Published in final edited form as:

Circulation. 2020 January 07; 141(1): 21–33. doi:10.1161/CIRCULATIONAHA.119.043916.

Coronary microvascular dysfunction, left ventricular remodeling and clinical outcomes in patients with chronic kidney impairment

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Abstract

Background—Cardiac dysfunction and cardiovascular (CV) events are prevalent among patients with chronic kidney disease (CKD) without overt obstructive coronary artery disease (CAD) but the mechanisms remain poorly understood. Coronary microvascular dysfunction (CMD) has been proposed as a link between abnormal renal function and impairment of cardiac function and CV events. We sought to investigate the relationships between CKD, CMD, cardiac dysfunction and adverse CV outcomes.

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Contributions: Literature search: NSB, AS, MDC Figures: NSB, AS, WZ, MDC Study design: NSB, MDC Data collection: NSB, AS, WZ, AG, KF, CB, CB, JH, MTO, MS Data Analysis: NSB, AS, WZ, KF, CA, MDC Data interpretation: NSB, AG, RB, RD, RB, SDP, SDS, MDC Manuscript writing: NSB, AS, WZ, AG, KF, CB, HJH, MTO, PB, EA, SD, CB, JH, HS, VT, MS, SD, DMC, SDP, RB, RD, SDS, MDC

Disclosure statement:

Dr Charytan: Personal Fees for Consulting or Advisory Boards-Fresenius Medical Care, Medtronic, Amgen, Eli Lilly-Boehringer Ingelheim, Fees for service on trial steering, safety and monitoring, or clinicals event committees-PLC medical, Zoll Medical, Janssen, Merck, Allena Pharmaceuticals, Astra Zeneca. Dr. Dorbala received consulting fees from General Electric Health Care. HJ Harms has a financial interest in MedTrace Pharma, Inc. Dr. Di Carli received consulting fees from Sanofi Aventis and GE Healthcare, and investigator-initiated research grants from Spectrum Dynamics and Gilead Sciences. Other authors reported no disclosures

Methods—Patients undergoing cardiac stress positron emission tomography (PET), echocardiogram and renal function ascertainment at Brigham and Women's Hospital were studied longitudinally. Patients free of overt coronary (summed stress score < 3 & without history of ischemic heart disease), valvular and end-organ disease were followed for adverse composite outcome of death, hospitalization for myocardial infarction or heart failure. Coronary flow reserve (CFR) was determined from PET. Echocardiograms were used to measure cardiac mechanics: diastolic (lateral and septal E/e') and systolic [global longitudinal (GLS), radial (GRS) and circumferential strain (GCS)]. Image analyses and event adjudication were blinded. The associations between estimated glomerular filtration rate (eGFR), CFR, diastolic, systolic indices and adverse CV outcomes were assessed in adjusted models and mediation analyses.

Results—352 patients (median age 65 years, 63% women and 22% black) were studied. 35% of patients had eGFR<60 ml/min/1.73 m^2, median LVEF of 62% and median CFR of 1.8. eGFR and CFR were associated with diastolic and systolic indices, as well as future CV events (all $p<0.05$). In multivariable models, CFR but not eGFR was independently associated with cardiac mechanics and CV events. The associations between eGFR, cardiac mechanics and CV events were partly mediated via CFR.

Conclusions—CMD but not eGFR was independently associated with abnormal cardiac mechanics and an increased risk of CV events. CMD may mediate the effect of CKD on abnormal cardiac function and CV events in those without overt CAD.

Journal Subject Terms:

Chronic kidney disease; coronary microvascular disease; myocardial mechanics; cardiovascular risk

Keywords

chronic kidney disease; coronary flow reserve; coronary microvascular function; cardiovascular outcomes

Introduction

Approximately 14% of the adult US population has chronic kidney disease (CKD).[1] There is clear evidence of a graded association between the severity of CKD and adverse cardiovascular (CV) risk,[2] which begins early in the natural history of the disease even when serum creatinine is within normal limits.[3] In fact, patients with early CKD are more likely to die of CV disease than progress to ESRD.[4] The mechanisms mediating increased risk of CV mortality and morbidity in CKD patients are not well understood. Although CKD clusters with conventional atherosclerotic risk factors, age-adjusted CV mortality is several fold higher in patients with CKD than in the general population.[5] Interestingly, sudden cardiac death (SCD) and heart failure related deaths are more common than the classic type 1 myocardial infarction (MI) related deaths in CKD patients,[5] which is in keeping with the relatively lower prevalence of obstructive coronary artery disease (CAD) on autopsy and coronary angiography.[6, 7] These findings collectively suggest that other mechanisms may contribute to cardiovascular risk in CKD patients. One such mechanism may involve the

effects of CKD and its associated risk factors on coronary epicardial and microcirculatory dysfunction, thereby increasing the risk of subclinical myocardial ischemia and injury, myocardial dysfunction, heart failure and, ultimately, mortality.[8-12]

We designed this study to test the hypothesis that coronary microvascular dysfunction (CMD) is associated with abnormalities in myocardial structure and function in patients across a spectrum of eGFR, and that this may help explain the increased risk of heart failure and death related with worsening renal function.

Methods

The analytic methods will be/have been made available in the supplement to other researchers for purposes of reproducing the results or replicating the procedure. The study was reviewed and approved by the Partners Institutional Review Board. Informed consent was waived as all data were collected as part of standard clinical care.

Patient population

We included consecutive patients referred to the Brigham and Women's Hospital between January 1, 2006 and December 31, 2016 for stress myocardial perfusion positron emission tomography (PET) who also underwent 2-dimensional (2-D) echocardiography and serum creatinine determination within 90 days of the PET study. Patients with known coronary artery disease, as defined by a history of prior revascularization (percutaneous coronary intervention or coronary artery bypass grafting) and/or MI or imaging evidence of flow-limiting coronary artery disease (summed stress score>2 on PET) were excluded as were those with any of the following: severe valvular heart disease, infiltrative cardiomyopathy, congenital heart disease, history of active malignancy or end-stage liver or lung disease, history of organ transplantation and poor quality echocardiogram (Supplemental Figure 1).

Renal Function

Estimated GFR (eGFR) was calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration formula.[13] CKD was defined as eGFR< 60 ml/min/1.73 m^2.

