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Relationship Between the Severity of Coronary Artery Disease and Renal Function

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Abstract

The American Heart Association's Predicting Risk of cardiovascular disease EVENTs (PREVENT) equations established estimated glomerular filtration rate (eGFR) as a component of cardiovascular risk assessment. However, the anatomical substrate underlying this risk—coronary atherosclerotic burden—remains inadequately characterized across renal function spectrum. This retrospective study included 1181 patients (mean age: 60.2 ± 8.9 years, 65.7% male) undergoing elective coronary angiography. Patients divided groups using eGFR; eGFR ≥90 (n = 596), 60 to 89 (n = 497), and 30 to 59 mL/min/1.73 m^2 (n = 88) were evaluated by stratification. Coronary atherosclerotic burden was determined using Gensini score. eGFR demonstrated a strong correlation with Gensini score ($\rho = -0.352$, $P < .001$). Each 10 mL/min/1.73 m^2 eGFR decline conferred 40% increased odds of severe coronary atherosclerosis (odds ratio [OR] = 0.960, 95% CI: 0.951-0.970, $P < .001$). Patients with eGFR 30 to 59 mL/min/1.73 m^2 exhibited 6-fold higher odds compared with preserved renal function (OR 6.073, 95% CI: 3.352-11.005, $P < .001$), independent of traditional risk factors. This study provides an anatomical validation for incorporating eGFR into cardiovascular risk assessment. Our angiographic evidence demonstrates that even mild renal dysfunction is accompanied by increased atherosclerotic burden. These findings bridge the gap between epidemiological risk prediction and pathophysiological reality, reinforcing the cardiovascular-kidney-metabolic health continuum and supporting aggressive risk modification strategies in patients with declining renal function, particularly among diabetic women.

Keywords

chronic kidney disease, coronary artery disease, Gensini score, heart disease risk factors

Introduction

Chronic kidney disease (CKD) and coronary artery disease (CAD) exhibit a well documented bidirectional relationship. Estimated glomerular filtration rate (eGFR), the most extensively validated biomarker of kidney function, serves as the primary criterion for CKD classification. Comprehensive epidemiological research has revealed a pronounced inverse relationship between reduced eGFR and cardiovascular (CV) event frequency.[1-3] This association is characterized by an ~5% to 10% increase in CV mortality per 10-unit decline in eGFR.[3,4]

CAD in patients with CKD demonstrates significant differences compared with patients without renal dysfunction. These patients typically exhibit a CAD pattern characterized by more extensive, diffuse, and calcified plaques, making traditional risk scoring systems inadequate.[5] CKD-specific pathophysiological mechanisms including uremic toxin accumulation, persistent inflammatory processes, mineral-bone metabolism disorders, endothelial dysfunction, and enhanced oxidative stress play pivotal roles in accelerating coronary atherosclerotic progression and morphogenesis of complex plaque architecture.[6]

The Gensini score (GS), established in 1983, represents a systematic angiographic tool for quantifying both the anatomical severity and distribution of CAD.[7] This system calculates stenosis severity as a percentage for each arterial segment and multiplies this value by a segment-specific coefficient that reflects its contribution to myocardial perfusion, yielding a cumulative score. However, precise quantification of the

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CKD-CAD relationship using comprehensive coronary scoring systems across the spectrum of kidney function remains inadequately characterized, particularly in mild-to-moderate CKD where preventive interventions may be most effective.

Despite growing recognition of the CKD-CAD nexus, several critical knowledge gaps persist. First, most studies have focused on advanced CKD (stages 4-5), leaving the relationship between mild-to-moderate renal dysfunction and coronary burden poorly characterized. Second, comprehensive anatomical scoring systems such as the GS, which capture both stenosis severity and lesion location, have been underutilized in CKD populations, with most investigations relying on simple vessel counts or binary CAD classification. Third, data from Middle Eastern populations, particularly Turkish cohorts, remain scarce despite regional variations in CKD etiology and CV risk profiles. The Chronic REnal Disease In Turkey (CREDIT) study, the first nationwide epidemiological investigation, reported a CKD prevalence of 15.7% in the Turkish population, which is higher than global estimates.[8] Despite the high burden of CKD and established CV risk, comprehensive investigations employing detailed coronary scoring systems to quantify the CKD-CAD relationship remain limited in the Turkish populations.

Recently, the American Heart Association (AHA) introduced the cardiovascular-kidney-metabolic (CKM) syndrome framework—a 5-stage continuum from excess adiposity to clinical cardiovascular disease that recognizes the multidirectional relationships among metabolic risk factors, CKD, and the cardiovascular system.[9] This paradigm shift formally integrates eGFR and albuminuria into cardiovascular risk prediction. In parallel, the AHA developed the Predicting Risk of cardiovascular disease EVENTs (PREVENT) equations in 2023, which incorporate eGFR as a fundamental component alongside traditional cardiovascular and metabolic factors, moving beyond earlier tools such as the Framingham Risk Score, Pooled Cohort Equations, and European Society of Cardiology (ESC) SCORE.[10,11] While PREVENT predicts future clinical event risk, comprehensive characterization of the anatomical substrate underlying these predictions—specifically, the actual coronary atherosclerotic burden across the renal function spectrum—is of paramount importance. This study addresses this knowledge gap by quantifying the relationship between declining eGFR and angiographically-determined coronary disease severity using the comprehensive Gensini scoring system.

Therefore, the present retrospective analysis utilizing a cross-sectional cohort design was undertaken to: (1) systematically quantify the relationship between eGFR and angiographic coronary atherosclerotic burden using the comprehensive Gensini scoring system, (2) determine whether this correlation persists across the entire spectrum of glomerular filtration capacity, with a focus on mild and moderate decrements in renal function, and (3) determine whether eGFR independently predicts CAD severity after adjusting for established CV risk factors.

Materials and Methods

The present cross-sectional retrospective study systematically examined the medical records of 2264 patients aged 30 to 75 years who underwent elective coronary angiography at our hospital in accordance with current ESC and American College of Cardiology/AHA guidelines.[12,13] The indications for coronary angiography, number of diseased vessels identified, and treatment decisions are summarized in Table 1. We excluded patients with previous coronary revascularization procedures, acute coronary syndromes, structural heart abnormalities (congenital heart disease, cardiomyopathy, and significant valvular disease), patients undergoing maintenance dialysis (hemodialysis or peritoneal dialysis) or with prior renal transplantation, severe CKD (stages 4-5 according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative classification; estimated glomerular filtration rate $<30\,mL/min/1.73\,m^2$), or acute kidney injury (Figure 1). Patients with angiographically normal coronary arteries were excluded to focus on the correlation between the renal functional capacity and CAD severity. Patients with insufficient laboratory or angiographic information were excluded from analysis. After the systematic implementation of these selection criteria, the final study population comprised 1181 patients for whom data were available. The investigation was approved the Gaziosmanpaşa University Health Sciences Clinical Research Ethics Committee (approval number: 11-BADK-077, date: July 26, 2011) and was executed in strict adherence to the ethical framework established by the Declaration of Helsinki.

Written informed consent was obtained from all participants. Artificial intelligence tools were used for English language editing and literature search assistance during the manuscript preparation. All scientific content, analysis, and conclusions remain entirely the authors' own work. Python software (Python Software Foundation, https://www.python.org) was used solely for generating Figures 2 to 4.

