Abnormalities in Cardiac Structure and Function among Individuals with CKD: The COMBINE Trial


Key Points
- Individuals with CKD had lower mitral valve E/A ratio on cardiac magnetic resonance imaging compared with healthy volunteers, suggestive of early diastolic dysfunction.
- Higher urine albumin-creatinine ratio was significantly associated with lower mitral valve E/A ratio in individuals with CKD with and without baseline cardiovascular disease (CVD).
- Early changes in diastolic dysfunction in patients with CKD may identify individuals at greatest risk for progression to clinical CVD.

Abstract
Background Individuals with CKD have a high burden of cardiovascular disease (CVD). Abnormalities in cardiac structure and function represent subclinical CVD and can be assessed by cardiac magnetic resonance imaging (cMRI).

Methods We investigated differences in cMRI parameters in 140 individuals with CKD stages 3b–4 who participated in the CKD Optimal Management with Binders and NicotinamidE (COMBINE) trial and in 24 age- and sex-matched healthy volunteers. Among COMBINE participants, we examined the associations of eGFR, urine albumin-creatinine ratio (UACR), phosphate, fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH) with baseline (N = 140) and 12-month change (N = 112) in cMRI parameters.

Results Mean (SD) ages of the COMBINE participants and healthy volunteers were 64.9 (11.9) and 60.4 (7.3) years, respectively. The mean (SD) baseline eGFR values in COMBINE participants were 32.1 (8.0) and 85.9 (16.0) ml/min per 1.73 m² in healthy volunteers. The median (interquartile range [IQR]) UACR in COMBINE participants was 154 (20.3–540.0) mg/g. Individuals with CKD had lower mitral valve E/A ratio compared with healthy volunteers (for CKD versus non-CKD, β estimate, −0.13; 95% CI, −0.24 to −0.012). Among COMBINE participants, multivariable linear regression analyses showed that higher UACR was significantly associated with lower mitral valve E/A ratio (β estimate per 1 unit increase in natural-log UACR, −0.06; 95% CI, −0.09 to −0.03). This finding was preserved among individuals without baseline CVD. UACR was not associated with 12-month change in any cMRI parameter. eGFR, phosphate, FGF23, and PTH were not associated with any cMRI parameter in cross-sectional or change analyses.

Conclusions Individuals with CKD stages 3b–4 have evidence of cMRI abnormalities. Albuminuria was independently associated with diastolic dysfunction, as assessed by mitral valve E/A ratio, in individuals with CKD with and without clinical CVD. Albuminuria was not associated with change in any cMRI parameter.

Introduction
Individuals with CKD are at a disproportionately high risk for development of cardiovascular disease (CVD) (1–4). Reduced glomerular filtration and higher levels of albuminuria are each independently associated with risk of CVD development and CVD-related mortality (4–7). Pathophysiologic consequences of CKD, including volume overload, renin-aldosterone-angiotensin system activation, disturbances to the vitamin D–phosphate–parathyroid hormone (PTH)–fibroblast growth factor 23 (FGF23)–Klotho axis, and chronic systemic inflammation may mediate the relationship between low kidney function and CVD development in individuals with CKD (3,8–10). Cardiac magnetic resonance imaging (cMRI) can assess cardiac structure and function with excellent reproducibility and is being used clinically with increased frequency for diagnostic and prognostic purposes and in research as a surrogate outcome (11). Identifying determinants of abnormalities in cardiac structure and function using...
cMRI in patients with CKD may allow for better phenotyping and may guide preventive and therapeutic strategies.

The CKD Optimal Management with Binders and Nicotinamide (COMBINE) trial was a four-arm, parallel-group, randomized, double-blind, placebo-controlled clinical trial that tested the safety and efficacy of nicotinamide and lanthanum carbonate as phosphate-lowering therapies in patients with moderate-to-severe CKD (12,13). Participants in the COMBINE trial had serial laboratory measurements of kidney function and cMRI completed at baseline and at the 12-month follow-up visit (12,13). The results of the COMBINE trial demonstrated no significant effects of interventions on phosphate and FGF23 levels (12,13). In this post hoc study of COMBINE trial participants and healthy volunteers, we aimed to characterize structural and functional cardiac abnormalities in patients with CKD by first examining differences in cMRI parameters between COMBINE participants and healthy volunteers. Next, we studied the associations of baseline eGFR and urine albumin-creatinine ratio (UACR) in COMBINE participants with baseline and 12-month change in cMRI parameters. Our primary hypothesis was that, compared with healthy volunteers, COMBINE participants would demonstrate evidence of structural and functional cardiac abnormalities on cMRI, and that, in COMBINE participants, eGFR and UACR would be significantly associated with baseline and change in cMRI parameters over 12 months.

