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

Ann A. Wang,1 Xuan Cai,2 Anand Srivastava,2,3 Pottumarthi V. Prasad,4 Stuart M. Sprague,5,6 James Carr,7 Myles Wolf,8,9 Joachim H. Ix,10 Geoffrey A. Block,11 Michel Chonchol,12 Kalani L. Raphael,13 Alfred K. Cheung,14 Dominic S. Raj,15 Jennifer J. Gassman,16 Amir Ali Rahsepar,17 John P. Middleton,9 Linda F. Fried,18 Roberto Sarnari,7 Tamara Isakova,2,19 and Rupal Mehta2,3,19

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 and 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 Blnders 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 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. In additional analyses of COMBINE participants, we tested the associations of baseline phosphate, FGF23, and PTH 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

---

**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 COM-
BINE participants who completed both baseline and
12-month follow-up cMRI (Figure 1).

Imaging Data Collection
Trained personnel in the Cardiac Core Imaging Labo-
ratory at the Northwestern University, who were blinded to
study participant data, developed and implemented the
COMBINE imaging protocol, which was applied to COM-
BINE 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 retrospec-
tively electrocardiogram-gated 2D steady-state free pres-
cession 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 1.3 x 1.3 x 10.0 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 ade-
quate 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, signi-
ficant 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 ana-
yzed and parameters were calculated on the basis of SAX
cine steady-state free precession images using dedicated
software (Leonardo; Siemens Medical Solutions). Semiauto-
matic segmentation of end systolic and end diastolic phases
were performed for the LV and LA with manual adjust-
ment, and parameters were automatically calculated by the
software. Endocardial and epicardial borders were seg-
mented 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 vol-
unteers and individuals with CKD, the exposure was the
presence of CKD. In analyses that investigated the associ-
ations 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 equa-
tion (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
diastolic volume index (LVEDV), LA end systolic vol-
ume index (LAESV), LA end diastolic volume index (LAEDV), 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 height$^2$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 wors-
ening 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 sam-
pled twice 1 week apart and averaged to define each
participant’s baseline value. Serum phosphate was mea-
sured at Spectra Clinical Research (Rockleigh, NJ) by colori-
metry. 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 Spect-
tra Clinical Research using an immunochemiluminescence
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,
LAEDV, 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, LAEDV, 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]).

**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 founders 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 1. Baseline characteristics in COMBINE trial participants with CKD and healthy volunteers

| Characteristic | Participants with CKD (N=140) | Healthy Volunteers (N=24) |
|---------------|-----------------------------|--------------------------|
| Age, yr, mean±SD | 64.9±11.9 | 60.4±7.3 |
| Female, n (%) | 52 (37) | 9 (38) |
| Black, n (%) | 41 (29) | 2 (8) |
| Hispanic, n (%) | 14 (10) | — |
| Current smoking, n (%) | 6 (4) | — |
| BMI, kg/m², mean±SD | 31.6±6.8 | 26.5±4.0 |
| SBP, mm Hg, mean±SD | 128.3±16.8 | 118.5±11.5 |
| Diabetes, n (%) | 68 (49) | 0 (0) |
| Congestive heart failure, n (%) | 16 (11) | 0 (0) |
| Stroke, n (%) | 8 (6) | 0 (0) |
| Ischemia, n (%) | 8 (6) | 0 (0) |
| Revascularization, n (%) | 23 (16) | 0 (0) |
| eGFR, ml/min per 1.73 m², mean±SD | 32.1±8.0 | 85.9±16.0 |
| UACR, mg/g, median (IQR) | 154.0 (20.3–540.0) | — |
| Hemoglobin, g/dl, mean±SD | 12.9±1.7 | — |
| Serum phosphate, mg/dl, mean±SD | 3.7±0.5 | — |
| PTH, pg/ml, median (IQR) | 86.5 (56.0–129.0) | — |
| Plasma FGF23, pg/ml, median (IQR) | 105.8 (79.1–144.3) | — |
| BNP, pg/ml, median (IQR) | 53.0 (26.5–117.6) | — |
| Hs-troponin, ng/L, median (IQR) | 6.5 (4.3–9.1) | — |
| Left ventricular end systolic volume index, ml/m²², mean±SD | 12.8±6.2 (n=140) | 13.0±3.5 (n=24) |
| Left ventricular end diastolic volume index, ml/m²², mean±SD | 33.1±9.9 (n=140) | 33.7±6.9 (n=24) |
| Left atrial end systolic volume index, ml/m²², mean±SD | 12.8±7.1 (n=134) | 10.6±3.2 (n=24) |
| Left atrial end diastolic volume index, ml/m²², mean±SD | 21.0±8.2 (n=134) | 20.8±6.4 (n=24) |
| Left ventricular mass index, g/m²², mean±SD | 29.5±8.4 (n=140) | 23.4±4.0 (n=24) |
| Mitral valve E/A ratio, mean±SD | 0.8±0.3 (n=116) | 1.0±0.2 (n=24) |
| Ejection fraction, %, mean±SD | 62.3±9.7 (n=140) | 61.7±4.0 (n=24) |