Data Collection

Patient data including age, sex, smoking habits, presence of diabetes mellitus (DM) and hypertension (HT), prior cerebrovascular disease, and referral indications for angiography were extracted from electronic medical records. Documentation of concurrent CV pharmacotherapy includes statin therapy, renin-angiotensin system inhibitors, beta-adrenergic blockers, and antiplatelet agents. Body mass index (BMI) was calculated from anthropometric measurements obtained before angiographic assessment, using a standard formula. Blood samples for laboratory analysis were drawn after at least 12 h of overnight fasting before coronary angiography (CAG). Biochemical assessments encompassed comprehensive lipid parameters, kidney function biomarkers (serum creatinine and urea nitrogen), and standard hematological parameters.

Table 1. Distribution of CAG Indications[a], Diseased Vessel, and Treatment Decision[b] by CKD-EPI Groups.

Variable	Category	Overall (n = 1181)	Group 1 (n = 596)	Group 2 (n = 497)	Group 3 (n = 88)
Number of diseased vessels	0, n (%)	383 (32.4)	234 (39.3)	140 (28.2)	9 (10.2)
	1, n (%)	305 (25.8)	180 (30.2)	105 (21.1)	20 (22.7)
	2, n (%)	275 (23.3)	120 (20.1)	132 (26.6)	23 (26.1)
	3, n (%)	218 (18.5)	62 (10.4)	120 (24.1)	36 (40.9)
					$P < .001$
Indications for CAG	1, n (%)	261 (22.1)	135 (22.7)	108 (21.7)	18 (20.5)
	2, n (%)	404 (34.2)	208 (34.9)	174 (35.0)	22 (25.0)
	3, n (%)	94 (8.0)	56 (9.4)	31 (6.2)	7 (8.0)
	4, n (%)	422 (35.7)	197 (33.1)	184 (37.0)	41 (46.6)
					$P = .112$
Treatment decision	1, n (%)	660 (55.9)	379 (63.6)	256 (51.5)	25 (28.4)
	2, n (%)	192 (16.3)	101 (16.9)	77 (15.5)	14 (15.9)
	3, n (%)	329 (27.9)	116 (19.5)	164 (33.0)	49 (55.7)
					$P < .001$

Data are presented as n (%). *P* values were calculated using Pearson chi-square test.
Abbreviation: CAG, coronary angiography.
[a]Indications: (1) Stable angina pectoris with ongoing anginal symptoms despite optimal medical therapy or with risk factors such as family history, diabetes mellitus, hypertension, smoking; (2) positive non-invasive tests (coronary CTA, myocardial perfusion scintigraphy, stress echocardiography, and exercise test); (3) preoperative evaluation; and (4) other.
[b]Treatment decision: (1) Medical therapy; (2) percutaneous coronary intervention; and (3) coronary artery bypass surgery.

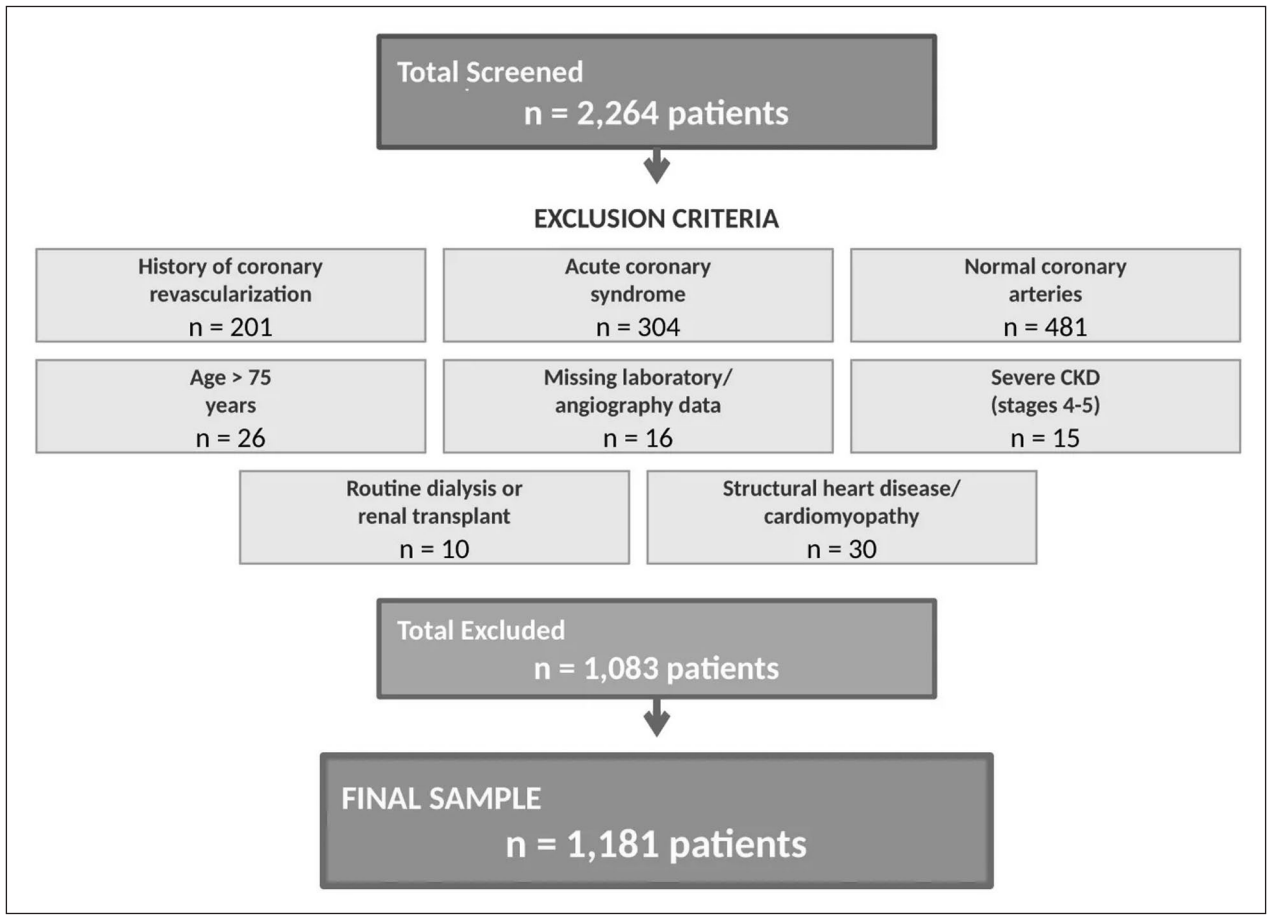

Figure 1. Patient selection flowchart.
CKD, chronic kidney disease.