Materials and Methods

The COMBINE Trial

The rationale, design, and primary results of the COMBINE trial (clinicaltrials.gov, NCT02258074) were previously published (12,13). Participants were recruited across seven clinical sites in the United States. Key inclusion criteria were an eGFR of 20–45 ml/min per 1.73 m², serum phosphate concentration of ≥2.8 mg/dl, and the ability to provide informed consent. Key exclusion criteria were known allergy to any study treatment; presence of secondary hyperparathyroidism, defined as a PTH value more than five times the upper limit of normal range or cinacalcet use; severe anemia or liver disease; recent blood or platelet transfusion; and hypoalbuminemia. Investigators collected demographic and clinical information, and obtained laboratory studies at the baseline visit and every 3 months across the 12-month follow-up period (12–14). All studies and procedures were conducted after receiving informed consent from participants and were approved by institutional review boards at each site.

Study Population

Of the 273 total participants recruited into the COMBINE trial, 140 participants had cMRIs of sufficient quality to be included in this secondary analysis. Reasons for not completing cMRI included not consenting, logistical issues related to the patient or MRI facility, claustrophobia, incompatible body habitus, and medical contraindications to MRI completion, such as pacemaker or metallic implantation (Figure 1).

At Northwestern University, we contemporaneously recruited 24 healthy volunteers without hypertension, diabetes, or CKD. The healthy volunteers were recruited from existing healthy volunteer registries at the Radiology Research Core and were age- and sex-matched (±5 years in age) to the COMBINE study population. The healthy volunteers underwent a single study visit with collection of demographics, limited laboratory data, and cMRI according to a protocol that was identical to the one used in the COMBINE trial.

In the change analyses that investigated the associations of eGFR and UACR with 12-month change in cMRI parameters, 171 participants consented for kidney cMRI study and 148 participants performed kidney cMRI study. The reasons for not consenting are as follows: did not consent for cMRI study (n=102), excluded from kidney cMRI study (n=23), logistics related to participant, COMBINE clinical center or local MRI facility (n=18), claustrophobia (n=10), large body habitus (n=3), unsatisfactory quality (n=8), and excluded for history of cardiovascular disease (n=43).

Figure 1. | Flow diagram for inclusion/exclusion of participants in cardiac MRI (cMRI) substudy of the COMBINE trial.
findings in participants with CKD, we included 112 COMBINE participants who completed both baseline and 12-month follow-up cMRI (Figure 1).

Imaging Data Collection

Trained personnel in the Cardiac Core Imaging Laboratory at the Northwestern University, who were blinded to study participant data, developed and implemented the COMBINE imaging protocol, which was applied to COMBINE participants and healthy volunteers. All images were read centrally by Core personnel. cMRI was performed at each performing site on a 3T MR system (Siemens, Erlangen, Germany), including long-axis and short-axis (SAX) cine images and mitral valve phase contrast (PC) imaging. Cine images were acquired using a retrospectively electrocardiogram-gated 2D steady-state free precession technique with parallel imaging and acceleration factor of two. The following parameters were used for SAX slices: 5-mm thickness and no gap for left atrium (LA), 8-mm slice and no gap for left ventricle (LV), and spatial resolution of 1.3x1.3x10.0 mm. Mitral valve PC images were acquired using a Flash sequence with through-plane velocity encoding direction and velocity encoding (VENC) set at 80 cm/s. The sequence was repeated and VENC increased if flow artifacts were present with the initial VENC setting. No contrast was administered as part of the imaging protocol.

