. Indeed, if the relative risk of death in patients with proximal culprit lesions is truly 1.5- to 2.0-fold higher[9,10] than in patients with nonproximal lesions, then the 15.9% increase in the percentage of lesions located within the proximal 50 mm of the coronary tree that we observed in individuals with CKD compared to those without CKD could potentially account for a substantial portion of the increased risk of death in patients with CKD. Our findings argue for the addition of proximal culprit lesion location to the growing list of risk factors and risk markers that have been associated with the post-MI mortality in patients with CKD. Although lesion location as a risk factor does not suggest a particular pharmacologic intervention as do dyslipidemia, inflammation, and oxidative stress, there are nevertheless potentially important therapeutic implications to our findings. Because the proximal coronary tree is more likely to contain culprit lesions for MI, this region can be considered to be an anatomically high-risk region that could potentially be targeted for preemptive interventions to prevent MI.

In fact, the high risks of cardiovascular death in patients with CKD,[1,2] the uncertain benefit of standard medical therapies in this population,[11,12] and the more proximal distribution of plaque ruptures in patients with CKD suggest that the CKD population may be a particularly attractive group in which to investigate novel medical or interventional therapies designed to target anatomic regions at higher risk of plaque rupture. Natural history studies of proximal atherosclerotic lesions in patients with CKD, as well as studies

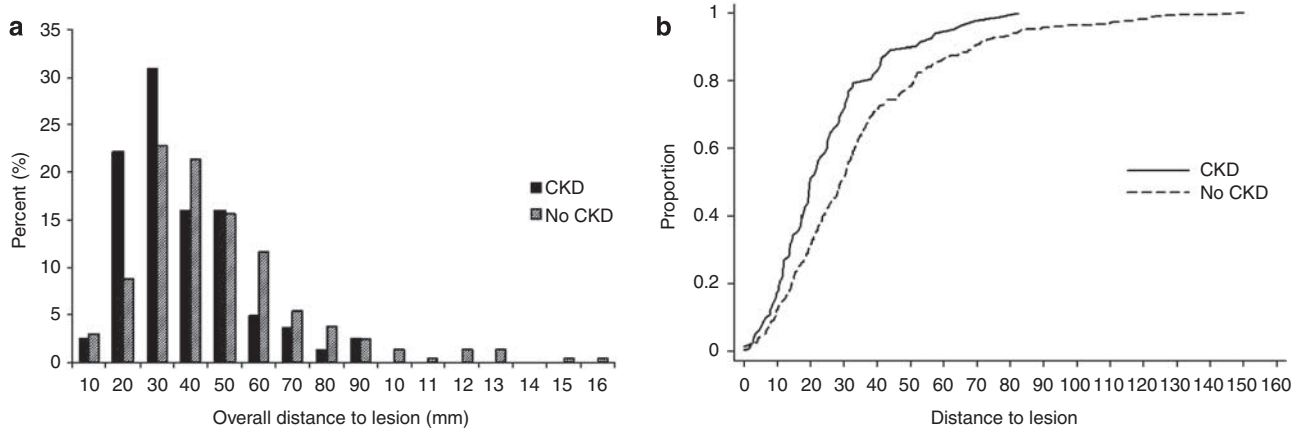

Figure 2 | Infarct location in patients with and without CKD. (**a**) Frequency distribution and (**b**) cumulative frequency distribution.

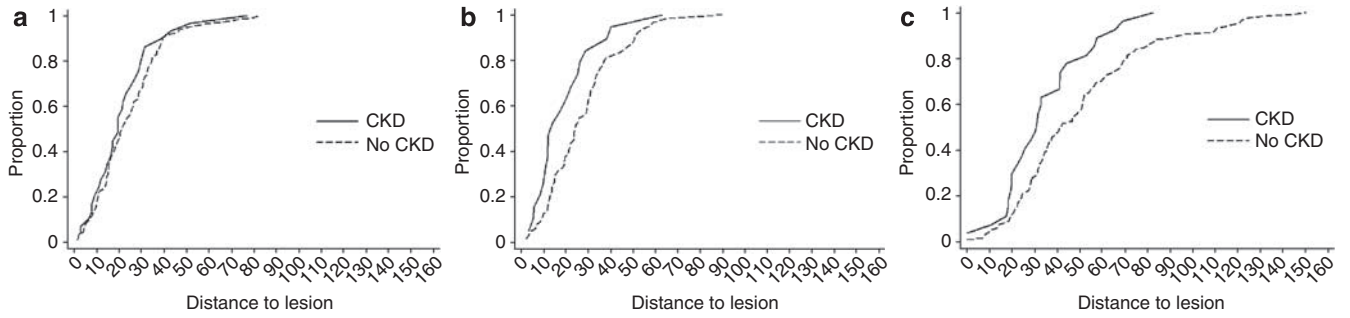

Figure 3 | Cumulative frequency distribution of infarct location according to CKD status and vessel. (**a**) Left anterior descending artery, (**b**) left circumflex artery, (**c**) right coronary artery.