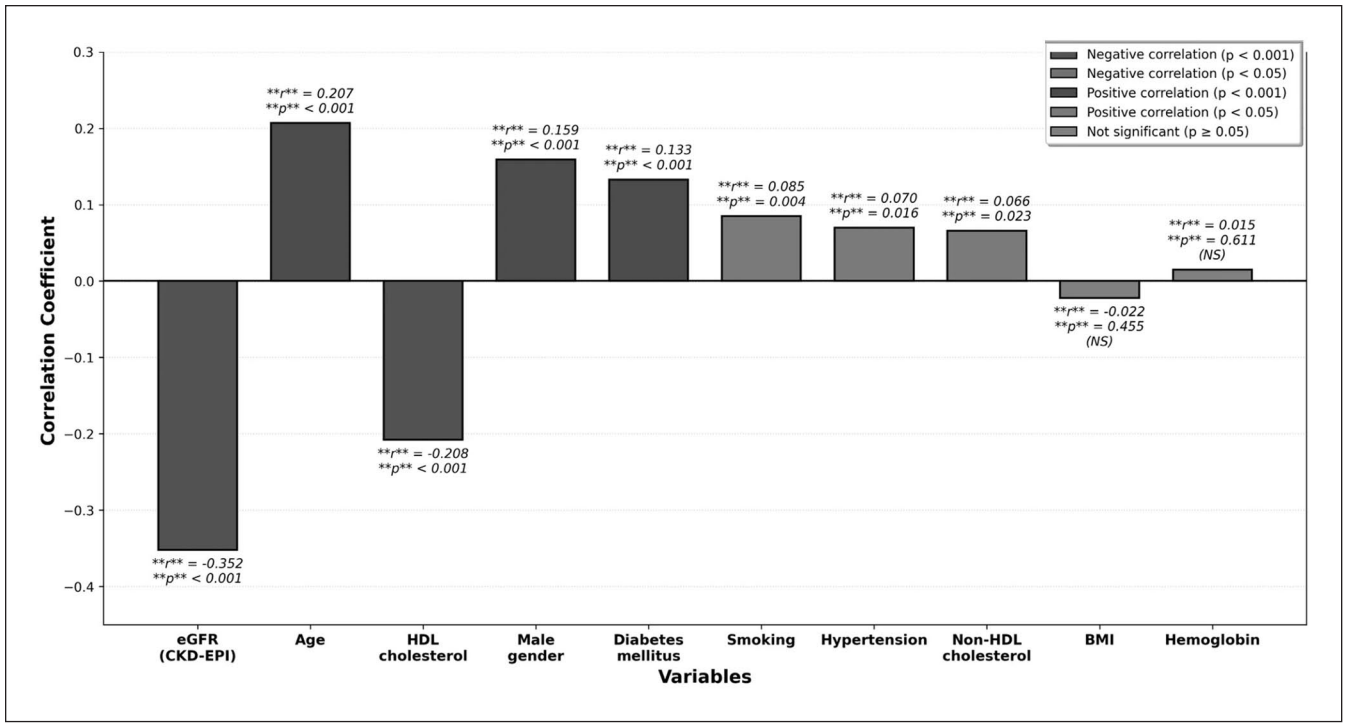

Figure 2. Correlation between Gensini score and study variables (correlation, N = 1181).
eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; BMI, body mass index.

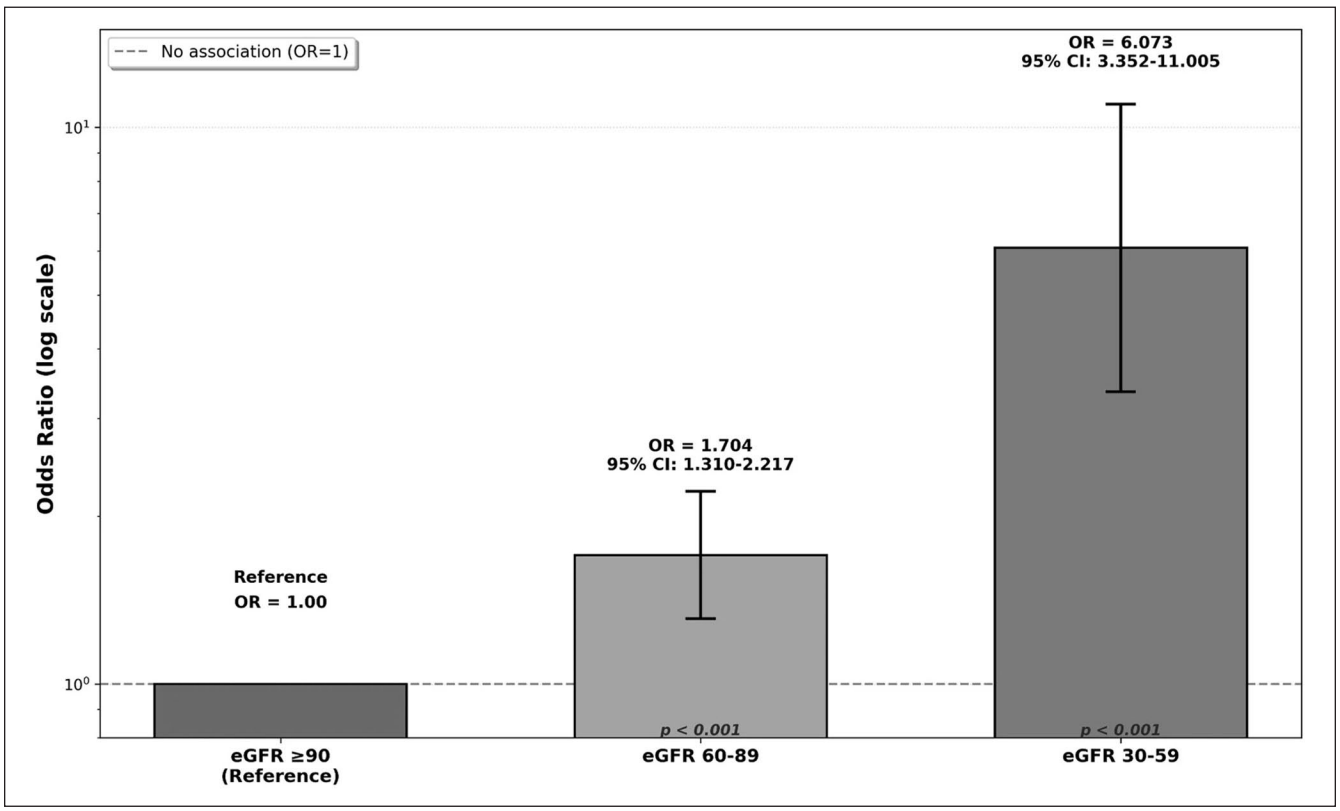

Figure 3. Association between eGFR categories and high Gensini score (adjusted for all covariates).
eGFR, estimated glomerular filtration rate; OR, odds ratios.

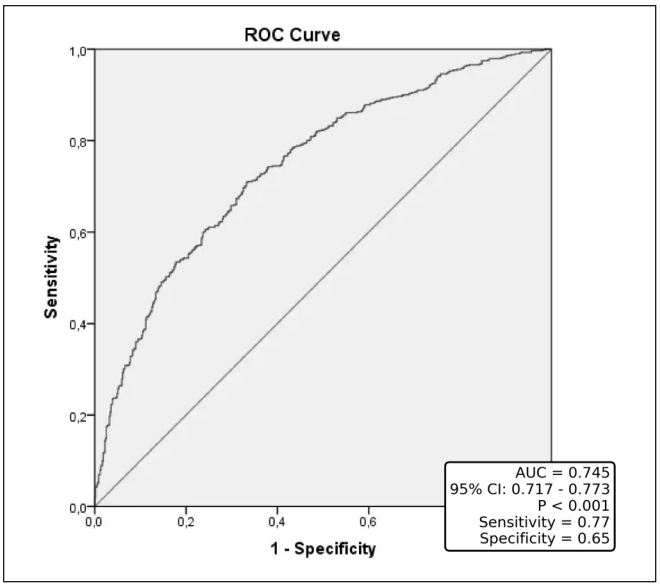

Figure 4. ROC curve for predicting high Gensini score.
ROC, receiver operating characteristic; AUC, area under curve.