Image quality was reviewed for cine and PC-acquired images and scored according to a uniform protocol. Only images with diagnostic quality and no significant artifact affecting the area of interest were accepted for analysis. Cine images were rejected if the quality level was not adequate for LV parameter measurement or if the LA or LV chamber coverage was incomplete. Mitral PC images were rejected if the scan plane was positioned incorrectly, significant flow artifacts were present in the area of interest, or the acquisition was incomplete. SAX images were used for parameter measurement and calculation, and long-axis cine images were used as reference. LV and LA were analyzed and parameters were calculated on the basis of SAX cine steady-state free precession images using dedicated software (Leonardo; Siemens Medical Solutions). Semi-automatic segmentation of end systolic and end diastolic phases were performed for the LV and LA with manual adjustment, and parameters were automatically calculated by the software. Endocardial and epicardial borders were segmented for LV volumes, function, and mass calculation; the endocardial border was segmented for calculation of LA parameters.

Exposures

In analyses that compared cMRI findings in healthy volunteers and individuals with CKD, the exposure was the presence of CKD. In analyses that investigated the association of kidney laboratory indices with cMRI in COMBINE participants, the exposure variables included eGFR and UACR. eGFR was calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation (15). Urine albumin and creatinine was measured at a central laboratory using a standard assay. Because UACR was not normally distributed, it was natural-log (ln) transformed. Our additional exposure variables included baseline FGF23, PTH, and phosphate levels.

Outcomes

We analyzed the following measures of cardiac structure and function: LV end systolic volume index (LVESV), LV end diastolic volume index (LVEDV), LA end systolic volume index (LAESV), LA end diastolic volume index (LADEV), LV mass index (LVM), and mitral valve E/A ratio. The ratio of peak velocity blood flow in early diastole (E wave) to peak velocity flow in late diastole (A wave) was used as a measure of diastolic dysfunction. Parameters were indexed to height2.7 (16).

Covariates

We used demographic and laboratory data collected at baseline. Covariates included demographic and laboratory measurements related to severity of CKD and presence of CVD. High-sensitivity troponin (hs-troponin) and B-type (brain) natriuretic peptide (BNP) are associated with worsening of CKD and CVD (17,18) and were measured using automated assays on the Beckman Coulter DXL 800 at a central laboratory at the University of Washington. The hs-troponin I levels at 10% coefficient of variation and 20% coefficient of variation imprecision are 0.0033 and 0.0016 μg/L, respectively, on the basis of prior reports (19). On the basis of prior work, the within-run imprecision for BNP is 3.4% and 1.6%, respectively, and total imprecision is 8.4% and 5.9% (20). FGF23 and serum phosphate rise with worsening kidney function and are significantly associated with risk of CVD (21,22). Baseline phosphate and plasma FGF23 concentrations were measured in venous blood samples taken twice 1 week apart and averaged to define each participant’s baseline value. Serum phosphate was measured at Spectra Clinical Research (Rockleigh, NJ) by colorimetry. EDTA-plasma samples for FGF23 measurements were frozen to −80°C and shipped on dry ice to the central laboratory at the University of Washington. Plasma FGF23 was measured using an intact ELISA assay (Kainos, Tokyo, Japan) with interassay coefficients of variation ranging from 4.7% and 10.5% (12,13). Intact PTH was measured at Spectra Clinical Research using an immunochromiluminescence assay. FGF23 and PTH were ln transformed for all analyses.

Statistical Analyses

Participants with CKD Compared with Healthy Volunteers

We first examined baseline clinical characteristics of the participants with CKD and the healthy volunteers using means (SD) and medians (interquartile range). Next, in cross-sectional analyses, we used multivariable linear regression to investigate the association of CKD status with baseline cMRI parameters (LVESV, LVEDV, LAESV, LADEV, LVM, and mitral valve E/A ratio) after adjusting for confounders that included age, sex, race, body mass index (BMI), and systolic BP (SBP).

Cross-Sectional Associations of CKD Parameters and cMRI

We first tested Spearman correlations of baseline kidney laboratory indices, eGFR and UACR, with cMRI outcomes (LVESV, LVEDV, LAESV, LADEV, LVM, and mitral valve E/A ratio) in COMBINE trial participants. Next, we
performed multivariable linear regression to investigate the associations of eGFR and UACR with baseline cMRI parameters. We adjusted for possible confounders, including demographic covariates (age, sex, race, ethnicity), cardiovascular risk factors (smoking, BMI, SBP, history of CVD, diabetes, hemoglobin, BNP, hs-troponin), and markers of CKD (phosphate, PTH, FGF23, and eGFR [when UACR was the exposure] or UACR [when eGFR was the exposure]).