Quantification of coronary vascular function

Coronary vascular function was quantified in all patients using a whole-body PET/computed tomography scanner (PET/CT Discovery RX or STE LightSpeed 64, GE Healthcare, Milwaukee, WI). Myocardial blood flow (MBF, in mL/min/g) was measured at rest and during maximal hyperemia by a standard intravenous infusion of adenosine, dipyridamole or regadenoson using either ^{13}N-ammonia or ^{82}Rubidium as the flow tracers, as described previously.[14] The image acquisition and post processing techniques for quantification of myocardial blood flow (MBF) and flow reserve did not change over the study period. Previous studies have demonstrated that equivalence of dipyridamole, regadenoson, and adenosine as vasodilators for myocardial perfusion imaging and quantitative myocardial blood flow.[15, 16] Furthermore, the use of different vasodilator stress agents has not affected the value of quantitative myocardial blood flow by PET for risk stratification.[15, 17-19] The

heart rate, blood pressure, and 12-lead electrocardiogram were recorded at baseline and every minute during and after the vasodilator infusion.

Image analysis: For semi-quantitative assessment of myocardial scarring and ischemia, 17-segment visual interpretation of gated myocardial perfusion images was performed by experienced operators using a standard five-point scoring system.[20] Rest left ventricular ejection fraction (LVEFs) was calculated from gated myocardial perfusion images with commercially available software (Corridor4DM; Ann Arbor, Michigan).

Absolute regional and global MBF was quantified at rest and at peak hyperemia using a validated two-compartment kinetic model, as described previously.[21] Per-patient CFR was calculated as the ratio of MBF during maximal hyperemia over that at rest for each coronary territory and for the entire left ventricle. This method for quantitation of MBF is highly reproducible. In our laboratory, the intra-class correlation coefficient for CFR among four readers is 0.94 (95% confidence interval (CI) 0.88–0.98), indicating excellent reproducibility.[18]

Quantification of cardiac structure and function

Left ventricular diastolic and systolic function was quantified from 2-D echocardiograms. The echocardiograms were acquired as recommended by the American Society of Echocardiography (ASE) and in a manner consistent with standard practices for patient comfort and position. All echocardiographic readers were blinded to the results of PET imaging. No cardiovascular events occurred between echocardiography and PET imaging.

Echocardiograms with views to: (1) assess LV diastolic function, and (2) ensure optimal imaging for off-line LV deformation analysis with speckle-tracking software were analyzed with following methods:

Diastolic function: peak early mitral annular relaxation velocity (e') was measured from both the septal and lateral aspects of the mitral annulus from the apical 4-chamber view.[22] Mitral inflow velocity (E) was assessed by pulsed wave Doppler from the apical 4-chamber view by positioning the sample volume at the tip of the mitral leaflets.[22]

Systolic function: Deformational indices were estimated using B-mode speckle-tracking analysis, which was performed off-line using commercially available software (Cardiac Performance Analysis, Tomtec system, Munich, Germany).[23] The endocardial border was traced at an end-diastolic frame in apical 4– 2- & 3- chamber views and at an end-systolic frame in short axis view, where end-diastole is defined by the QRS complex from the electrocardiogram (ECG) or the frame just before mitral valve opening. Adequate tracking of speckles along the endocardial and the epicardial borders throughout the cardiac cycle was visually assessed. Peak global longitudinal (GLS), radial (GRS) and circumferential strain (GCS) curves were then computed automatically and provided as global and segmental data including 6 segments in each view[24]. LV volumes were determined by the modified Simpson's method in the apical 4 and 2 chamber views, and LVEF was calculated from volumes in the standard manner.[25]

LV mass was calculated by the ASE recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area (LVMI), and relative wall thickness (RWT) was calculated in accordance with ASE guidelines, this information was used to identify those with abnormal LV geometry.[25]

The intra-class correlation coefficient for echocardiographic parameters were good, the details are presented in Supplemental Table 1.

Circulating biomarkers

N-terminal pro–B-type natriuretic peptide (NTproBNP) was measured using an electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN) in clinical laboratory, and values within 90 days of cardiac PET study were used in the analysis.

Clinical outcomes

A Clinical Endpoints Committee (CEC) reviewed and adjudicated the primary composite endpoint (all cause death, non-fatal MI, and hospitalizations for heart failure). The members of CEC were blinded to image analyses. Time to first event major adverse cardiovascular event (MACE), defined as a composite of all cause death, and hospitalization for nonfatal MI or heart failure was analyzed. Time to first event was analyzed. Ascertainment of clinical endpoints were determined by CEC from the longitudinal medical record, Partners Healthcare Research Patient Data Registry, the National Death Index, mail surveys and telephone calls. The details of clinical outcomes are presented in the supplement (Supplemental methods). The follow up was censored on December 31st, 2017.

Statistical Analysis

Baseline characteristics were reported as frequency with percentage (%) for categorical variables and median with interquartile ranges for continuous variables. We used $\chi 2$ and Wilcoxon rank sum tests to evaluate for differences in categorical and continuous baseline characteristics, respectively. Poisson regression models were used to estimate the annualized rate of adverse events and its components. Global MBF and CFR values were used in all analyses.

Unadjusted and multivariable-adjusted relationships between eGFR & CFR, diastolic indices (Lateral E/e' and Septal E/e'), systolic indices (GLS, GRS and GCS), marker of LV wall stress (NTproBNP) and adverse composite clinical endpoint were evaluated using appropriate linear, Poisson and Cox proportional hazard models while accounting for non-linearity of relationships using restricted cubic splines. All the adjusted models included demographic factors (age, sex, race), clinical factors (history of hypertension, diabetes, peripheral vascular disease, stroke, diabetes, body mass index (BMI), LVMI, LVEF and eGFR as well as CFR. The variables and number of knots were selected based on optimal values of the Akaike information criterion after including clinically important covariates. We also tested for a statistical interaction between CFR and eGFR in the multivariate model in the Poisson model. Cox proportional hazards models were used to determine the effect of abnormal eGFR[26] (<60 ml/min/1.73m^2) and abnormal CFR (<1.5). The cox proportional

hazard (PH) assumptions test based on Schoenfeld residuals was used to verify non-violation of PH assumption in the adjusted model.