Definitions

DM was identified according to the American Diabetes Association diagnostic criteria, including fasting plasma glucose level ≥126 mg/dL or concurrent administration of antidiabetic agents.[14] Patients were categorized as hypertensive if blood pressure measurements reached ≥140/90 mmHg or if they were receiving antihypertensive pharmacotherapy. Hyperlipidemia was determined based on a fasting total cholesterol level ≥200 mg/dL or ongoing statin therapy.

Renal Function Assessment and Stratification

Renal functional capacity was determined through eGFR calculation based on the CKD Epidemiology Collaboration (CKD-EPI) formula,[15] which provides superior accuracy compared with older formulas, particularly at higher eGFR values.[15] The CKD-EPI formula was selected as the primary method based on current guideline recommendations.[16] The cohort was divided into 3 categories according to eGFR values in conformity with NKF-KDOQI Clinical Practice Guideline recommendations[16] and as part of sensitivity testing, eGFR estimation was additionally performed using the Modification of Diet in Renal Disease (MDRD) formula.[17] However, CKD-EPI-derived eGFR was used for all primary analyses because of the strong correlation between MDRD and CKD-EPI estimates (Spearman's $r = 0.944$, $P < .001$), which would have resulted in multicollinearity if both were included simultaneously in the regression models.

Coronary Angiography and Gensini Score Assessment

The standard Judkins technique was used to perform elective CAG in all study participants. Independent angiographic evaluation was carried out by 2 experienced interventional cardiology experts who were blinded to the clinical and biochemical data. Both vessel-based classification (categorization based on the number of major coronary vessels with ≥50% stenosis: single, double, or triple vessel disease) and the Gensini scoring system[7] were used to quantify coronary atherosclerotic burden.

Definition of Significant CAD and Vessel Classification

CAD was considered significant when ≥50% stenosis was present in any major epicardial coronary artery. Coronary involvement severity was stratified according to the number of diseased vessels, yielding single-, 2-, or 3-vessel disease classifications. According to the established criteria, isolated left main coronary artery (LMCA) stenosis was categorized as a 2-vessel disease equivalent.

Gensini Score (GS) Calculation

We utilized GS to provide a comprehensive quantification of the total coronary atherosclerotic burden. The stenosis severity for each lesion was assigned a base score proportional to stenosis severity as follows: 1 point for minimal stenosis (1%-25%), 2 points for mild-moderate stenosis (26%-50%), 4 points for moderate-severe stenosis (51%-75%), 8 points for severe stenosis (76%-90%), 16 points for critical stenosis (91%-99%), and 32 points for total occlusion.

Each base score was then multiplied by a segment-specific coefficient according to the affected vessel: ×5.0 for LMCA; ×2.5 for proximal left anterior descending (LAD) and proximal circumflex artery (LCx); ×1.5 for mid LAD; ×1.0 for right coronary artery, distal LAD, posterolateral branch, and obtuse marginal branch of LCx; and ×0.5 for all other segments. The cumulative GS represents the summation of the weighted scores across all coronary segments.

Statistical Analysis

SPSS version 22.0 software (IBM Corp, Armonk, NY, USA) was utilized for statistical analyses, and Python software programs were used to draw figures. The assumption of normality for continuous parameters was determined through the Kolmogorov-Smirnov statistic. Additionally, skewness and kurtosis parameters were analyzed to evaluate deviation from normal distribution; variables with absolute values exceeding 2.0 were considered to demonstrate substantial

Table 2. Baseline Characteristics of the Study Cohort Stratified by eGFR Category.

Variables	Overall (n = 1181)	CKD stage 1 (n = 596, 50.5%)	CKD stage 2 (n = 497, 42%)	CKD stage 3 (n = 88, 7.5%)	*P* value
Age (y)	60.2 ± 8.9	56.4 ± 8.3	63.8 ± 8.0	65.8 ± 6.4	<.001
Male gender, n (%)	776 (65.7)	404 (67.8)	335 (67.4)	37 (42.0)	<.001
BMI (kg/m^2)	27.1 ± 4.1	27.0 ± 4.0	27.2 ± 4.2	27.8 ± 4.3	.284
Diabetes mellitus, n (%)	343 (29.0)	144 (24.2)	153 (30.8)	46 (52.3)	<.001
Hypertension, n (%)	711 (60.2)	333 (55.9)	307 (61.8)	71 (80.7)	<.001
Dyslipidemia, n (%)	505 (42.8)	246 (41.3)	212 (42.7)	47 (53.4)	.050
Smoking, n (%)	415 (35.1)	247 (41.4)	154 (31.0)	14 (15.9)	<.001
Hemoglobin (g/dL)	13.7 ± 1.5	13.8 ± 1.5	13.7 ± 1.5	12.7 ± 1.4	<.001
Glucose (mg/dL)	115.3 ± 40.3	109.7 ± 34.3	119.2 ± 43.9	132.2 ± 49.6	<.001
HDL-cholesterol (mg/dL)	42.6 ± 12.3	42.3 ± 11.7	42.8 ± 12.6	43.7 ± 14.4	.533
Non-HDL-cholesterol (mg/dL)	151.2 ± 46.2	151.9 ± 45.7	148.8 ± 45.8	159.7 ± 51.2	.107
Triglycerides (mg/dL)	161.3 ± 82.6	161.3 ± 83	160.3 ± 82.4	167.2 ± 82.3	.769
AST (U/L)	38 ± 7	37.4 ± 7.3	38.4 ± 6.7	38.5 ± 6.7	.044
ALT (U/L)	27.2 ± 13.5	27.4 ± 14	27.3 ± 13.3	25.6 ± 11.4	.496
Creatinine (g/dL)	0.8 ± 0.20	0.75 ± 0.13	0.94 ± 0.14	1.25 ± 0.21	<.001
eGFR	87.6 ± 16.6	100.6 ± 7.3	78.4 ± 8.3	51.6 ± 6.8	<.001
Gensini score	31.4 ± 15.4	23.2 ± 12.2	36.7 ± 16.4	56.9 ± 14.3	<.001

Data are presented as mean ± SD or n (%).
Abbreviations: CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

deviation from normality.[18] Although some variables demonstrated mild deviations from normality based on skewness and kurtosis values, parametric methods were deemed appropriate given the large sample size (n = 1181), which ensures robustness of parametric procedures through the Central Limit Theorem.[19] Nevertheless, key analyses were confirmed using non-parametric methods where appropriate. Parametric continuous variables meeting normality assumptions are expressed as mean ± standard deviation (SD), whereas discrete categorical data were presented as absolute frequencies with their corresponding percentages. Intergroup comparative analyses of continuous variables were performed using 1 way analysis of variance (ANOVA) tests, supplemented by Tukey and Bonferroni post hoc testing for individual paired comparisons. Categorical data were analyzed using Pearson's chi-square or Fisher's exact tests. Correlations between variables were evaluated using Pearson or Spearman methods according to the normality of distribution. To elucidate the independent correlates of significant coronary atherosclerotic burden, subjects were classified into low and high GS cohorts relative to the median distribution value. Logistic regression analysis, both univariate and multivariate, were used to explore the associations between eGFR, traditional CV risk variables, and a high GS. Variables achieving $P < .10$ in univariable screening were assessed for multicollinearity using variance inflation factor (VIF) analysis (VIF >5 indicating problematic collinearity) before entry into multivariable models. Two models were constructed: Model 1 included eGFR as a continuous variable, whereas Model 2 divided, eGFR into 3 categories according to the NKF-KDOQI Clinical Practice Guidelines to examine the CKD-CAD relationship from a categorical perspective. Logistic regression results are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI). Additionally, independent predictors of continuous Gensini score were investigated using multivariate linear regression modeling. Standardized regression coefficients (β) with corresponding 95% CIs were reported to facilitate the comparison of the relative predictor importance.