**Sensitivity Analyses**

To investigate if eGFR and UACR are associated with cardiac structural and functional changes over time, we tested Spearman correlations between baseline eGFR and UACR and 12-month change in cMRI parameters in COMBINE trial participants. We performed multivariable linear regression for our change analyses that adjusted for possible confounders (demographics, cardiovascular risk factors, and markers of kidney function), similar to the cross-sectional analyses. We also adjusted for randomization arm (dual placebo, lanthanum carbonate and nicotinamide placebo, nicotinamide and lanthanum carbonate placebo, or lanthanum carbonate and nicotinamide) and an interaction term for exposure × randomization.

**Associations of CKD Parameters and 12-Month Change in cMRI**

To investigate if eGFR and UACR are associated with cardiac structural and functional changes over time, we tested Spearman correlations between baseline eGFR and UACR and 12-month change in cMRI parameters in COMBINE trial participants. We performed multivariable linear regression for our change analyses that adjusted for possible confounders (demographics, cardiovascular risk factors, and markers of kidney function), similar to the cross-sectional analyses. We also adjusted for randomization arm (dual placebo, lanthanum carbonate and nicotinamide placebo, nicotinamide and lanthanum carbonate placebo, or lanthanum carbonate and nicotinamide) and an interaction term for exposure × randomization.

**Sensitivity Analyses**

To investigate the associations of kidney indices with subclinical CVD, we excluded 43 individuals with baseline CVD, defined as history of heart failure, ischemia, revascularization, myocardial infarction, or angina. We performed similar correlation and linear regression analyses as in the primary analyses.

**Additional Analyses**

We investigated the associations of baseline FGF23, PTH, and phosphate with baseline and 12-month change in cMRI parameters. Similar to our primary analyses, we tested Spearman correlations between baseline FGF23, PTH, and phosphate and baseline and 12-month change in cMRI parameters. We next performed multivariable linear regression with baseline and 12-month change in cMRI parameters as the outcomes and adjusted for the same confounders in the primary analyses.

Two-sided P values of <0.05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS, Cary, NC).

**Results**

**Cross-Sectional Analyses of Participants with CKD and Healthy Volunteers**

Baseline characteristics of the study population are displayed in Table 1. Individuals with CKD were older, more likely to be Black or Hispanic, and had higher BMI and SBP than healthy volunteers. Individuals with CKD demonstrated higher LVM, and lower mitral valve E/A ratio compared with healthy volunteers. Both groups had