To understand the interplay between LV structure, myocardial mechanics and coronary microvascular dysfunction on future outcomes, we performed an exploratory analysis where we stratified patients by abnormal geometry, diastolic dysfunction (E/e'<15), systolic dysfunction (GLS<−17%) and CFR (<1.5) and compared the rate of adverse events as well as a composite of heart failure admissions and non-fatal MI. The cutoff for GLS was median values in our cohort, whereas ASE definitions were used to define abnormal geometry[25], cutoffs for E/e' and CFR were based on previous studies.[10, 18]

Mediation analysis (i.e. path analysis)-which tests a putative causal relation among variables—was also performed to test whether renal function exerts its effect on cardiovascular disease via microvascular dysfunction. eGFR was chosen as measure of renal function, CFR was chosen as marker of microvascular disease whereas measures of diastolic/systolic function, NTproBNP and clinical composite endpoint were chosen as markers of cardiovascular disease.[27] The details of statistical analysis are provided in the supplement (Supplementary methods).

Two-sided p-values < 0.05 were considered significant. Stata software version 15.1 (StataCorp, College Station, Texas) and R (version 3.6.0) were used for analyses. The results are presented in accordance with STROBE checklist (Supplemental table 2).

Results

Baseline characteristics

The final study cohort consisted of 352 patients. The distribution of baseline characteristics by categories of CKD is summarized in Table 1. The median (Q1–Q3) age of patients in the overall cohort was 65 (55–75) years, 63% were women, and 22% were Black. One-third of the patients had CKD 3 or higher. The median (Q1–Q3) LVEF was 62% (55–68%) by echocardiography and 59% (50–66%) by PET. More than three-quarters of patients had a history of hypertension, approximately two-thirds had dyslipidemia and one-third had diabetes mellitus. More than 70% of the patients had an abnormally remodeled left ventricle.

Compared to patients with preserved eGFR (≥60 ml/min/1.73 m^2), those with CKD 3 or greater had higher prevalence of hypertension and diabetes and lower BMI (all p<0.05), lower stress MBF (1.7 vs. 2.1 mL/min/g, p<0.001) and lower CFR (1.5 vs. 1.9, p<0.001) (Table 1), here reflecting coronary microvascular dysfunction. Rest and stress MBF and CFR were comparable across all three coronary artery territories. Measurements of eGFR and CFR were modestly correlated (r=0.26, p<0.001), this correlation was independent of clinical important confounders (Supplemental Table 3).

Association between eGFR, coronary flow reserve and left ventricular mechanics

Compared to patients with preserved eGFR (≥ 60 ml/min/1.73 m^2), those with CKD stage 3 or greater had higher lateral E/e'(14.1 vs. 10.8, p<0.001) and septal E/e'(8.3 vs. 9.8, p<0.001), reflecting increased left ventricular filling pressure, as well as impaired GLS

(−15.1% vs. −18.6%, p<0.001), GCS (−21.3% vs. −25.3%, p<0.001) and GRS (25.5% vs. 34.6%, p<0.001), reflecting systolic dysfunction (Table 1).

In unadjusted models, both eGFR and CFR were associated with measures of diastolic function (i.e. lateral and septal E/e'), such that lower eGFR and CFR were associated with worse diastolic function (all p-trends <0.05) (Table 2). Likewise, lower eGFR and CFR were associated with worse systolic strain (GLS, GRS and GCS) (all p-trends <0.05) (Table 2).

In the multivariable models including both CFR and eGFR, only the association between CFR, but not eGFR, with lateral and septal E/e' (Figure 1, A & B) as well as measures of systolic deformation indices (Figure 1 C, D & E) remained significant, indicating that variability in diastolic and systolic indices was explained independently by variability in CFR, but not renal function.

We also evaluated the associations between renal function, CFR and indices of myocardial mechanics in those with a history of diabetes. The effect estimates and statistical significance for association of CFR and eGFR with measures of myocardial mechanics remained unchanged in this sub-group analysis as compared to overall population indicating that associations hold true in diabetics as well as non-diabetics (Table 2 & Supplemental Table 4)

Association between eGFR, coronary flow reserve and LV wall stress

As measures of diastolic and systolic LV mechanics worsened with impaired renal and coronary microvascular function, we hypothesized that NTproBNP- a biomarker of LV wall stress- would also show similar associations with eGFR and CFR. Indeed, patients with CKD stage 3 or greater had higher NTproBNP as compared to those with preserved eGFR (p<0.001) (Table 1). In unadjusted and adjusted models, both eGFR and CFR were independently associated with elevated NTproBNP levels (p-trend<0.05) (Table 2 and Supplemental Figure 2).

Association between eGFR, coronary flow reserve and clinical outcomes

Over a median follow-up of 4.4 years (Q1–Q3, 1.2–7.7 years), 108 patients met the primary composite endpoint of major adverse cardiac events (MACE) including death or hospitalization for non-fatal myocardial infarction or heart failure (Table 3). Individual components of the composite endpoint increased with worsening renal function (Table 3).

In unadjusted models, there was a significant association between the primary composite endpoint and eGFR and CFR (both p-trend<0.001). However, in multivariable models including both CFR and eGFR, only CFR (p-trend=0.015), but not eGFR (p-trend=0.116), was significantly associated with MACE (Figure 2 A & B). No significant interaction was observed between CFR and eGFR on the occurrence of MACE (p=0.840). In a stratified analysis by abnormal eGFR (<60 ml/min/1.73m^2) and severely abnormal CFR (<1.5), only abnormal CFR (adjusted Hazard Ratio (HR): 1.61: 95% CI: 1.05–2.46, p=0.029), but not eGFR (adjusted HR= 1.29, 95% CI: 0.82–2.04, p=0.278), remained significantly associated with MACE (Figure 3). These results were unchanged after imputation of the missing LVMI and BMI data in 25 patients (Supplemental Table 5 & 6).

To explore the potential confounding of the association between ESRD and microvascular dysfunction, we also performed a sensitivity analysis of the association between renal function and MACE after excluding the 7 patients with end stage renal disease. We observed that the association between eGFR, CFR and MACE did not change after excluding the 7 ESRD patients.

Risk stratification across categories of LV structure/function and coronary flow reserve

To explore the hypothesis that severe coronary microvascular dysfunction is an important determinant of the transition from adaptive to maladaptive LV remodeling in CKD, we next explored the prognostic value of abnormal CFR across categories of LV geometry, diastolic and systolic function. (Figure 4 A & B) summarizes the annualized rates of MACE and the composite of hospitalizations for heart failure and non-fatal MI by categories of CFR and LV structure and function. We observed a consistent higher rate of MACE and hospitalizations for heart failure and non-fatal MI when abnormalities in LV geometry, systolic and diastolic function coexisted with severe coronary microvascular dysfunction (all $p < 0.05$).