Discriminatory performance was evaluated through receiver operating characteristic (ROC) curve analysis, calculating the area under the curve (AUC) with 95% CI to distinguish between patients with high and low GS. AUC values of 0.70 to 0.79, 0.80 to 0.89, and ≥0.90 represented acceptable, excellent, and outstanding discrimination, respectively.

Results

Our study included 1181 consecutive patients undergoing CAG (mean age 60.2 ± 8.9 years, 65.7% male). Patients were stratified according to eGFR values derived using the CKD-EPI formula. The distribution was: 596 patients (50.5%) had eGFR ≥90 mL/min/1.73 m^2 (stage 1), 497 (42%) had eGFR 60 to 89 mL/min/1.73 m^2 (stage 2), and 88 (7.5%) had eGFR 30 to 59 mL/min/1.73 m^2 (stage 3; Table 2). Baseline characteristics demonstrated significant differences across eGFR categories, with a clear increase in CV risk burden accompanying declining renal function. Patients with lower eGFR

were significantly older (56.4 ± 8.3 vs 63.8 ± 8.0 vs 65.8 ± 6.4 years for stage 1, stage 2, and stage 3, respectively; $P < .001$) and had higher prevalence of DM (24.2% vs 30.8% vs 52.3%, $P < .001$) and HT (55.9% vs 61.8% vs 80.7%, $P < .001$). Laboratory parameters reflect the physiological changes associated with CKD progression. Hemoglobin levels declined significantly in the lowest eGFR group (13.8 ± 1.5 vs 13.7 ± 1.5 vs 12.7 ± 1.4 g/dL, $P < .001$), consistent with CKD-related anemia.

Coronary Atherosclerotic Burden by eGFR Category

A striking relationship was observed between declining renal function and coronary atherosclerotic burden. Mean GS increased progressively across eGFR categories: 23.2 ± 12.2 (stage 1), 36.7 ± 16.4 (stage 2), and 56.9 ± 14.3 (stage 3; $P < .001$). Patients with CKD stage 3 had a 2.5-fold higher mean GS than those with stage 1 CKD. This relationship is further reflected in the distribution of multivessel coronary diseases. The prevalence of 3-vessel disease increased dramatically from 10.4% in patients with stage 1 disease to 24.1% in those with stage 2 disease, and to 40.9% in patients with stage 3 disease ($P < .001$).

Table 3. Correlation Analysis for Variables Associated with Gensini Score.

Variables	r^a	*P* value
eGFR (mL/min/1.73 m^2)	−0.352	<.001
Age (y)	0.207	<.001
HDL-cholesterol (g/dL)	−0.208	<.001
Male gender	0.159	<.001
Diabetes mellitus	0.133	<.001
Smoking	0.085	.004
Hypertension	0.070	.016
Non-HDL-cholesterol (g/dL)	0.066	.023
Body mass index (kg/m^2)	0.022	.455
Hemoglobin (g/dL)	0.015	.611

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein.
[a]*r* indicates Pearson correlation coefficient.

Correlation Analysis

Correlation analyses demonstrated that among all examined parameters, renal function assessed by eGFR exhibited the strongest association with GS ($r = -0.352$, $P < .001$), whereby declining kidney function corresponded with an increased severity of coronary atherosclerosis (Table 3 and Figure 2). Additional variables showing significant relationships with GS included patient age ($r = 0.207$, $P < .001$), HDL-cholesterol levels ($r = -0.208$, $P < .001$), male sex ($r = 0.159$, $P < .001$), presence of diabetes ($r = 0.133$, $P < .001$), tobacco use ($r = 0.085$, $P = .004$), arterial HT ($r = 0.070$, $P = .016$), and non-HDL-cholesterol concentrations ($r = 0.066$, $P = .023$). Neither BMI ($r = -0.022$, $P = .455$) nor hemoglobin levels ($r = 0.015$, $P = .611$) were significantly associated with CAD severity.

Regression Analysis

Univariate analyses were performed by stratifying the patients into 2 groups according to the median Gensini score (20.5) to evaluate determinants of CAD severity (Table 4). The entire spectrum of traditional CV risk factors are significantly associated with increased odds of severe coronary atherosclerosis. eGFR emerged as the strongest predictor and was analyzed as a continuous variable (OR = 0.960/1 mL/min/1.73 m^2 increase,

Table 4. Univariate Logistic Regression Analysis for High Gensini Score.

Variables	*B*	SE	Wald	*P* value	OR (95% CI)
Age (y)	0.040	0.007	35.314	<.001	1.041 (1.027-1.055)
Male gender	0.649	0.125	27.057	<.001	1.913 (1.498-2.443)
Diabetes mellitus	0.419	0.129	10.506	.001	1.521 (1.180-1.959)
Hypertension	0.343	0.119	8.255	.004	1.409 (1.115-1.781)
Smoking	0.333	0.122	7.384	.007	1.395 (1.097-1.773)
HDL-cholesterol (mg/dL)	−0.031	0.005	37.262	<.001	0.969 (0.959-0.979)
Non-HDL-cholesterol (mg/dL)	0.004	0.001	7.903	.005	1.004 (1.001-1.006)
eGFR (mL/min/1.73 m^2)	−0.041	0.004	101.857	<.001	0.960 (0.952-0.967)
eGFR categories (age adjusted)			41.903	<.001	
≥90 (reference)	–	–	–	–	1.00
eGFR 60-89 vs ≥90	0.533	0.134	15.755	<.001	1.704 (1.310-2.217)
eGFR 30-59 vs ≥90	1.804	0.303	35.479	<.001	6.073 (3.352-11.005)

High Gensini score defined as above median value.
Abbreviations: *B*, regression coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; OR, odds ratio; SE, standard error.

Table 5. Multivariable Logistic Regression Analysis for High Gensini Score.

Variables	*B*	SE	Wald	*P* value	OR (95% CI)
Age (y)	0.019	0.009	4.851	.028	1.019 (1.002-1.037)
Male gender	0.762	0.162	22.078	<.001	2.143 (1.559-2.946)
Diabetes mellitus	0.485	0.151	10.306	.001	1.625 (1.208-2.185)
Hypertension	0.375	0.136	7.567	.006	1.455 (1.114-1.900)
Smoking	0.470	0.157	8.918	.003	1.600 (1.175-2.179)
HDL-cholesterol (mg/dL)	−0.029	0.006	25.045	<.001	0.971 (0.960-0.982)
Non-HDL-cholesterol (mg/dL)	0.006	0.001	14.824	<.001	1.006 (1.003-1.008)
eGFR (CKD-EPI; mL/min/1.73 m^2)	−0.041	0.005	68.572	<.001	0.960 (0.951-0.970)

Abbreviations: *B*, regression coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; OR, odds ratio; SE, standard error.

95% CI: 0.952-0.967, $P < .001$) or categorically. When examined categorically, patients with CKD stage 2 had 1.7-fold higher odds of high GS than those with CKD stage 1 (OR = 1.704, 95% CI: 1.310-2.217, $P < .001$), whereas those with CKD stage 3 demonstrated more than 6-fold increased odds (OR = 6.073, 95% CI: 3.352-11.005, $P < .001$). Among the demographic and clinical variables, male sex (OR = 1.913, 95% CI: 1.498-2.443, $P < .001$), HT (OR = 1.409, 95% CI: 1.115-1.781, $P = .004$), DM (OR = 1.521, 95% CI: 1.180-1.959, $P = .001$), and current smoking (OR = 1.395, 95% CI: 1.097-1.773, $P = .007$) were all significantly associated with high GS. Higher HDL-cholesterol level (OR = 0.969/1 mg/dL increase, 95% CI: 0.959-0.979, $P < .001$) demonstrated a protective association.