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants with CKD (N=140)</th>
<th>Healthy Volunteers (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean±SD</td>
<td>64.9±11.9</td>
<td>60.4±7.3</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>52 (37)</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>41 (29)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>14 (10)</td>
<td>—</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>6 (4)</td>
<td>—</td>
</tr>
<tr>
<td>BMI, kg/m², mean±SD</td>
<td>31.6±6.8</td>
<td>26.5±4.0</td>
</tr>
<tr>
<td>SBP, mm Hg, mean±SD</td>
<td>128.3±16.8</td>
<td>118.5±11.5</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>68 (49)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>16 (11)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>8 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ischemia, n (%)</td>
<td>8 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Revascularization, n (%)</td>
<td>23 (16)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m², mean±SD</td>
<td>32.1±8.0</td>
<td>85.9±16.0</td>
</tr>
<tr>
<td>UACR, mg/g, median (IQR)</td>
<td>154.0 (20.3 – 540.0)</td>
<td>—</td>
</tr>
<tr>
<td>Hemoglobin, g/dl, mean±SD</td>
<td>12.9±1.7</td>
<td>—</td>
</tr>
<tr>
<td>Serum phosphate, mg/dl, mean±SD</td>
<td>3.7±0.5</td>
<td>—</td>
</tr>
<tr>
<td>PTH, pg/ml, median (IQR)</td>
<td>86.5 (56.0 – 129.0)</td>
<td>—</td>
</tr>
<tr>
<td>Plasma FGF23, pg/ml, median (IQR)</td>
<td>105.8 (79.1 – 144.3)</td>
<td>—</td>
</tr>
<tr>
<td>BNP, pg/ml, median (IQR)</td>
<td>53.0 (26.5 – 117.6)</td>
<td>—</td>
</tr>
<tr>
<td>hs-troponin, ng/L, median (IQR)</td>
<td>6.5 (4.3 – 9.1)</td>
<td>—</td>
</tr>
<tr>
<td>Left ventricular end systolic volume index, ml/m²⁷, mean±SD</td>
<td>12.8±6.2 (n=140)</td>
<td>13.0±3.5 (n=24)</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume index, ml/m²⁷, mean±SD</td>
<td>33.1±9.9 (n=140)</td>
<td>33.7±6.9 (n=24)</td>
</tr>
<tr>
<td>Left atrial end systolic volume index, ml/m²⁷, mean±SD</td>
<td>12.8±7.1 (n=134)</td>
<td>10.6±3.2 (n=24)</td>
</tr>
<tr>
<td>Left atrial end diastolic volume index, ml/m²⁷, mean±SD</td>
<td>21.0±8.2 (n=134)</td>
<td>20.8±6.4 (n=24)</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²⁷, mean±SD</td>
<td>29.5±8.4 (n=140)</td>
<td>23.4±4.0 (n=24)</td>
</tr>
<tr>
<td>Mitral valve E/A ratio, mean±SD</td>
<td>0.8±0.3 (n=116)</td>
<td>1.0±0.2 (n=24)</td>
</tr>
<tr>
<td>Ejection fraction, %, mean±SD</td>
<td>62.3±9.7 (n=140)</td>
<td>61.7±4.0 (n=24)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic BP; UACR, urine albumin-creatinine ratio; PTH, parathyroid hormone; IQR, interquartile range; FGF23, fibroblast growth factor 23; BNP, B-type natriuretic peptide; hs-troponin, high-sensitivity troponin; —, no data.
similar ejection fraction. In cross-sectional analyses using multivariable linear regression models, CKD status at baseline was independently associated with baseline mitral valve E/A ratio after adjusting for age, sex, race, BMI, and SBP (Table 2).

**Cross-Sectional Associations of CKD Parameters and cMRI**

Associations of eGFR and UACR with baseline cMRI parameters are shown in Table 3. Baseline UACR positively correlated with baseline LVESV and LVM. We observed no significant correlations between baseline eGFR and baseline cMRI parameters (Table 3).

In multivariable linear regression models that adjusted for demographics, cardiovascular risk factors, mineral metabolism parameters, and eGFR, increased UACR was significantly associated with lower baseline mitral valve E/A ratio (Table 3). eGFR was not significantly associated with any baseline cMRI parameter in linear regression models. No nonlinear relationships were appreciated between ln UACR and eGFR and baseline cMRI parameters upon visualization of scatterplots.

**Associations of CKD Parameters and 12-Month Change in cMRI**

cMRI parameters did not significantly change over the 12-month follow-up period (Supplemental Table 1). Additionally, randomization arm was not associated with 12-month change in any cMRI parameter (data not shown). Baseline UACR positively and baseline eGFR negatively correlated with 12-month change in LVM, but neither was associated with 12-month change in any cMRI parameter in multivariable linear regression models (Table 4). No nonlinear relationships were appreciated between ln UACR and eGFR and 12-month change in cMRI parameters upon visualization of scatterplots.

**Sensitivity Analyses: Exclusion of Individuals with Baseline CVD**

In sensitivity analyses that excluded 43 individuals with a known history of CVD at baseline, CKD status at baseline was associated with higher LVM and lower mitral valve E/A ratio at baseline in cross-sectional analyses. However, these associations were attenuated in multivariable models (Supplemental Table 2). Baseline UACR remained significantly associated with baseline mitral valve E/A ratio in individuals without CVD in multivariable linear regression models in cross-sectional analyses (Supplemental Table 3). UACR was not significantly associated with 12-month change in any cMRI parameter in multivariable linear regression models of change analyses (Supplemental Table 4). eGFR was not associated with any baseline or 12-month change in cMRI parameter (Supplemental Tables 3 and 4).