Table 5 | Multivariable adjusted predictors of distance to lesion

Variable	β	Standard 95% CI	Bias-corrected 95% CI	*P*-value
Demographics				
Age				
40–59 (years)[a]	−5.09	−10.43–0.25	−10.56–0.38	0.06
Male sex	7.31	2.05–12.58	2.22–12.50	0.01
Medical history				
CKD	−7.00	–13.39 to -0.61	–13.14 to –0.98	0.03
Infarct characteristics				
ST elevation MI	4.57	−0.37–9.51	−0.81–9.02	0.07
RCA[b]	10.54	5.14–15.94	4.99–16.43	<0.001

MI, myocardial infarction; CI, confidence interval; CKD, chronic kidney disease; RCA, right coronary.
Significant and borderline significant predictors of lesion location after adjusting for age, sex, race, hypertension, smoking history, family history, diabetes, infarct type, and infarct location.
[a]Compared to age 60–79 years.
[b]Compared to LAD infarct.

analyzing the role of lesion location as an adjunct to the measurement of established risk factors in cardiovascular risk-stratification tools should help determine whether pursuing such novel approaches to the prevention of MI are warranted.

Our findings should be interpreted within the context of the study design. The relatively small sample size limited our ability to analyze for differences in DTL according to stage of CKD or infarct vessel. Nevertheless, our analysis suggested that higher stages of CKD are associated with progressively more proximal coronary occlusions, and that the association of CKD with DTL was more pronounced in the LCX and RCA than in the LAD. However, the CIs around these estimates were wide, and the mean DTL in the LAD remained lower in patients with CKD than in those without CKD. Furthermore, the adjusted interaction between CKD and LAD infarct location was nonsignificant. Thus, larger studies with greater power to perform subgroup and stratified analyses are needed to refine our estimates of the relationship between CKD, DTL, and infarct vessel.

Estimates of renal function have an imperfect correlation with true GFR. In this study, a single serum creatinine was used to define CKD status, and although all samples were analyzed by a single laboratory, serum creatinine was not calibrated against the Cleveland Clinic Laboratory.[13] Although some misspecification of CKD status may have occurred, our results were qualitatively unchanged when an alternative creatinine was used to estimate eGFR. Furthermore, misclassification of CKD status would most likely have been nondifferential with respect to culprit lesion location, and misclassification of renal function is thus unlikely to fully explain our finding of a positive association between CKD and lesion location. An additional concern is that angiography was used to assess distance from coronary ostia to culprit lesions. Future studies should consider using intravascular ultrasound to assess DTL as this technique may be more accurate than angiography in measuring absolute distances. However, intravascular ultrasound is a time-consuming, invasive technique. Its use to measure DTL would have delayed intervention on the acute coronary occlusions we studied and would not have been feasible in all cases, particularly in the setting of STEMI. Standardized angiographic views were used to minimize foreshortening, and foreshortening effects should have been similar in both groups. Nevertheless, it is possible that our methods have underestimated the true DTL in some patients.

Finally, we cannot exclude the possibility that the differences in DTL were confounded by differential referral of patients with and without CKD for coronary angiography. If patients with CKD are referred for coronary angiography only when MI is clinically severe, then the more proximal distribution that we observed could be a surrogate for MI severity rather than a consequence of renal failure. If this were the case, however, the prevalence of CKD in our cohort should have been lower than the prevalence of CKD in unselected cohorts of MI patients. In fact, we observed rates of stage 3 or higher CKD and a distribution of eGFR that were strikingly similar to those seen in several recent MI cohorts.[14–16] Although further studies with noninvasive modalities of coronary imaging will be required to definitively rule out significant confounding from referral bias, we believe that differential referral patterns are unlikely to fully explain our findings.