Table 5 displays results from multivariable logistic regression modeling evaluating the independent association of renal function with CAD severity after comprehensive adjustment for established CV risk factors and lipid profiles. In Model 1, eGFR was entered as a continuous variable. Following comprehensive adjustment for all confounders, each 1 mL/min/1.73 m^2 decrease in eGFR corresponded to 4% increased odds of high GS (OR = 0.960, 95% CI: 0.951-0.970, $P < .001$). This represented the strongest independent predictor in the model based on the Wald statistic ($\chi^2 = 68.572$). All traditional CV risk factors remained independently associated with high GS. Male gender was the strongest demographic predictor (OR = 2.143, 95% CI: 1.559-2.946, $P < .001$), while DM (OR = 1.625, 95% CI: 1.208-2.185, $P = .001$), HT (OR = 1.455, 95% CI: 1.114-1.900, $P = .006$), and current smoking (OR = 1.600, 95% CI: 1.175-2.179, $P = .003$) also showed significant independent associations. Among lipid parameters, both HDL-cholesterol (OR = 0.971, 95% CI: 0.960-0.982, $P < .001$) and non-HDL cholesterol (OR = 1.006, 95% CI: 1.003-1.008, $P < .001$) demonstrated independent effects on coronary atherosclerotic burden.

To better characterize the dose-response relationship, Model 2 incorporated eGFR as a categorical variable (Figure 3). The overall effect of eGFR category was highly significant (Wald $\chi^2 = 43.717$, $P < .001$), demonstrating a clear gradient of risk across categories (Figure 1). Patients with CKD stage 2 exhibited 73% higher odds of severe coronary atherosclerotic burden than those in the reference group of CKD stage 1 patients (OR = 1.732, 95% CI: 1.312-2.287, $P < .001$). This relationship was dramatically amplified in patients with stage 3 CKD, with moderately reduced kidney function conferring >6-fold elevated odds (OR = 6.073, 95% CI: 3.352-11.005, $P < .001$).

Linear Regression Analysis

With the aim of evaluating the independent contribution of each study variable to the continuous GS, we performed multiple linear regression analysis (Table 6). A total of 20.2% of the variance in the GS was explained by the regression model, which achieved high statistical significance ($F = 37.019$, $P < .001$, $R^2 = 0.202$, adjusted $R^2 = 0.196$). Collinearity diagnostics revealed no multicollinearity concerns, with variance inflation factors <1.5. Consistent with logistic regression findings, renal function assessed by eGFR emerged as the principal independent predictor of GS (standardized $\beta = -.309$, unstandardized $B = -0.563$, $P < .001$); each 1 mL/min/1.73 m^2 decrease was independently associated with a 0.56-point increment in GS. HDL-cholesterol was the second strongest predictor ($\beta = -.134$, $B = -0.334$, $P < .001$), with each 1 mg/dL increase associated with a 0.33-point decrease in GS. Other significant independent predictors included DM ($B = 7.698$, $P < .001$), male gender ($B = 7.431$, $P < .001$), smoking ($B = 5.882$, $P = .003$), non-HDL-cholesterol ($B = 0.073$/mg/dL, $P < .001$), and age ($B = 0.324$/year, $P = .002$). HT demonstrated a borderline significant association ($B = 3.232$, $P = .057$), with its independent contribution diminishing following adjustment for additional CV risk factors and eGFR.

Model Discrimination and Calibration

The discriminatory capacity of the multivariable model in identifying patients with severe coronary atherosclerotic burden was determined using ROC analysis (Figure 4). The model showed good discriminatory capacity with an AUC of 0.745 (95% CI: 0.717-0.773, $P < .001$), demonstrating that the combination of age, sex, traditional CV risk factors, lipid

Table 6. Multiple Linear Regression Analysis for Gensini Score.

Variables	*B*	β[a]	*t*	*P* value	95% CI
Age (y)	0.324	.095	3.048	.002	0.115-0.532
Male gender	7.431	.116	3.729	<.001	3.522-11.341
Diabetes mellitus	7.698	.115	4.180	<.001	4.085-11.311
Hypertension	3.232	.052	1.909	.057	−0.090 to 6.555
Smoking	5.882	.092	3.016	.003	2.055-9.708
HDL-cholesterol (mg/dL)	−0.334	−.134	−4.885	<.001	−0.468 to 0.200
Non-HDL-cholesterol (mg/dL)	0.073	.110	4.159	<.001	0.038-0.107
eGFR (CKD-EPI; mL/min/1.73 m^2)	−0.563	−.309	−10.077	<.001	−0.672 to 0.453

B, partial regression coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.
[a]β indicates standardized regression coefficient.

Table 7. Gender-Stratified Logistic Regression Analysis.

Variable	Men OR (95% CI)	Women OR (95% CI)	*P* for Interaction
Age (y)	1.021 (1.00-1.04)*	1.017 (0.98-1.05)	.717
Diabetes mellitus	1.37 (0.93-2.02)	**2.09 (1.32-3.31)***	**<.05**
Hypertension	1.33 (0.97-1.82)	**1.96 (1.15-3.36)***	<.10
Smoking	**1.55 (1.12-2.14)***	1.81 (0.65-5.06)	NS
HDL-cholesterol (per mg/dL)	0.970 (0.96-0.99)*	0.970 (0.95-0.99)*	NS
Non-HDL-cholesterol (per mg/dL)	1.005 (1.00-1.01)*	1.006 (1.00-1.01)*	NS
eGFR (per mL/min/1.73 m^2)	0.959 (0.95-0.97)*	0.961 (0.95-0.98)*	NS
Nagelkerke R^2	**0.180**	**0.280**	**<.05**

Abbreviations: NS: Not significant. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.
*$P < .05$.
Boldface indicates independent predictors identified in the sex-specific multivariable regression analyses.

parameters, and eGFR accurately classified 74.5% of the patients into high versus low GS categories. The observed discriminatory performance is consistent with that of established CV risk calculation models such as the Framingham Risk Score (AUC ~0.74-0.76) and highlights the clinical utility of incorporating renal function assessment into coronary atherosclerosis risk stratification.

Gender-Stratified Subgroup Analysis

In the gender-based subgroup analysis (Table 7), the effects of risk factors showed distinct differences between men and women. The proportion of variance in CAD severity explained by the model was significantly higher in women than in men (Nagelkerke R^2: 0.280 vs 0.180, $P < .05$).

DM was a very strong risk factor in women (OR = 2.09, 95% CI: 1.32-3.31, $P = .002$), whereas no significant association was found in men (OR = 1.37, $P = .117$; P for interaction <.05). Similarly, HT doubled the risk of cardiac event in women (OR = 1.96, $P = .014$), whereas this association remained borderline in men (OR = 1.33, $P = .075$).

Smoking was a significant risk factor in men (OR = 1.55, 95% CI: 1.12-2.14, $P = .009$) but was not statistically significant in women ($P = .256$). Age was identified as a significant risk factor in men only (OR = 1.021, $P = .048$ vs $P = .335$).

HDL-cholesterol, non-HDL-cholesterol, and eGFR showed similar and significant effects in both sexes, with no sex-specific differences observed (P for interaction >.10).