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 systolic BP (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.

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 2. Associations of CKD status with cMRI parameters

| cMRI Parameter                                | Parameter Estimate (95% Confidence Interval) | P Value | Parameter Estimate (95% Confidence Interval) | P Value | Parameter Estimate (95% Confidence Interval) | P Value |
|-----------------------------------------------|---------------------------------------------|---------|---------------------------------------------|---------|---------------------------------------------|---------|
| Left ventricular end systolic volume (n=164)  | -0.26 (-2.84 to 2.32)                       | 0.84    | -0.01 (-2.66 to 2.63)                       | 0.99    | 0.68 (-2.37 to 3.73)                       | 0.66    |
| Left ventricular end diastolic volume (n=164)| -0.60 (-4.75 to 3.55)                       | 0.78    | 0.19 (-4.06 to 4.44)                       | 0.93    | -2.55 (-6.81 to 1.70)                      | 0.24    |
| Left atrial end systolic volume index (n=158)| 2.14 (-0.77 to 5.05)                        | 0.15    | 1.85 (-1.05 to 4.75)                       | 0.21    | 0.68 (-2.37 to 3.73)                      | 0.66    |
| Left atrial end diastolic volume (n=158)     | 0.24 (-3.25 to 3.73)                        | 0.89    | 0.12 (-3.36 to 3.59)                       | 0.95    | -1.77 (-5.36 to 1.83)                     | 0.33    |
| Left ventricular mass index, g/m^2 (n=164)   | 6.04 (2.57 to 9.51)                         | 0.0008  | 5.77 (2.39 to 9.15)                       | 0.0009  | 1.49 (-1.49 to 4.48)                     | 0.33    |
| Mitral valve E/A ratio (n=140)               | -0.20 (-0.33 to -0.07)                      | 0.002   | -0.14 (-0.25 to -0.04)                    | 0.009   | -0.13 (-0.24 to -0.012)                  | 0.03    |

cMRI, cardiac magnetic resonance imaging.

*Minimally adjusted model was adjusted for covariates in the minimally adjusted model plus body mass index and systolic BP.

**Fully adjusted** model was adjusted for covariates in the minimally adjusted model plus body mass index and systolic BP.
Table 3. Associations between baseline eGFR and UACR and baseline cMRI parameters in participants with CKD

| Participants with CKD (N=140) | Left Ventricular End Systolic Volume Index (N=140) | Left Ventricular End Diastolic Volume Index (N=140) | Left Atrial End Systolic Volume Index (N=134) | Left Atrial End Diastolic Volume Index (N=134) | Left Ventricular Mass Index (N=140) | Mitral Valve E/A Ratio (N=116) |
|-------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------|---------------------------------------------|-----------------------------------|----------------------------------|
| Spearman correlation coefficients (P values) | Baseline eGFR, ml/min per 1.73 m² | −0.06 (0.47) | −0.08 (0.37) | −0.07 (0.42) | −0.01 (0.88) | −0.07 (0.41) | 0.13 (0.18) |
|                               | Baseline UACR, mg/g | 0.19 (0.03) | 0.15 (0.07) | 0.07 (0.41) | 0.002 (0.99) | 0.39 (<0.001) | −0.14 (0.14) |
| Linear regression analyses with β estimates (95% CI) | Baseline eGFR, ml/min/1.73m² | 0.03 (0.12 to 0.17) | 0.005 (−0.21 to 0.22) | 0.02 (−0.14 to 0.19) | 0.09 (−0.09 to 0.26) | 0.07 (−0.09 to 0.23) | 0.004 (−0.003 to 0.01) |
|                               | Baseline ln UACR | 0.013 (−0.66 to 0.68) | −0.45 (−1.45 to 0.55) | 0.04 (−0.71 to 0.79) | −0.50 (−1.31 to 0.31) | 0.54 (−0.21 to 1.29) | −0.06 (−0.09 to −0.03) |

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.