Table 6 | Adjusted association of CKD stage and distance to lesion

CKD Class	β	95% CI	P-value
eGFR estimated from creatinine at time of angiography			
No CKD/class 1	Referent	Referent	Referent
Class 2	−0.51	−6.07–5.04	0.86
Class 3	−6.64	−14.51–1.22	0.10
Class 4/5	−10.83	−24.63–2.97	0.12
eGFR estimated from alternative serum creatinine[a]			
No CKD/class 1	Referent	Referent	Referent
Class 2	0.73	−5.34–6.80	0.81
Class 3	−4.83	−14.14–4.48	0.31
Class 4/5	−13.69	−27.06–0.32	0.05

Abbreviations: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.
Adjusted association of CKD stage and lesion location after adjusting for age, sex, race, hypertension, smoking history, family history, diabetes, infarct type, and infarct location.
[a]Serum creatinine drawn 1–2 days before angiography or, if not available, the serum creatinine drawn on the day of discharge.

How the presence of CKD leads to more proximal culprit lesions is uncertain. One possibility is that the effects of arterial calcification,[17] hypertension, and metabolic disturbances in individuals with CKD alters arterial elasticity and leads to higher levels of proximal shear stress in patients with CKD compared to patients without CKD. Over time this increase in shear stress may contribute to endothelial damage and lead to more frequent plaque ruptures[18] in patients with CKD. In this respect, the recent observation that outward remodeling is increased in the proximal coronary arteries of patients with CKD[19] is highly intriguing and may provide a clue toward the underlying biologic processes in patients with and without CKD. Further studies of shear stress forces and plaque biology in the coronary arteries of patients with and without CKD may provide additional insight into the mechanisms behind our findings. Differences in these forces due variations in the shape and size of the LAD, LCX, and RCA might also explain the apparent differences we observed in the effect of CKD in the epicardial coronary arteries.

It is also intriguing that despite the more proximal overall distribution of coronary occlusions in patients with CKD, the frequency of CKD among those who presented with STEMI was lower than it was among patients who presented with NSTEMI. The DTL was more proximal in patients with CKD regardless of whether they presented with STEMI or NSTEMI, and it should be noted that our analysis combined a STEMI cohort with an equally sized cohort of NSTEMIs, and thus cannot address the true, relative prevalences of STEMI vs NSTEMI in the overall population of patients with or without CKD who present with MI. Nevertheless, prior observations suggest that patients with advanced CKD present with NSTEMI more frequently than they present with STEMI.[20] Deficiencies in coronary collateral[21] and myocardial capillary supply,[22] a high frequency of electrolyte abnormalities, and left ventricular hypertrophy[23] and a high prevalence of baseline electrocardiographic abnormalities such as bundle branch block[24] and changes in QRS intervals[25] may explain why STEMI is apparently less prevalent in patients with CKD despite the more proximal distribution of MI occlusions. In summary, we found that the culprit lesions in acute MI are significantly more proximal in patients with CKD than in those without CKD and that differences in the spatial distribution of MI are independent of other medical conditions. Proximal lesion location may be an important factor in determining the increased risk of MI as well as the increase risk of post-MI death in patients with CKD. Additional studies to determine how these findings can be used clinically are warranted.

MATERIALS AND METHODS

Subjects

Two cohorts of patients who presented to Brigham and Women's Hospital with acute MI and who underwent coronary angiography were retrospectively identified as described previously[7] and combined for the purposes of this analysis. Consecutive patients presenting with STEMI between 1 January 2001 and 31 August 2002 were identified in the first cohort and patients with NSTEMI between 1 January 2002 and 1 February 2003 were identified in the second. Besides MI type, the two cohorts used identical inclusion and exclusion criteria, data extraction, and methods of subject identification. All patients were required to meet standardized definitions of MI. STEMI was confirmed when chest pain was accompanied by ST elevation of at least 1 mm in two contiguous leads on a surface electrocardiogram. For NSTEMI, symptoms consistent with acute coronary ischemia, such as chest pain or dyspnea, had to be present and accompanied by ischemic electrocardiographic changes (other than ST elevation in two contiguous leads), elevation in cardiac troponin, or elevation in creatinine kinase.

Within this cohort, individuals with a history of coronary artery bypass grafting, cardiac transplant, or a history angioplasty within the previous 30 days were excluded. In the remaining patients angiograms were reviewed. Individuals in whom a clear culprit lesion could not be identified, those with evidence of in-stent-thrombosis, and those with inadequate angiographic views for quantitative coronary angiography were excluded from further analysis. A total of 408 patients met inclusion criteria. In 27 patients, there was insufficient data to estimate glomerular filtration rate, leaving 381 individuals for the final analysis.