Discussion

The present study found that declining renal function assessed by eGFR independently correlates with increased coronary disease burden as reflected by GS in patients undergoing elective CAG. Our primary observations reveals that declining eGFR, even at mild to moderate levels of kidney dysfunction, strongly predicts the severity and extent of CAD. Importantly, this strong association persisted even after thorough adjustment for known CV risk variables, suggesting that a reduced eGFR represents an independent determinant of coronary atherosclerotic burden.

The inverse relationship between eGFR and GS ($r = -0.352$, $P < .001$) is consistent with previous studies exploring the CKD-CAD association.[1,20,21] In multivariable regression analysis, each 1 mL/min/1.73 m^2 decrease in eGFR conferred a 4% increase in the odds of high coronary atherosclerotic burden (OR = 0.960, 95% CI: 0.951-0.970, $P < .001$). Our linear regression model demonstrated that eGFR emerged as the most powerful independent determinant of GS (standardized

β = −.309, $P < .001$), surpassing traditional risk factors including DM, male sex, and dyslipidemia.

Stage 3 CKD demonstrated a markedly elevated risk profile, with the odds of severe coronary disease surpassing that of stage 1 CKD with preserved renal function by more than 6-fold (OR = 6.073, 95% CI: 3.352-11.005, $P < .001$). The substantial OR for moderate CKD (eGFR 30-59: OR = 6.073, 95% CI: 3.352-11.005) warrants explanation. This magnitude is consistent with prior angiographic studies reporting ORs of 4.1 to 5.7 for moderate to severe renal dysfunction[22,23] and reflects 3 factors: First, as an age-adjusted estimate (OR = 1.023/year, $P = .003$), this represents independent pathophysiological effects beyond aging. Second, anatomic disease burden (GS >20) typically yields stronger associations than incident events. Third, the clear dose-response gradient (OR: 1.0 → 1.7 → 6.0 across eGFR categories) satisfies the Bradford Hill causality criteria[24,25] and reflects the cumulative synergistic effects of CKD-mediated atherogenic processes including chronic inflammation, oxidative stress, vascular calcification, RAAS activation, and uremic toxin accumulation.[4,26]

The biological mechanisms underlying the augmented atherosclerotic burden in CKD are multifactorial. CKD promotes accelerated atherosclerosis through several interrelated pathways beyond traditional Framingham risk factors.[4,26] Renal impairment precipitates a chronic inflammatory state with elevated levels of inflammatory mediators including interleukin-6, C-reactive protein, and tumor necrosis factor-alpha, which sustain endothelial dysfunction.[27-29] Concurrently, CKD-associated mineral metabolism derangements including hyperphosphatemia and secondary hyperparathyroidism drive vascular calcification.[30,31] Retention of uremic toxins, particularly asymmetric dimethylarginine (ADMA), impairs nitric oxide bioavailability and promotes oxidative stress.[32,33] Additionally, patients with a reduced eGFR frequently exhibit dysregulated lipid metabolism with elevated triglyceride and low-density lipoprotein (LDL) particle levels.[34]

The association between renal dysfunction and coronary plaque characteristics warrants further investigation. Recent data on sclerostin levels and coronary calcification revealed that patients with a greater calcified plaque burden had lower eGFR values than those with non-calcified plaques, while those with a mixed plaque composition exhibited the most severe renal impairment.[35] This stepwise decline in kidney function across plaque phenotypes suggests that CKD not only increases atherosclerotic burden but may also influence plaque composition and stability, potentially through dysregulated mineral metabolism and chronic inflammation.

GS may be particularly sensitive to CKD-related atherosclerosis owing to its unique methodology. Unlike the vessel score (which counts affected vessels) or SYNTAX score[36,37] (which focuses on revascularization complexity), GS integrates stenosis severity on a nonlinear scale (capturing lesions as mild as 25%), anatomic location weighting (eg, left main ×5.0, proximal LAD ×2.5), and cumulative burden across all coronary segments.[7,36] This multidimensional approach aligns with the CKD phenotype, which is characterized by diffuse multifocal disease, extensive calcification, and proximal high-risk lesions driven by uremia, inflammation, and endothelial dysfunction.[26,38,39] By capturing intermediate stenoses (25%-50%) missed by vessel score and non-obstructive lesions (<50%) omitted by SYNTAX score, the GS more comprehensively quantifies the widespread atherosclerotic burden typical of CKD patients, explaining its stronger associations with eGFR and CV outcomes.[2,40]

These findings have important clinical implications for CV risk stratification. Patients with mild to moderate renal impairment may have their CV risk underestimated by current CV risk prediction models, such as the Framingham Risk Score and the recently created ESC SCORE2 system, which incorporate limited renal function assessment typically only severe CKD or proteinuria.[25,26] The ESC SCORE2, while representing a significant advancement in European CV risk prediction by providing age-specific risk estimates, similarly does not adequately account for the graded relationship between eGFR decline and atherosclerotic burden demonstrated in our study.[41,42]

Our findings provide anatomical validation for the CKM health paradigm and PREVENT equations recently endorsed by major cardiology societies.[9,10] The AHA CKM staging system designates moderate-to-high risk CKD as stage 2 and subclinical CV disease as stage 3.[9] Our results demonstrate concordance: patients with eGFR 60 to 89 mL/min/1.73 m^2 exhibited 73% increased odds of severe coronary atherosclerosis (OR = 1.732), while those with an eGFR of 30 to 59 mL/min/1.73 m^2 demonstrated 6-fold higher odds (OR = 6.073), substantiating the classification of even mild-to-moderate renal dysfunction as a high-risk condition.

Our study provides pathophysiological evidence that support PREVENT's methodological innovations. PREVENT is the first large-scale CV risk calculator that comprehensively integrates eGFR as a continuous variable.[10,11] Our demonstration that eGFR exhibited the strongest correlation with GS (ρ = −0.352) and emerged as the most powerful independent predictor (standardized β = −.309) validateds PREVENT's positioning of renal function as a core risk component. The dose-response relationship we observed (40% increased odds per 10 mL/min/1.73 m^2 decline) supports PREVENT's consideration of eGFR as a continuous variable, capturing risk gradation across the entire renal function spectrum.[10]

While PREVENT predicts future clinical events in the general populations, our angiographic data bridge the gap between epidemiological risk prediction and pathophysiological reality by demonstrating substantial atherosclerotic burden accumulation in patients with declining renal function.[4,43] This anatomical validation is particularly relevant given that traditional risk calculators such as the Framingham Risk Score and ESC SCORE2 incompletely capture mild-to-moderate renal dysfunction, potentially underestimating CV risk in this population.[41,44] Our findings reinforce the CKM health

continuum and support the integration of routine eGFR assessment into CV risk stratification strategies, particularly in populations with a high CKD prevalence.

Our data suggest that routine eGFR measurement should be integrated more prominently into CV risk algorithms, particularly for patients undergoing evaluation for CAD. These findings corroborate previous Turkish population data that demonstrated strong associations between eGFR and CAD severity assessed using the SYNTAX score.[45] Our investigation extends these observations by employing the more accurate CKD-EPI equation for renal function estimation, utilizing GS for comprehensive atherosclerotic burden assessment, and examining a nearly 3-fold larger patient cohort (n = 1181 vs n = 411), thereby strengthening the evidence for this relationship across different methodological approaches.