**Additional Analyses: Associations of Mineral Metabolism Parameters and cMRI**

In additional analyses, we investigated the associations of baseline FGF23, PTH, and phosphate with baseline cMRI and 12-month change in cMRI parameters. In correlation analyses, FGF23 was significantly correlated with LVESV (Spearman correlation coefficient, 0.18; \( P = 0.03 \)), LVEDV (Spearman correlation coefficient, 0.24; \( P = 0.005 \)), and LVM (Spearman correlation coefficient, 0.26; \( P = 0.002 \); Supplemental Table 5). PTH was significantly correlated with LVM (Spearman correlation coefficient, 0.21; \( P = 0.01 \); Supplemental Table 5). However, neither FGF23, PTH, nor phosphate was associated with any cMRI parameter at baseline in multivariable linear regression models. Neither FGF23, PTH, nor phosphate was associated with 12-month change in cMRI parameter in correlation or linear regression analyses (Supplemental Table 5).
### Table 3. Associations between baseline eGFR and UACR and baseline cMRI parameters in participants with CKD

<table>
<thead>
<tr>
<th>Participants with CKD (N=140)</th>
<th>Left Ventricular End Systolic Volume Index (N=140)</th>
<th>Left Ventricular End Diastolic Volume Index (N=140)</th>
<th>Left Atrial End Systolic Volume Index (N=134)</th>
<th>Left Atrial End Diastolic Volume Index (N=134)</th>
<th>Left Ventricular Mass Index (N=140)</th>
<th>Mitral Valve E/A Ratio (N=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spearman correlation coefficients (P values)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline eGFR, ml/min per 1.73 m²</td>
<td>-0.06 (0.47)</td>
<td>-0.08 (0.37)</td>
<td>-0.07 (0.42)</td>
<td>-0.01 (0.88)</td>
<td>-0.07 (0.41)</td>
<td>0.13 (0.18)</td>
</tr>
<tr>
<td>Baseline UACR, mg/g</td>
<td>0.19 (0.03)</td>
<td>0.15 (0.07)</td>
<td>0.07 (0.41)</td>
<td>-0.002 (0.99)</td>
<td>0.39 (&lt;0.001)</td>
<td>-0.14 (0.14)</td>
</tr>
<tr>
<td><strong>Linear regression analyses with β estimates (95% CI)³</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline eGFR, ml/min/1.73m²</td>
<td>0.005 (0.21 to 0.22)</td>
<td>0.02 (0.14 to 0.19)</td>
<td>0.09 (0.09 to 0.26)</td>
<td>0.07 (0.09 to 0.23)</td>
<td>0.004 (0.003)</td>
<td>-0.06 (0.09)</td>
</tr>
<tr>
<td>Baseline ln UACR</td>
<td>0.013 (0.66 to 0.68)</td>
<td>-0.45 (1.45 to 0.55)</td>
<td>0.04 (0.71 to 0.79)</td>
<td>-0.50 (1.31 to 0.31)</td>
<td>0.54 (0.21 to 1.29)</td>
<td>to 0.03³</td>
</tr>
</tbody>
</table>

Models adjusted age, sex, race, ethnicity, smoking, body mass index, systolic BP, history of cardiovascular disease (heart failure, ischemia, stroke, revascularization, angina, myocardial infarction), diabetes, hemoglobin, B-type natriuretic peptide; high-sensitivity troponin, phosphate, parathyroid hormone, fibroblast growth factor 23, and eGFR (when UACR is the exposure) or UACR (when eGFR is the exposure). UACR, urine albumin-creatinine ratio; cMRI, cardiac magnetic resonance imaging; ln, natural log.

³P<0.05.
³β estimate per 1 unit increase in parameter.