Mediation analysis to explore the link between renal dysfunction, impaired cardiac mechanics and adverse cardiovascular events

We assumed a biologically plausible path where CMD mediates the effect of impaired renal function on LV remodeling and adverse CV outcomes. In fully adjusted models, CMD was a significant mediator of the relationship between impaired renal function and LV diastolic dysfunction, accounting for 19–24% of the total effect; LV systolic dysfunction, accounting for 19–42% of the total effect; and LV wall stress, accounting for 7% of the total effect. Similarly, CMD was also a significant mediator of the relationship between impaired renal function and adverse cardiovascular events, accounting for 32% of the total effect in fully adjusted models (Table 4 and Supplemental Table 7).

Discussion

Our results show that in symptomatic patients with chronic renal impairment without overt obstructive CAD, the severity of coronary microvascular dysfunction is a significant predictor of abnormalities in left ventricular mechanics and adverse cardiovascular outcomes. The link between impaired renal function, myocardial dysfunction and cardiovascular disease events was substantially mediated by coronary microvascular dysfunction. These findings provide new and important mechanistic insights into the pathophysiology and associated clinical risk of CKD associated cardiomyopathy.

Chronic kidney dysfunction has been independently associated with a graded reduction in coronary microvascular function[8, 9, 18, 28-34] and abnormal left ventricular structure and function even in the absence of obstructive coronary artery disease.[5-7, 35, 36] Consequently, the current study was designed to investigate the inter-relationship between coronary microvascular dysfunction, abnormalities in cardiac structure and mechanics, and clinical outcomes. The findings in the current study suggest that coronary microvascular dysfunction is an important link between CKD, adverse left ventricular remodeling, and clinical risk. Exactly how coronary microvascular dysfunction may lead to impaired LV mechanics and

increased risk cannot be determined from this study. However, there are several possible mechanisms that may help explain our findings. Chronic renal dysfunction has been associated with structural (arteriolar remodeling and capillary rarefaction) and functional (endothelial- and smooth muscle-cell dysfunction) abnormalities in the coronary microvasculature in animal models[37, 38] and humans.[39-41] In the setting of left ventricular hypertrophy, a very common feature in CKD-associated cardiomyopathy, abnormalities in microvascular structure and function lead to myocardial ischemia, subclinical injury and fibrosis.[42, 43] The significant associations between severely impaired coronary flow reserve, measures of diastolic and systolic dysfunction independent of LV mass, and clinical outcomes in our study provide important new evidence that the development of severe microvascular dysfunction likely signals the transition from physiologic to pathologic LV remodeling that increases the risk of heart failure and death in patients with CKD. This is also supported by the fact that CFR, but not eGFR, predicted adverse LV mechanical dysfunction and clinical outcomes. In fact, the association between measures of LV mass, structure, diastolic and systolic dysfunction with severely impaired CFR identified patients at the highest risk for hospitalizations for heart failure and myocardial infarction.

To our knowledge, our study is first and largest to comprehensively explore these associations and suggest a possible pathway to development of uremic cardiomyopathy in human beings without overt ischemic heart disease. Our study is clinically important because it advances this understanding and suggests CMD as a target for novel therapeutic approaches to reduce cardiovascular disease risk in uremic cardiomyopathy. In addition, these data help validate intermediate endpoints may be helpful in design of future clinical trials in CKD patients.

Study Limitations

Our study is a single-center observational study and, as such, has some inherent limitations. First, the study cohort was identified from a clinical database of symptomatic patients referred for evaluation of suspected ischemic heart disease, thus possibly limiting the generalizability of our findings to lower risk asymptomatic individuals. Second, the patients in the study had no overt obstructive CAD on the basis of a normal myocardial perfusion PET scan with preserved LV function. In addition, patients with known CAD, as defined by a history of prior revascularization and/or myocardial infarction were excluded. A visually normal rest/stress myocardial perfusion PET scan, as used in this study, has very high sensitivity and negative predictive value to exclude significant flow-limiting coronary artery disease.[44] Diffuse quantitative flow abnormalities in the context of visually normal myocardial perfusion PET scans (i.e., no perfusion defects) largely represent diffuse atherosclerosis and microvascular dysfunction.[45] However, we do acknowledge that although it is conceivable that some patients in this cohort may have had some flow-limiting CAD without perfusion abnormalities, our clinical experience and the available evidence with PET suggests this to be unlikely.[46, 47] Third, a positive mediation analysis, as we report here, is consistent with, but not demonstrative of, causation—particularly given that the data are cross-sectional. The mediation analyses were exploratory to guide further longitudinal or interventional studies. Although the percent mediation effect is included as hypothesis-generating, we acknowledge the fact that the results are not as robust in analysis with

relatively modest sample size.[48, 49] Fourth, the data on etiology of CKD in those with eGFR<60 was not available limiting our ability to determine if the associations observed in this study are modified by the cause of CKD. The mediation analyses were exploratory, to infer causation, further longitudinal or interventional studies are needed. These limitations are substantially counterbalanced by several important innovations, including the unique, demonstration of a possible pathway for development of uremic cardiomyopathy and their associations with cardiovascular disease events in human beings.

In conclusion, our study shows for the first time, an association between impaired renal function, coronary microvascular dysfunction, adverse LV remodeling and myocardial dysfunction, and subsequent risk of adverse cardiovascular events. Furthermore, our study raises the possibility that efforts to attenuate microvascular disease could produce benefits on myocardial dysfunction and cardiovascular events. Future longitudinal studies are needed to validate our findings and provide insights into how to further reduce the burden of cardiovascular events in CKD associated cardiomyopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Sources of Funding: This work was supported in part by American College of Cardiology Presidential Career Development Award to Dr Bajaj, and grants from the National Institutes of Health including T32 HL094301 to Drs. Bajaj, Zhou, Gupta, Fujikura, Bravo and Divakaran; T32 HL076136 and KL2TR002542 to Dr. Osborne; R01HL132021 to Dr. Di Carli; and K23HL135438 to Dr. Taqueti. Dr Bajaj is also supported by Walter B. Frommeyer, Junior Fellowship in Investigative Medicine and National Center for Advancing Translational Research of the National Institutes of Health under award number UL1TR001417. The content is solely the responsibility of the authors and does not necessarily represent the official views of the American College of Cardiology or National Institutes of Health.