Notably, we observed no significant correlation between BMI and coronary atherosclerotic burden, consistent with the "obesity paradox" reported in CV populations.[46,47] This paradoxical finding may reflect BMI's limitations in differentiating visceral from subcutaneous fat, variations in metabolic phenotypes among obese individuals, or survival bias in angiographic cohorts.[48]

Our gender-stratified analysis reveals the profound "diabetic woman paradox": DM was an exceptionally strong risk factor in women (OR = 2.09, $P = .002$) but showed no significant association in men (OR = 1.37, $P = .117$; P for interaction $< .05$). This 2-fold gender disparity aligns with the Framingham Heart Study demonstrating 3.5- versus 1.5-fold CV risk increases in diabetic women versus men[49] and meta-analyses confirming a 2- to 3-fold higher relative risk in diabetic women.[50,51] Potential mechanisms include loss of estrogen cardioprotective effects post-menopause, increased atherogenic lipid profiles, heightened systemic inflammation, and pronounced endothelial dysfunction in diabetic women.[52-54]

The substantially higher explanatory power in women (Nagelkerke $R^2 = 0.280$) than men ($R^2 = 0.180$, $P < .05$) indicates that classical risk factors exert more predictable effects on coronary disease in women, paralleling observations from contemporary risk prediction models.[52,55] Smoking showed significant effects only in men (OR = 1.55, $P = .009$), likely reflecting marked differences in prevalence (52.3% vs 18.7%) rather than biological interaction. Importantly, eGFR, HDL-cholesterol, and non-HDL-cholesterol demonstrated universal sex-independent effects (P for interaction $> .10$), confirming that renal function and lipoprotein metabolism represent fundamental risk determinants irrespective of sex.

These findings support sex-specific CV risk stratification: diabetic women warrant aggressive multifactorial risk reduction including intensive glycemic control and lower LDL targets,[55] whereas male smokers require prioritized cessation interventions. Risk prediction tools should incorporate sex-specific weighting of DM and HT to enhance the predictive accuracy and guide personalized preventive strategies. The sex-independent effects of renal function and lipid parameters underscore their universal importance across both sexes.

Study Strengths and Limitations

Our study had several strengths. First, invasive CAG with standardized GS provides an objective, quantitative assessment of atherosclerotic burden. Second, comprehensive multivariable models were adjusted for numerous confounders thereby reducing the potential bias. Third, the relatively large sample size across a spectrum of renal function levels enabled a robust statistical analysis. Fourth, the CKD-EPI equation represents current best practice.[15,56]

However, several important limitations should be noted. Cause-and-effect relationships are limited by the cross-sectional study design; longitudinal studies with serial eGFR and coronary imaging assessments would clarify directionality. We did not assess proteinuria or albuminuria as additional markers that independently predict CV outcomes.[3] The generalizability of our study findings may be limited because the study cohort included patients with clinical indications for CAG. Although GS provides a detailed anatomical assessment, it does not capture plaque composition or physiological significance.[57]

An important limitation of this study is that the GS quantifies only epicardial coronary stenosis and does not capture microvascular coronary disease (CMD), which may contribute substantially to ischemic burden, particularly in women and patients with DM.[40,58] CMD is highly prevalent in CKD patients and can manifest as angina and adverse CV events even in the absence of obstructive epicardial disease.[59,60] Given that renal dysfunction promotes endothelial dysfunction, chronic inflammation, and oxidative stress—the key drivers of CMD—our findings may underestimate the true CV risk, especially in early-stage CKD where microvascular pathology may precede macrovascular stenosis.[43,61] Future investigations incorporating microvascular assessment techniques (coronary flow reserve measurement, cardiac magnetic resonance perfusion imaging) and prospective clinical endpoints (myocardial infarction, cardiovascular mortality) would provide a more comprehensive validation of the renal-cardiac risk relationship across both macrovascular and microvascular domains.

Other important limitation is the potential heterogeneity of our reference group (eGFR ≥ 90 mL/min/1.73 m^2), which may include patients with diabetic hyperfiltration—an early marker of kidney damage characterized by supranormal GFR—alongside individuals with genuinely normal renal function.[62-64] Hyperfiltration is associated with an increased CV risk and accelerated CKD progression,[65,66] potentially attenuating the observed risk gradient across eGFR categories. Future investigations should stratify high-normal eGFR ranges or incorporate albuminuria measurements to better differentiate hyperfiltration from true renal health.[43]

An important limitation of our cross-sectional design is the inability to establish temporal relationships or definitive causality between renal dysfunction and CAD severity. The observed association between a reduced eGFR and elevated GS may reflect 3 potential scenarios. First, CKD may directly

promote coronary atherosclerosis through non-traditional risk factors including uremic toxins, oxidative stress, inflammation, endothelial dysfunction, vascular calcification, and activation of the renin-angiotensin-aldosterone system.[1,2,4] Second, the "common soil" hypothesis posits that shared upstream risk factors—particularly DM, HT, dyslipidemia, and smoking—simultaneously drive both renal and coronary pathologies through overlapping pathophysiological mechanisms.[26,67] Third, reverse causality may occur whereby systemic atherosclerosis causes renal artery stenosis (ischemic nephropathy), thereby reducing eGFR as a consequence rather than a cause of CV disease.[68] Prospective longitudinal studies with serial eGFR measurements, imaging-confirmed renal artery patency, and incident CV events are necessary to disentangle these temporal relationships and to elucidate the relative contributions of direct CKD effects versus shared pathophysiology.[3]

Furthermore, when interpreting our results according to gender distribution, we need to consider statistical power and gender distribution. This is because our cohort consisted of 776 men (65.7%) and 405 women (34.3%). The observed correlation data (Spearman $r = -0.352$ overall; -0.402 in women; -0.330 in men) confirmed sufficient statistical power (>0.99) to detect associations between CKD and CAD in both the entire cohort and each gender subgroup. In particular, the multivariate regression model showed significantly better explanatory power in women than in men (Nagelkerke $R^2 = 0.280$ vs 0.180, $P < .05$), indicating that the included risk factors explain a larger proportion of CAD severity in women. Although sufficient statistical power was present in both subgroups, the smaller female sample size may limit the accuracy of some gender-specific estimates. Further studies with a balanced gender distribution and incorporating gender-specific risk factors (eg, reproductive history, hormonal status) are needed to examine these differences in more detail.

Our study did not include measurements of inflammatory biomarkers, oxidative damage, or antioxidant enzyme activity. These measurements could provide valuable information regarding the biological mechanisms between renal dysfunction and coronary atherosclerosis.

Conclusion

This investigation demonstrates that declining renal function represents the most powerful independent predictor of coronary atherosclerotic burden among all traditional CV risk factors, exhibiting a clear dose-response gradient across eGFR categories. These findings provide crucial anatomical validation for the recently endorsed PREVENT CKM health framework, confirming that even mild-to-moderate renal impairment substantially increases CAD severity. The unique sensitivity of the GS to the CKD phenotype—capturing diffuse disease and calcification patterns missed by simpler scoring systems—strengthens the clinical relevance of our observations. Our gender-stratified analysis revealing the "diabetic woman paradox" alongside universal gender-independent effects of renal function underscores the need for both sex-specific and universal kidney function assessments in CV risk stratification. These results compellingly support the integration of eGFR as a continuous variable into CV risk prediction algorithms such as Framingham and ESC SCORE2, which currently underestimate the risk in patients with mild-to-moderate renal dysfunction. Future prospective studies with serial eGFR measurements and incident CV endpoints are essential to determine whether the early identification and intensive management of patients with declining renal function can attenuate atherosclerosis progression and improve CV outcomes.

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