### Table 4. Associations between eGFR and UACR and 12-month change in cMRI parameters in participants with CKD

<table>
<thead>
<tr>
<th>Participants with CKD (N=112)</th>
<th>Left Ventricular End Systolic Volume Index (N=112)</th>
<th>Left Ventricular End Diastolic Volume Index (N=112)</th>
<th>Left Atrial End Systolic Volume Index (N=105)</th>
<th>Left Atrial End Diastolic Volume Index (N=105)</th>
<th>Left Ventricular Mass Index (N=112)</th>
<th>Mitral Valve E/A Ratio (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spearman correlation coefficients (P values)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Baseline eGFR, ml/min per 1.73 m²</td>
<td>0.09 (0.35)</td>
<td>0.03 (0.79)</td>
<td>0.12 (0.23)</td>
<td>0.11 (0.24)</td>
<td>-0.19 (0.04)</td>
<td>-0.06 (0.61)</td>
</tr>
<tr>
<td>Baseline UACR, mg/g</td>
<td>-0.06 (0.55)</td>
<td>0.10 (0.28)</td>
<td>-0.004 (0.96)</td>
<td>0.10 (0.33)</td>
<td>0.23 (0.02)⁴</td>
<td>0.19 (0.11)</td>
</tr>
<tr>
<td><strong>Linear regression analyses with β estimates (95% CI)³</strong></td>
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</tr>
<tr>
<td>Baseline eGFR, ml/min/1.73m²</td>
<td>0.095 (0.14 to 0.33)</td>
<td>0.10 (0.27 to 0.48)</td>
<td>0.13 (0.09 to 0.36)</td>
<td>0.05 (0.21 to 0.31)</td>
<td>-0.13 (0.35)</td>
<td>0.002 (0.02 to 0.03)</td>
</tr>
<tr>
<td>Baseline ln UACR</td>
<td>0.46 (0.52 to 1.45)</td>
<td>0.70 (0.86 to 2.26)</td>
<td>0.18 (0.79 to 1.14)</td>
<td>0.43 (0.68 to 1.54)</td>
<td>0.08 (0.83 to 1.00)</td>
<td>to 0.07</td>
</tr>
</tbody>
</table>

Models adjusted for baseline age, sex, race, ethnicity, smoking, body mass index, systolic BP, history of cardiovascular disease (heart failure, ischemia, stroke, revascularization, angina, myocardial infarction), diabetes, hemoglobin, B-type natriuretic peptide, high-sensitivity troponin, phosphate, parathyroid hormone, fibroblast growth factor 23, eGFR (when UACR is the exposure) or UACR (when eGFR is the exposure), randomization arm, and interaction term of exposure x randomization arm. UACR, urine albumin-creatinine ratio; cMRI, cardiac magnetic resonance imaging; ln, natural log.

³P<0.05.
³β estimate per 1 unit increase in parameter.
Discussion

We investigated differences in cMRI parameters between health and CKD and studied the associations of baseline kidney laboratory markers with baseline and 12-month change in cMRI parameters. Compared with healthy volunteers, patients with CKD had lower mitral valve E/A ratio, a finding suggestive of diastolic dysfunction (23). Among individuals with CKD, higher levels of UACR were independently associated with a lower mitral valve E/A ratio at baseline, but not with change in any cMRI parameter over 12 months.

These findings are consistent with prior studies that observed cardiac structural and functional abnormalities in patients with CKD (24,25). Individuals with CKD develop hemodynamic, neurohormonal, inflammatory, and metabolic disturbances that can negatively affect the heart (4–7). Elevations in preload and afterload in patients with CKD can worsen myocardial strain and oxidative stress (26). Dysregulation of the renin-angiotensin-aldosterone system and upregulation of the sympathetic nervous system in CKD promote interstitial fibrosis and pathologic myocardial remodeling (26,27). Similarly, abnormalities in mineral metabolism also contribute to left ventricular hypertrophy and can accelerate vascular calcification (28–32). Although most evident in ESKD, these mechanisms are also present in earlier stages of CKD and can lead to structural and functional cardiac changes, as observed in our CKD stage 3–4 cohort (33).

Abnormalities in diastolic function can be evident before clinical heart failure. A lower mitral valve E/A ratio represents early diastolic dysfunction, early impairment in LV filling, and a stiffened LV (34). As diastolic dysfunction worsens, there is paradoxical normalization of the E/A ratio and, subsequently, an increase in the E/A ratio that can be greater than two with severe diastolic dysfunction (34). Although LVM and ejection fraction were similar in both groups, we demonstrated that our CKD population had a mean E/A ratio less than one and that CKD status significantly associated with lower E/A ratio, suggesting the presence of early diastolic dysfunction in the CKD population.