Abbreviations:

CV	cardiovascular
CKD	chronic kidney disease
CMD	coronary microvascular dysfunction
CAD	coronary artery disease
PET	positron emission tomography
CFR	Coronary flow reserve
GLS	global longitudinal
GRS	Global radial strain
GCS	Global circumferential strain
eGFR	estimated glomerular filtration rate

LV	left ventricle
SCD	sudden cardiac death
MI	myocardial infarction
PET	Positron emission tomography
2-D	2-dimensional
BMI	body mass index
SSS	summed stress score
CT	Computed tomography
LVEF	left ventricular ejection fraction
MBF	myocardial blood flow
ASE	American Society of Echocardiography
NTproBNP	N-terminal pro–B-type natriuretic peptide
ECG	electrocardiogram
LVMI	left ventricular mass index
RWT	relative wall thickness
MACE	major adverse cardiovascular event

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Clinical Perspective

What is new?

- Among patients with chronic kidney disease without obstructive coronary artery disease, coronary microvascular disease is associated with impaired LV mechanics and cardiovascular risk
- The link between impaired renal function, myocardial dysfunction and cardiovascular disease events is partially mediated by coronary microvascular dysfunction.

What are the clinical implications?

- Presence of coronary microvascular dysfunction signals the transition from physiologic to pathologic LV remodeling that increases the risk of heart failure and death in patients with CKD
- Coronary microvascular disease is a potential target for novel therapeutic approaches to reduce cardiovascular disease risk in uremic cardiomyopathy

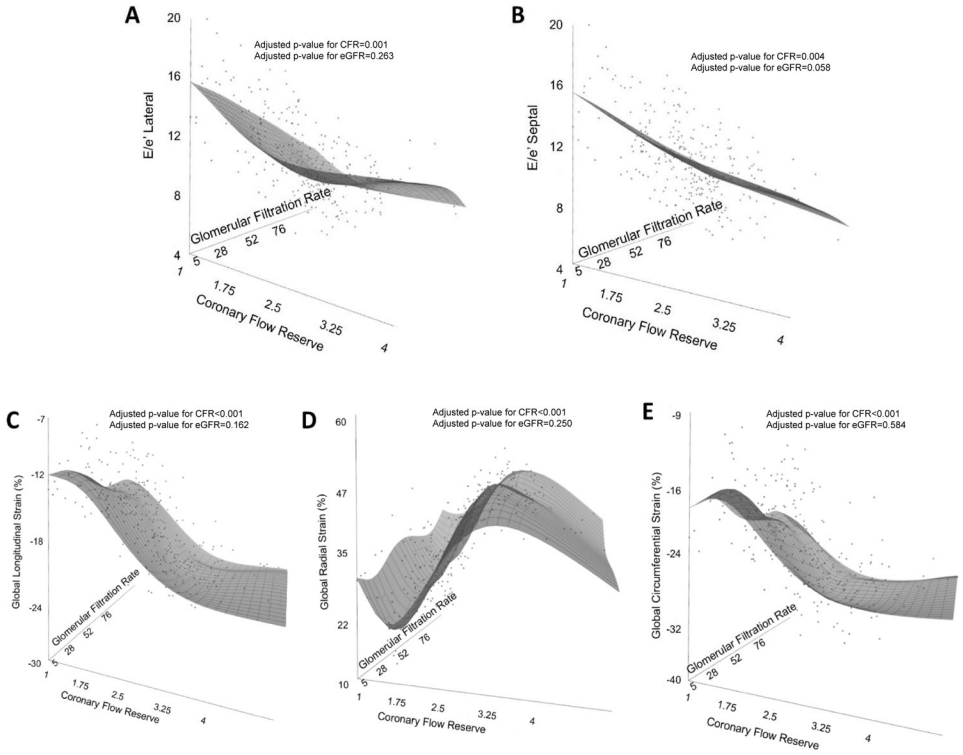


Figure 1:

Relationship between cardiac mechanics (diastolic and systolic indices), eGFR and CFR using a three dimensional scatter plot and restricted cubic spline linear regression plane (Black grid on gray surface).

Panel A & B: Diastolic indices (Lateral and Septal E/e'), eGFR and CFR

Panel C, D & E: Systolic indices (GLS, GRS & GCS), eGFR and CFR

Adjusted linear regression models included CFR (coronary flow reserve), eGFR (estimated glomerular filtration rate), age, sex, race, hypertension, hyperlipidemia, diabetes, peripheral vascular disease, stroke, indexed left ventricular mass, and resting left ventricular ejection fraction

E = Early wave of mitral inflow, e'= early diastolic mitral annular velocity, GLS= peak global longitudinal strain, GRS= peak global radial strain, GCS = peak global circumferential strain