P<0.05.

bβ 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

| Participants with CKD (N=112) | Left Ventricular End Systolic Volume Index (N=112) | Left Ventricular End Diastolic Volume Index (N=112) | Left Atrial End Systolic Volume Index (N=105) | Left Atrial End Diastolic Volume Index (N=105) | Left Ventricular Mass Index (N=112) | Mitral Valve E/A Ratio (N=73) |
|-------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------|---------------------------------------------|-----------------------------------|----------------------------------|
| Spearman correlation coefficients (P values) | Baseline eGFR, ml/min per 1.73 m² | 0.09 (0.35) | 0.03 (0.79) | 0.12 (0.23) | 0.11 (0.24) | −0.19 (0.04) | −0.06 (0.61) |
|                               | Baseline UACR, mg/g | −0.06 (0.55) | 0.10 (0.28) | −0.004 (0.96) | 0.10 (0.33) | 0.23 (0.02) | 0.19 (0.11) |
| Linear regression analyses with β estimates (95% CI) | Baseline eGFR, ml/min per 1.73m² | 0.095 (−0.14 to 0.33) | 0.10 (−0.27 to 0.48) | 0.13 (−0.09 to 0.36) | 0.05 (−0.21 to 0.31) | −0.13 (−0.35 to 0.09) | 0.002 (−0.02 to 0.03) |
|                               | Baseline ln UACR | 0.46 (−0.52 to 1.45) | 0.70 (−0.86 to 2.26) | 0.18 (−0.79 to 1.14) | 0.43 (−0.68 to 1.54) | 0.08 (−0.83 to 1.00) | −0.01 (−0.09 to −0.07) |

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.

P<0.05.

bβ 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 was 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 MRI. 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

G.A. Block reports receiving research funding from Akebia, Ardelyx, and GlaxosmithKline; having consultancy agreements with Akebia, Keryx, Kirin, and Reata; receiving honoraria from Amgen and Kirin; serving as a scientific advisor for or member of Ardelyx, CJASN, Kirin, and Reata; having ownership interest in
Ardeleyx and Reata; and having other interests in/relationships with DaVita (previously medical director), Kidney Disease Improving Global Outcomes (previously on Executive Committee), and Reata (previous employment). J. Carr reports serving on a speakers bureau for Bayer; receiving honoraria from Bayer, Bracco, and Guerbet; having consultancy agreements with Bayer, Bracco, and Siemens; receiving research funding from Bayer, Guerbet, and Siemens; and serving as a scientific advisor for or member of the Society for Cardiovascular MRI. A.K. Cheung reports having consultancy agreements with, and receiving honoraria from, Boehringer Ingelheim, Calliditas, and UptoDate; serving as a scientific advisor for or member of Hong Kong Journal of Nephrology, JASN, and Kidney Diseases; having other interests in/relationships with KDIGO; and having ownership interest in Merck. M. Chonchol reports having consultancy agreements with Amgen, Corvidia, Otsuka, Reata, Tricidia, and Vifor; receiving honoraria from Amgen, Corvidia, Reata, Tricidia, and Vifor; serving as a scientific advisor for or member of the CJASN editorial board; and receiving research funding from the Corvidia, National Institutes of Health (NIH), Otsuka, Reata, and Sanofi. L.F. Fried reports having consultancy agreements with Bayer, and serving on data safety monitoring boards for CSI. Behring and Novo Nordisk. J.J. Gassman reports having consultancy agreements with, and receiving honoraria from, the Baim Institute (Harvard Clinical Research Institute). T. Isakova reports having consultancy agreements with, and receiving honoraria from, Akebia Therapeutics Inc.; and serving as an associate editor of American Journal of Kidney Diseases. J.H. Ix reports serving as a scientific advisor for or member of AlphaYoung; having consultancy agreements with Ardelyx, AstraZeneca, Bayer, Jnana, and Sanifit; and receiving research funding from Baxter International. R. Mehta reports having ownership interest in AbbVie Inc.; having consultancy agreements with, and receiving honoraria from, Akebia/Otsuka and AstraZeneca; and serving on the editorial board of the Journal of Cardiac Failure. J.P. Middleton reports serving on the editorial board for Advances in Chronic Kidney Disease and on a data safety monitoring board for the NIDDK; having consultancy agreements with AstraZeneca and Vifor/Relypsa; receiving research funding from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and Vifor/Relypsa; having other interests in/relationships with Raleigh Radiology (via spouse); and receiving honoraria from Relypsa/Vifor. D.S. Raj reports having other interests in/relationships with the American Association of Kidney Patients; serving as a scientific advisor for or member of the National Heart, Lung, and Blood Institute (NHLBI), NIDDK, and Novo Nordisk; receiving research funding from NIH; and having consultancy agreements with, and receiving honoraria from, Novo Nordisk. K.L. Raphael reports having consultancy agreements with AstraZeneca. S.M. Sprague reports serving as a scientific advisor for or member of the American Association of Endocrine Surgeons American Journal of Nephrology, International Federation of Clinical Chemistry and Laboratory Medicine Work Group for Parathyroid Hormone, and National Kidney Foundation of Illinois; having consultancy agreements with Amgen, Ardelyx, Fresenius, Horizon, Litholink Corp., OPKO, Shire, and Vifor; receiving research funding from Amgen, Ardelyx, OPKO, and Reata; receiving honoraria from Amgen, Ardelyx, Fresenius, Horizon, OPKO, and Vifor; serving on speakers bureaus for Amgen, Fresenius, Horizon, and OPKO; and having ownership interest via individually owned stocks in Apple, Bristol Myers, Coca Cola, First Australia Fund, IBM, Paycheck, US Concrete, and Walgreens. A. Srivastava reports serving on a speaker’s bureau for AstraZeneca; receiving honoraria from AstraZeneca, Bayer, and Horizon Therapeutics PLC; and having consultancy agreements with CVS Caremark and Tate & Latham (medicolegal consulting). M. Wolf reports having consultancy agreements with, and receiving honoraria from, Akebia, Amgen, Ardelyx, AstraZeneca, Bayer, Pharmacosmos, Unicycive, and Walden; and having ownership interest in, and serving as a scientific advisor for or member of, Akebia, Unicycive, and Walden. All remaining authors have nothing to disclose. All remaining authors have nothing to disclose.