Clinical variables

Medical records were reviewed to collect baseline demographics, baseline laboratory data, and information on comorbid medical conditions including diabetes, hypertension, hyperlipidemia, smoking, family history of MI, and prior history of MI. The peak creatinine kinase and troponin levels reached during the hospitalization were recorded as was the serum creatinine drawn at the time of angiography. eGFR was estimated using the abbreviated modification of diet in renal disease equation.[26] CKD was defined as an eGFR <60 ml/min per 1.73m^2 (equivalent to stage 3 or higher CKD) for the primary analysis. In a secondary analyses, CKD was defined according to the National Kidney Foundation guidelines: class 1/no CKD-eGFR >90 ml/min per 1.73 m^2; class 2 eGFR 60–89 ml/min per 1.73 m^2; class 3 eGFR 30–59 ml/min per 1.73 m^2; class 4/5 eGFR <30 ml/min per 1.73 m^2.[27] Sensitivity of the overall results to the choice of serum creatinine was assessed by substituting a serum creatinine drawn 1–2 days before angiography or, if not available, the serum creatinine drawn on the day of discharge.

Angiographic analysis

Quantitative coronary angiographic analysis was performed by a single reader blinded to renal function using a standard software package (Cardiology Medis System, version 5.1, Nuenen, the Netherlands). Coronary dimensions were measured following calibration against catheter dimensions using standard techniques.[28] Coronary segments were defined with minor modifications according to the coronary artery maps from the Bypass Angioplasty Revascularization Investigation[29] and Coronary Artery Surgery Study.[30] For each segment, standardized angiographic projections (Table 1) were used to minimize foreshortening and variability in measurements as described previously.[7]

The lesion responsible for the MI was identified as the site of significant stenosis or occlusion. In the event that more than one potential culprit lesion was present, the culprit lesion was assigned on the basis of the underlying electrocardiographic findings. Lesion location was defined as the distance from the coronary ostium to the point of occlusion or, when flow was present, as the site of the minimal luminal diameter within the lesion as described previously.[7] The length of each coronary segment was measured in millimeters and distance to lesion was defined as the sum of the intervening segment lengths between the coronary ostium and the acute lesion. The DTL was measured from the left main ostium (left-sided lesions) or the right coronary ostium (right-sided lesions). A secondary analysis (vessel analysis) excluded left main lesions and measured DTL from the ostia of the RCA, LCX or LAD artery, respectively.

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation (s.d.), or median and interquartile range if non-normally distributed. Binary variables are reported as counts (%). Cumulative density functions and histograms were constructed and graphical representations of cumulative frequencies of DTL in 10 mm increments were used to compare the distribution of DTL in patients with and without CKD. Student's *T*-tests and Mann–Whitney tests were used to compare continuous variables and χ^2-tests were used to compare categorical variables. Multivariable linear regression models were constructed to assess for independence of the association of CKD with DTL after adjusting for baseline characteristics. Age, sex, race, diabetes, hypertension, smoking, hyperlipidemia, and infarct vessel were pre-specified for inclusion because of the well-described associations of these variables with cardiovascular outcomes. Additional baseline variables that were associated with DTL at $P<0.10$ were included in the multivariable models. Sensitivity of the regression coefficients to sampling characteristics was analyzed with bootstrap resampling.[31] A total of 1000 samples were generated with replacement from the original dataset. Bias-corrected 95% CIs were generated for comparison with standard 95% CIs. All analyses were performed in STATA version 9.0 (STATA Corporation, College Station, TX, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

1. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
2. Anavekar NS, McMurray JJ, Velazquez EJ *et al.* Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351**: 1285–1295.
3. Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. *Hypertension* 2005; **45**: 1042–1049.
4. Roberts MA, Hare DL, Ratnaike S *et al.* Cardiovascular biomarkers in CKD: pathophysiology and implications for clinical management of cardiac disease. *Am J Kidney Dis* 2006; **48**: 341–360.
5. Kaysen GA, Eiserich JP. The role of oxidative stress-altered lipoprotein structure and function and microinflammation on cardiovascular risk in patients with minor renal dysfunction. *J Am Soc Nephrol* 2004; **15**: 538–548.
6. Gibson CM, Kirtane AJ, Murphy SA *et al.* Distance from the coronary ostium to the culprit lesion in acute ST-elevation myocardial infarction and its implications regarding the potential prevention of proximal plaque rupture. *J Thromb Thrombolysis* 2003; **15**: 189–196.
7. Wang JC, Normand SL, Mauri L *et al.* Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation* 2004; **110**: 278–284.
8. Mikkelsson J, Eskola M, Nikus K *et al.* Fatality of myocardial infarction in relation to the coronary anatomy: role of culprit lesion location. *Ann Med* 2004; **36**: 474–479.
9. Karha J, Murphy SA, Kirtane AJ *et al.* Evaluation of the association of proximal coronary culprit artery lesion location with clinical outcomes in acute myocardial infarction. *Am J Cardiol* 2003; **92**: 913–918.
10. Harjai KJ, Mehta RH, Stone GW *et al.* Does proximal location of culprit lesion confer worse prognosis in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction? *J Interv Cardiol* 2006; **19**: 285–294.
11. Wanner C, Krane V, Marz W *et al.* Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005; **353**: 238–248.
12. Charytan D, Kuntz RE. The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease. *Kidney Int* 2006; **70**: 2021–2030.
13. Coresh J, Astor BC, McQuillan G *et al.* Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002; **39**: 920–929.
14. Chew DP, Amerena J, Coverdale S *et al.* Current management of acute coronary syndromes in Australia: observations from the acute coronary syndromes prospective audit. *Intern Med J* 2007; **37**: 741–748.
15. Setoguchi S, Glynn RJ, Avorn J *et al.* Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. *J Am Coll Cardiol* 2008; **51**: 1247–1254.
16. Bradley EH, Herrin J, Wang Y *et al.* Racial and ethnic differences in time to acute reperfusion therapy for patients hospitalized with myocardial infarction. *JAMA* 2004; **292**: 1563–1572.
17. Raggi P, Boulay A, Chasan-Taber S *et al.* Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002; **39**: 695–701.

18. Slager CJ, Wentzel JJ, Gijsen FJ *et al.* The role of shear stress in the destabilization of vulnerable plaques and related therapeutic implications. *Nat Clin Pract Cardiovasc Med* 2005; **2**: 456–464.
19. Gross ML, Meyer HP, Ziebart H *et al.* Calcfication of coronary intima and media: immunohistochemistry, backscatter imagin, and X-ray anlaysis in renal and nonrenal patients. *Clin J AM Soc Nephrol* 2007; **2**: 121–134.
20. Herzog CA, Littrell K, Arko C *et al.* Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. *Circulation* 2007; **116**: 1465–1472.
21. Sezer M, Ozcan M, Okcular I *et al.* A potential evidence to explain the reason behind the devastating prognosis of coronary artery disease in uraemic patients: renal insufficiency is associated with poor coronary collateral vessel development. *Int J Cardiol* 2007; **115**: 366–372.
22. Amann K, Buzello M, Simonaviciene A *et al.* Capillary/myocyte mismatch in the heart in renal failure—a role for erythropoietin? *Nephrol Dial Transplant* 2000; **15**: 964–969.
23. Shlipak MG, Fried LF, Cushman M *et al.* Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 2005; **293**: 1737–1745.
24. McCullough PA, Hassan SA, Pallekonda V *et al.* Bundle branch block patterns, age, renal dysfunction, and heart failure mortality. *Int J Cardiol* 2005; **102**: 303–308.
25. Kestenbaum B, Rudser KD, Shlipak MG *et al.* Kidney function, electrocardiographic findings, and cardiovascular events among older adults. *Clin J Am Soc Nephrol* 2007; **2**: 501–508.
26. Levey AS, Coresh J, Greene T *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–254.
27. Reilly RF, Perazella MA. Chronic kidney disease: a new approach to an old problem. *Conn Med* 2002; **66**: 579–583.
28. Reiber JH, Jukema W, van Boven A *et al.* Catheter sizes for quantitative coronary arteriography. *Cathet Cardiovasc Diagn* 1994; **33**: 153–155; discussion 156.
29. Alderman EL, Stadius M. The angiographic definitions of the Bypass Angioplasty Revascularization Investigation. *Coron Artery Dis* 1992; **3**: 1189–1207.
30. Killip T, Fisher L, Mock M. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. *Circulation* 1981; **63**: I1–81.
31. Schumacher M, Hollander N, Sauerbrei W. Resampling and cross-validation techniques: a tool to reduce bias caused by model building? *Stat Med* 1997; **16**: 2813–2827.