UACR was also independently associated with changes consistent with early diastolic dysfunction at baseline, and this relationship persisted even in individuals without CVD at baseline. Prior cross-sectional studies in patients with CKD and in the general population also described significant associations of albuminuria with cardiac structural and functional abnormalities, including LVM, elevated LV pressures, and diastolic dysfunction (35–39). In prospective studies, albuminuria, even at levels below the threshold of microalbuminuria, is known to be independently associated with incident heart failure and CVD events (7,40–42). Albuminuria is a known marker of endothelial dysfunction and microvascular inflammation, both key mediators in the development and progression of coronary heart disease and heart failure (10). Microvascular inflammation and dysfunction are hypothesized to be a main determinant of LV diastolic dysfunction, eventually leading to heart failure with preserved ejection fraction (43,44). Lack of significant changes in cMRI parameters over 12 months may have prevented us from detecting longitudinal relationships between UACR and change in cMRI parameters. The absence of consistent correlations between baseline eGFR and cMRI parameters in our study was not surprising given that COMBINE participants had a narrow eGFR range.

Although we found some significant associations between baseline parameters of mineral metabolism and baseline cMRI parameters in correlation analyses, these associations were not consistent and did not persist in multivariable analyses for the baseline or 12-month change in cMRI outcomes. Prior observational studies have demonstrated strong associations between FGF23, PTH, and phosphate with increased left ventricular mass and heart failure events (28,45–49). Our results differ with these prior studies. In contrast to prior studies that demonstrated significant associations between markers of mineral metabolism and CVD, this study recruited a smaller sample size. A narrower eGFR range may also have contributed to the contradictory results.

Although we were able to comprehensively study the associations of kidney indices and baseline and 12-month change in cMRI in a well-phenotyped cohort of patients, we acknowledge several limitations. Given that we performed a post hoc study of a randomized controlled trial and did not adjust for multiple comparisons, our results should be regarded as exploratory. Although cMRI provides less interobserver variability and more accurate cardiac measurements when compared with echocardiography (50), the COMBINE protocol did not allow for measurement of cardiac fibrosis on cMRI. A smaller sample size for our analyses among individuals without CVD may have limited our ability to detect significant relationships in adjusted models. Additionally, all healthy controls were recruited from a single site, whereas individuals with CKD were recruited from multiple sites. Although our healthy volunteers were age and sex matched, there may have been other differences in baseline characteristics that we did not account for that may have led to the observed differences in cMRI parameters by CKD status. Finally, albuminuria was not measured in our healthy controls, and it was only measured at baseline in the CKD group. Therefore, possible intraindividual variation in albuminuria was not considered in our analyses (51).

Given that CVD is the leading cause of death in patients with CKD, identifying subclinical changes in cardiac function remains critically important. Recognizing subtle and early changes in diastolic dysfunction, such as lower mitral valve E/A ratio, in patients with CKD may identify individuals at greatest risk for progression to clinical CVD and help risk stratify patients for whom early referral, intervention with novel drug therapies, or monitoring may be warranted. Additionally, measurement of albuminuria would allow enrichment of CVD trial populations to include individuals with increased risk for development of clinical CVD.

Disclosures

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Author Contributions
X. Cai, J. Carr, T. Isakova, R. Mehta, P.V. Prasad, and R. Sarnari were responsible for methodology; X. Cai, T. Isakova, and R. Mehta were responsible for formal analysis; J.J. Gassman was responsible for data curation; J.J. Gassman, T. Isakova, R. Mehta, and M. Wolf conceptualized the study; T. Isakova and R. Mehta provided supervision; T. Isakova, R. Mehta, and A.A. Wang wrote the original draft; T. Isakova and M. Wolf were responsible for funding acquisition and investigation; R. Mehta was responsible for validation; and all authors reviewed and edited the manuscript.

Data Sharing Statement
Original data created for the study are or will be available in a persistent repository upon publication at the NIDDK Central Repository: https://repository.niddk.nih.gov/studies/combine/.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl?doi:10.34067/KID.00052021/-/DCSupplemental.

Supplemental Table 1. Change in cMRI from baseline to 12-month study visit in COMBINE participants.
Supplemental Table 2. Associations of CKD status with baseline cMRI parameters in individuals without baseline cardiovascular disease.
Supplemental Table 3. Associations between eGFR and UACR and baseline cMRI parameters in individuals without baseline cardiovascular disease in CKD participants.
Supplemental Table 4. Associations between eGFR and UACR and 12-month change in cMRI in individuals without baseline cardiovascular disease in CKD participants.
Supplemental Table 5. Associations between baseline parameters of mineral metabolism and baseline and 12-month change in cMRI in in CKD participants.

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