Funding
The COMBINE trial was supported by NIDDK grants U01DK099877, U01DK097093, U01DK099930, U01DK099933, and U01DK099924. This work was also supported by NIDDK grants R01DK102438 (T. Isakova), R01DK0811374 (M. Wolf), K23DK120811 (A. Srivastava), P30DK114857, and R01DK093793; and NHLBI grants K24HL150235 (T. Isakova) and K23HL150236 (R. Mehta). Research reported in this publication was also supported, in part, by the NIH National Center for Advancing Translational Sciences grants KL2TR001424 and UL1TR001422 and by an NIDDK Kidney Precision Medicine Project Opportunity Pool grant under U2CDK114886 (A. Srivastava).

Acknowledgments
The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US Government.

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.0005022021/-/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.

References

1. Ganevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J. Chronic Kidney Disease Prognosis Consortium: Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int 80: 93–104, 2011

2. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Ganevoort RT: Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. Lancet 375: 2073–2081, 2019

3. House AA, Wanner C, Sarnak MJ, Piernik A, Hunsicker LG, Klug MG, Kusek JW, Flessner MF, Block GA, Wolf M. Effects of nicotinamide and lanthanum carbonate on serum phosphate and fibroblast growth factor-23 in CKD: The COMBINE Trial. J Am Soc Nephrol 30: 1096–1108, 2019

4. Prasad PV, Li W, Raj DS, Carr J, Carr M, Thacker J, Li LP, Wang C, Sprague SM, Ix JH, Chonchol M, Block G, Cheung AK, Raphael K, Gassman J, Wolf M, Fried LF, Isakova T; CKD: Optimal Management with Blinders and Nicotinamide (COMBINE) study group: Multicenter study evaluating intrarenal oxygenation and fibroblast growth factor imaging in individuals with advanced CKD. Kidney Int 83: 1467–1472, 2016

5. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI): A new equation to estimate glomerular filtration rate. Ann Intern Med 150: 604–612, 2009 https://doi.org/10.7326/0003-4819-141-9-200905050-00006

6. Palmieri V, de Simone G, Arnett DK, Bella JN, Kitzman DW, Oberman A, Hopkins PN, Province MA, Devereux RB: Relation of various degrees of body mass index in patients with systemic hypertension to left ventricular mass, cardiac output, and peripheral resistance (The Hypertension Genetic Epidemiology Network Study). Am J Cardiol 88: 1163–1168, 2001 https://doi.org/10.1016/S0002-9149(01)00254-9