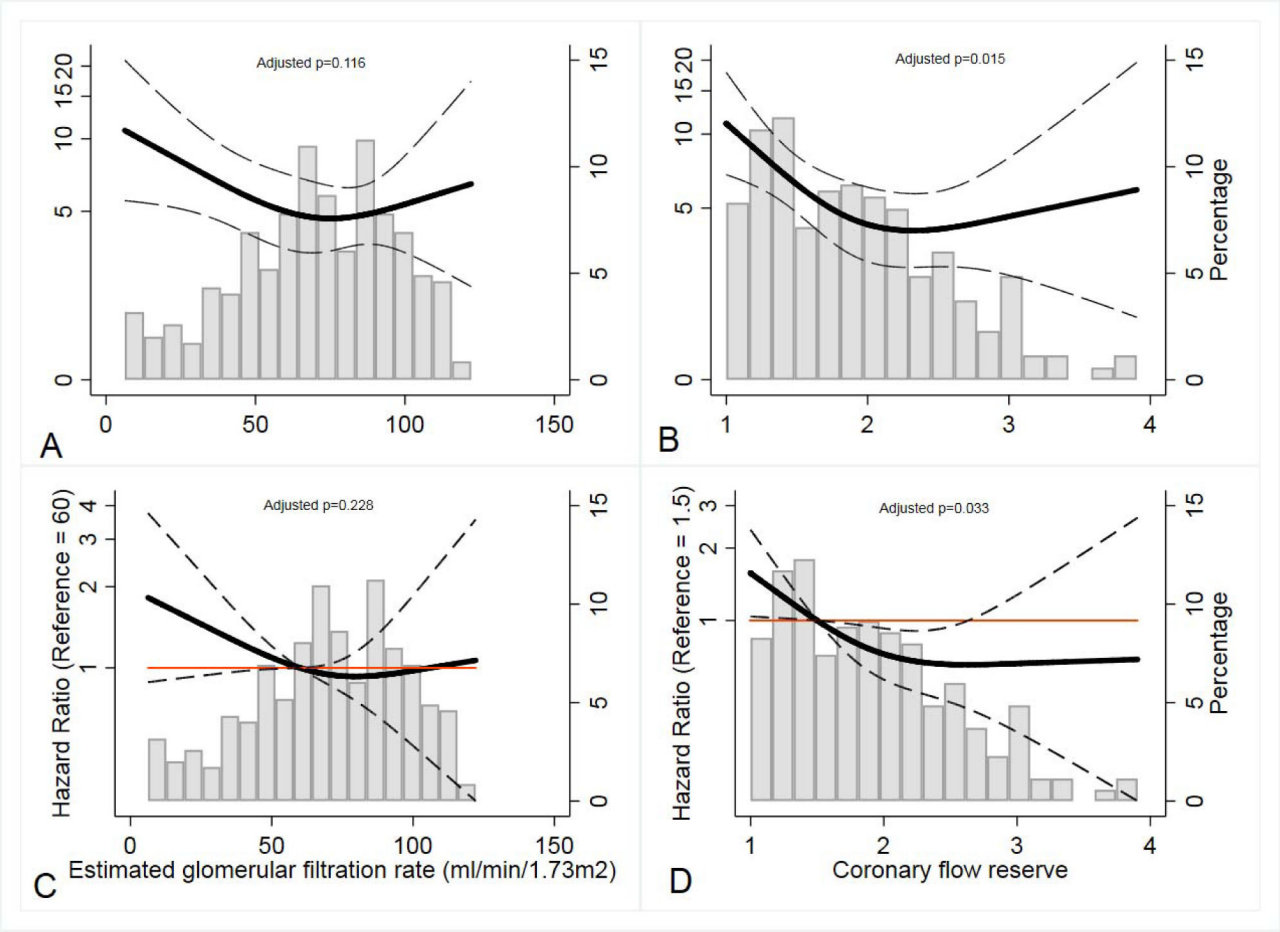


Figure 2:

Relationship between MACE, eGFR & CFR

Panel A: MACE and eGFR (Poisson model)

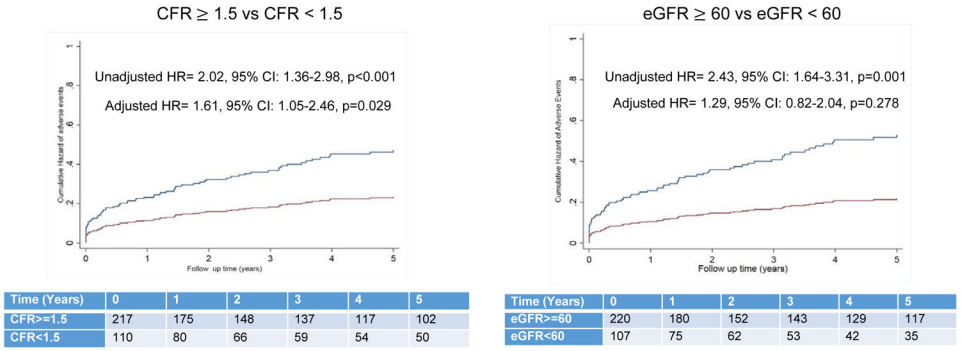
Panel B: MACE and CFR (Poisson model)

Panel C: MACE and eGFR (Cox proportional hazard model)

Panel D: MACE and CFR (Cox proportional hazard model)

Adjusted models included CFR (coronary flow reserve), eGFR (estimated glomerular filtration rate), age, sex, race, hypertension, hyperlipidemia, diabetes, peripheral vascular disease, stroke, indexed left ventricular mass, and resting left ventricular ejection fraction. Restricted cubic spline Poisson and Cox proportional hazard model regression model estimates with 95% confidence intervals are shown in black. The orange line in the Cox proportional hazard model is line of reference. (Gray histogram bars, secondary y-axis display % population with corresponding values of eGFR and CFR).

MACE= major adverse cardiovascular event (composite of death, non-fatal myocardial infarction and heart failure).



Time (Years)	0	1	2	3	4	5
CFR>=1.5	217	175	148	137	117	102
CFR<1.5	110	80	66	59	54	50

Time (Years)	0	1	2	3	4	5
eGFR>=60	220	180	152	143	129	117
eGFR<60	107	75	62	53	42	35

Figure 3.

Cumulative Hazard of MACE in Unadjusted Models stratified by abnormal CFR (<1.5) and abnormal eGFR (<60 ml/min/1.73 m2).

Hazard ratio for adjusted model was derived from model included CFR (coronary flow reserve), eGFR (estimated glomerular filtration rate), age, sex, race, hypertension, hyperlipidemia, diabetes, peripheral vascular disease, stroke, indexed left ventricular mass, and resting left ventricular ejection fraction.

MACE = major adverse cardiovascular event (composite of death, non-fatal myocardial infarction and heart failure).

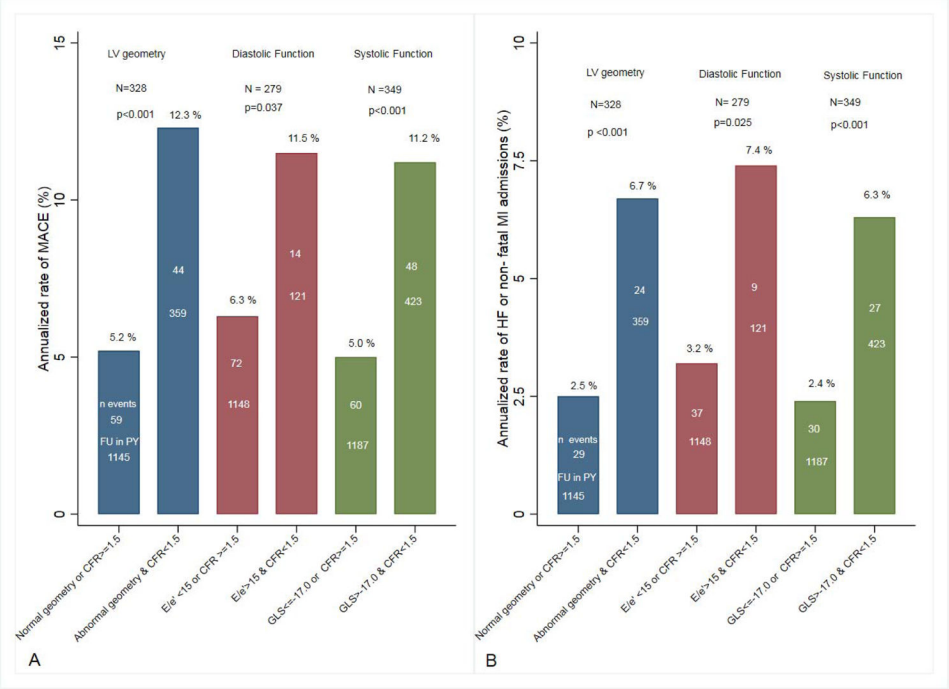


Figure 4.