7. Kang E, Ryu H, Kim J, Lee J, Lee KB, Chae DW, Sung SA, Kim SW, Ahn C, Oh KH: Association between high-sensitivity cardiac troponin T and echocardiographic parameters in chronic kidney disease: Results from the KNOW-CKD Cohort Study. J Am Heart Assoc 8: e013357, 2019

8. Bansal N, Hyre Anderson A, Yang W, Christensen RH, deFilippi CR, Deo R, Dries DL, Go AS, He J, Kusek JW, Lash JP, Raj D, Rosas S, Wolf M, Zhang X, Shlipak MG, Feldman HI: High-sensitivity troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study. J Am Soc Nephrol 26: 946–956, 2015 https://doi.org/10.1681/ASN.2014101018

9. Venge P, Johnston N, Lindalh B, James S: Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial Ischemia. J Am Coll Cardiol 54: 1165–1172, 2009 https://doi.org/10.1016/j.jacc.2009.05.031

10. Knuuti J, Lluch S, Badimon L, Badimon JJ, Zocchi GC, Clerico A: Comparison of a fully automated immunoassay with a point-of-care testing method for B-type natriuretic peptide. Clin Chim Acta 371: 1274–1276, 2005 https://doi.org/10.1016/j.cca.2005.04.096

11. Scialli JJ, Wolf M: Roles of phosphate and fibroblast growth factor factor 23 in cardiovascular disease. Nat Rev Nephrol 10: 278–278, 2014 https://doi.org/10.1038/nrneph.2014.49

12. Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialli J, Xie H, Appleby D, Nessel L, Bellovich K, Chen J, Hamm L, Gadebeku C, Horwitz E, Townsend RR, Anderson CAM, Lash JP, Hsu CY, Leonard MB, Wolf M: Fibroblast growth factor factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 79: 1370–1378, 2011 https://doi.org/10.1038/sj.ki.5008310

13. Webb J, Fournier L, Tondel K, Porter B, Snieciewicz B, Gould J, Rinaldi CA, Ismail T, Chibbiri A, Carr-White G: The emerging role of cardiac magnetic resonance imaging in the evaluation of patients with HFpEF. Circ Heart Fail Rep 15: 1–9, 2018 https://doi.org/10.1161/HFTR.117.103557

14. Paolotti E, Bellino D, Cassattana P, Rolla D, Cannella G: Left ventricular hypertrophy in non-diabetic predialysis CKD. Am J Kidney Dis 64: 320–327, 2015 https://doi.org/10.1053/j.ajkd.2005.04.031

15. Schneider MP, Scheppebach JB, Rui F, Runcyt S, Ritter C, Klink T, Stork F, Wanner C, Schiller G, Saritas T, Reinartz SD, Fiole, J, Friedrich N, Janke R, Ruder M, Schmirer RE, Eckardt
AFFILIATIONS

1 Graduate Medical Education, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
2 Center for Translational Metabolism and Health, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
3 Division of Nephrology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
4 Department of Radiology, Northwestern University Health System Evanston, Evanston, Illinois
5 Division of Nephrology and Hypertension, NorthShore University Health System, Evanston, Illinois
6 University of Chicago Pritzker School of Medicine, Chicago, Illinois
7 Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
8 Division of Nephrology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina
9 Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina
10 Division of Nephrology, Department of Medicine, University of San Diego School of Medicine and Veterans Affairs San Diego Healthcare System, San Diego, California
11 Reata Pharmaceuticals, Irving, Texas
12 Division of Renal Disease/Hypertension, Department of Internal Medicine, University of Colorado Hospitals, Aurora, Colorado
13 Division of Nephrology and Hypertension, Department of Medicine, Oregon Health and Science University and Veterans Affairs Portland Health Care System, Portland, Oregon
14 Division of Nephrology and Hypertension, Department of Internal Medicine, University of Utah Health, Salt Lake City, Utah
15 Division of Kidney Diseases and Hypertension, George Washington University School of Medicine, Washington, DC
16 Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio
17 Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland
18 Renal Section, Veterans Affairs Pittsburgh Healthcare System and Department of Medicine, Renal-Electrolyte Division, University of Pittsburgh, Pittsburgh, Pennsylvania
19 Division of Nephrology, Department of Medicine, Jesse Brown Veterans Administration Medical Center, Chicago, Illinois