Annualized Rate of MACE by categories of LV structure/function by Coronary Flow Reserve (Panel A).

Annualized Rate of Heart Failure or non-fatal myocardial hospitalizations by categories of LV structure/Function by Coronary Flow Reserve (Panel B).

Higher rates of adverse events were seen when abnormalities in coronary microvascular dysfunction co-existed with abnormalities in LV geometry, systolic and diastolic function (all $p<0.05$). Plots and p-values were derived from Poisson regression models.

CFR= Coronary flow reserve, LV= left ventricle, GLS= peak global longitudinal strain, E = Early wave of mitral inflow, e'= early diastolic mitral annular velocity, MACE = major adverse cardiovascular event (composite of death, non-fatal myocardial infarction and heart failure).

(N= total population, n events, annualized rate and follow up in person years (FU in PY))

Table 1:

Baseline Characteristics

	Overall (N=352)	**Preserved (eGFR≥60) (N=236)**	**CKD stage 3 or higher (eGFR<60) (N=116)**	**p-value***
Demographics				
Age, years	65.2 (55.4, 75.1)	61.8 (52.8, 69.9)	73.3 (64.1, 81.4)	<0.001
Female	222 (63.1%)	151 (64.0%)	71 (61.2%)	0.61
Black	76 (21.6%)	51 (21.6%)	25 (21.6%)	0.37
Clinical parameters				
Hypertension	273 (77.6%)	169 (71.6%)	104 (89.7%)	<0.001
Hyperlipidemia	225 (62.2%)	140 (59.3%)	85 (73.3%)	0.010
Diabetes	116 (33.0%)	71 (30.1%)	45 (38.8%)	0.10
Peripheral vascular disease	22 (6.3%)	9 (3.8%)	13 (11.2%)	0.007
Stroke	20 (5.7%)	13 (5.5%)	7 (6.0%)	0.84
Chronic obstructive pulmonary disease	41 (11.6%)	27 (11.4%)	14 (12.1%)	0.86
Tobacco use	24 (6.8%)	18 (7.6%)	6 (5.2%)	0.39
Family history of CAD	72 (20.5%)	54 (22.9%)	18 (15.5%)	0.11
Dialysis	7 (2.0%)	0	7 (6.0%)	<0.001
Body mass index, kg/m^2	29.4 (25.4, 35.7)	30.1 (25.8, 35.9)	27.8 (24.7, 35.2)	0.043
Positron emission tomography parameters				
Left ventricular ejection fraction, %	59.0 (50.0, 66.0)	60.0 (52.0, 67.0)	58.0 (46.0, 65.0)	0.044
Rest myocardial blood flow, ml/min/g	1.0 (0.8, 1.3)	1.1 (0.8, 1.3)	1.0 (0.8, 1.3)	0.62
Stress myocardial blood flow, ml/min/g	1.9 (1.4, 2.6)	2.1 (1.6, 2.7)	1.7 (1.2, 2.2)	<0.001
Coronary flow reserve	1.8 (1.4, 2.3)	1.9 (1.5, 2.5)	1.5 (1.3, 2.1)	<0.001
Echocardiography parameters				
Diastolic function				
Septal E/e' ratio	11.7 (8.8, 16.2)	10.8 (8.6, 14.6)	14.1 (9.6, 19.5)	<0.001
Lateral E/e' ratio	8.8 (6.5, 13.0)	8.3 (6.1, 11.4)	9.8 (7.1, 15.8)	<0.001
Systolic function				

Circulation. Author manuscript; available in PMC 2021 January 07.

	Overall (N=352)	Preserved (eGFR≥60) (N=236)	CKD stage 3 or higher (eGFR<60) (N=116)	p-value*
Peak GLS, %	−17.0 (−21.6, −13.4)	−18.6 (−22.2, −14.6)	−15.1 (−19.3, −10.9)	<0.001
Peak GRS, %	31.5 (22.0, 45.7)	34.6 (24.6, 48.1)	25.5 (19.2, 39.7)	<0.001
Peak GCS, %	−24.3 (−29.8, −18.5)	−25.7 (−30.9, −20.1)	−21.3 (−27.7, −15.5)	<0.001
LV structure/geometry				
LVESV, milliliters	30.0 (21.9, 45.0)	30.0 (21.3, 45.0)	30.8 (22.0, 50.5)	0.45
LVEDV, milliliters	81.9 (64.0, 108.3)	81.1 (63.5, 109.0)	82.8 (65.3, 106.8)	0.71
LV mass, grams	172.0 (132.1, 226.4)	169.9 (132.3, 224.6)	179.6 (130.7, 233.1)	0.49
LV mass index, grams/m^2	89.0 (71.4, 111.6)	88.0 (70.1, 110.6)	93.9 (73.1, 119.5)	0.13
RWT ratio	0.44 (0.38-0.53)	0.44 (0.38-0.52)	0.45 (0.39, 0.53)	0.58
LV remodeling				
Normal	98 (29.9%)	70 (31.8%)	28 (25.9%)	0.20
Eccentric hypertrophy	37 (11.3%)	21 (9.5%)	16 (14.8%)	
Concentric remodeling	122 (37.2%)	86 (39.1%)	36 (33.3%)	
Concentric hypertrophy	71 (21.6%)	43 (19.5%)	28 (25.9%)	
Circulating biomarkers				
Natural log NTproBNP	6.3 (4.9, 7.6)	5.3 (4.7, 7.0)	7.1 (6.1, 9.1)	<0.001
NTproBNP, pg/mL	548.0 (133.0, 1950.0)	198.0 (108.0, 1089.0)	1250.5 (468.0, 8603.0)	<0.001
Serum creatinine , mg/dl	1.0 (0.8, 1.2)	0.8 (0.7, 1.0)	1.4 (1.2, 2.3)	<0.001
eGFR, mL/min/1.73 m^2	72.3 (51.1, 90.5)	85.9 (71.9, 98.4)	41.0 (25.4, 51.0)	<0.001
Cardiovascular medications				
Calcium channel Blockers	99 (28.1%)	56 (23.7%)	43 (37.1%)	0.009
Beta Blockers	202 (57.4%)	120 (50.8%)	82 (70.7%)	<0.001
Angiotensin converting enzyme inhibitors	129 (36.6%)	86 (36.4%)	43 (37.1%)	0.91
Aspirin	213 (60.5%)	135 (57.2%)	78 (67.2%)	0.070
Lipid lowering therapy	216 (61.4%)	134 (56.8%)	82 (70.7%)	0.012

Values are median (interquartile range) or n (%).

CKD=Chronic kidney disease, eGFR = estimated glomerular filtration rate using chronic kidney disease epidemiology collaboration (CKD-EPI) formula, bpm= beats per minute, E = Early wave of mitral inflow, e'= early diastolic mitral annular velocity, LV= Left ventricle, ESV= end systolic volume, EDV= end diastolic volume, RWT= relative wall thickness, m/sec= meters/second, GLS= peak global

longitudinal strain, GRS= peak global radial strain, peak global circumferential strain, NTproBNP = N-terminal pro B-type natriuretic peptide, kg/m^2= kilograms per square meter, ml/min/g= milliliters per minute per gram, pg/mL= picogram per milliliter, mL/min= milliliters per minute.

*Comparison between the groups are based on the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Table 2.

Associations between LV mechanics, wall stress, cardiovascular outcomes, renal function and coronary flow reserve

Measure	Association with CFR					Association with eGFR				
	Shape	Correlation Coefficient	Partial Correlation Coefficient	Unadjusted p-value	Adjusted p-value	Shape	Correlation Coefficient	Partial Correlation Coefficient	Unadjusted p-value	Adjusted p-value
Diastolic indices										
Lateral E/e'	L-shaped	−0.29	−0.14	<0.001	0.001	L-shaped	−0.28	−0.05	0.001	0.263
Septal E/e'	L-shaped	−0.29	−0.17	<0.001	0.004	L-shaped	−0.27	−0.02	0.001	0.058
Systolic indices										
GLS	Reverse sigmoid	−0.56	−0.53	<0.001	0.001	Linear	−0.27	−0.10	0.001	0.162
GRS	Sigmoid	0.32	0.26	<0.001	0.001	Linear	0.19	0.10	0.002	0.250
GCS	Reverse sigmoid	−0.39	−0.38	<0.001	0.001	Linear	−0.19	−0.06	0.001	0.584
Markers of LV wall stress										
Natural log NTproBNP	L-shaped	−0.34	−0.21	<0.001	0.012	L-shaped	−0.43	−0.27	0.001	0.003
Adverse cardiovascular event										
Composite clinical endpoint (MACE)	L-shaped	NA	NA	<0.001	0.015	L-shaped	NA	NA	0.001	0.116

Adjusted regression models included CFR, eGFR, age, gender, race, hypertension, hyperlipidemia, diabetes, peripheral vascular disease, stroke, left ventricular mass indexed and left ventricular ejection fraction. For continuous outcomes (Lateral E/e', Septal E/e', GLS, GRS, GCS and Natural log NTproBNP linear regression restricted spline models were used) whereas for MACE Poisson regression restricted cubic spline models were used). Correlation and Partial correlation coefficients after accounting for aforementioned variables are presented as strength of association.

CFR = Coronary flow reserve, eGFR= estimated glomerular filtration rate using chronic kidney disease epidemiology collaboration (CKD-EPI) formula, E = Early wave of mitral inflow, e'= early diastolic mitral annular velocity, GLS= peak global longitudinal strain, GRS= peak global radial strain, GCS = peak global circumferential strain, NTproBNP = N-terminal pro B-type natriuretic peptide, NA= not applicable, MACE = major adverse cardiovascular event (composite of death, non-fatal myocardial infarction and heart failure)

Table 3.

Clinical endpoints * stratified by renal function

	Overall (N=352)	Preserved (eGFR≥60) (N=236)	CKD stage 3 or higher (eGFR<60) (N=116)	p-value **
	n events/ annualized event rate **			
Total composite clinical endpoint (MACE)	108/ 6.6%	56/ 4.6%	52/ 12.5%	<0.001
Death	74/ 4.1%	40/ 3.0%	34/ 7.0%	<0.001
Hospitalization for nonfatal myocardial infarction	18/ 1.0%	12/ 0.9%	6/ 1.1%	0.559
Hospitalization for heart failure	41/ 2.7%	19/1.7%	22/6.2%	<0.001

* Median (Q1-Q3) follow-up time was 4.4 (1.2, 7.7) years. Time to first event was analyzed.

** Annualized event rates and p-values were calculated using Poisson regression.

CKD=Chronic kidney disease, MACE = major adverse cardiovascular event (composite of death, non-fatal myocardial infarction and heart failure).

Table 4.

Results for Mediation model for hypothesized pathway via microvascular dysfunction to LV dysfunction and adverse cardiovascular event in chronic kidney disease

Diastolic indices	**Standardized Regression coefficients for CFR in mediation model, p-value**	**% effect mediated via CFR**
Lateral E/e’	−0.13, 0.027	19%
Septal E/e’	−0.15, 0.005	24%
Systolic indices		
GLS	−0.48, <0.001	42%
Radial	0.27, <0.001	19%
GCS	−0.35, <0.001	34%
Markers of LV wall stress		
Natural log NTproBNP	−0.20, 0.003	7%
Adverse cardiovascular event		
Composite clinical endpoint (MACE)	−0.30, 0.026	32%

Adjusted regression models included CFR=Coronary Flow Reserve, eGFR= estimated glomerular filtration rate using chronic kidney disease epidemiology collaboration (CKD-EPI) formula , Age, Gender, Race, Hypertension, Hyperlipidemia, Diabetes, Peripheral vascular disease, Stroke, Left ventricular mass indexed and resting left ventricular ejection fraction

LV= Left ventricle, E = Early wave of mitral inflow, e’= early diastolic mitral annular velocity, GLS= peak global longitudinal strain, GRS= peak global radial strain, GCS= peak global circumferential strain, NTproBNP = N-terminal pro B-type natriuretic peptide, MACE = major adverse cardiovascular event (composite of death, non-fatal myocardial infarction and heart failure).