Effects of Anemia and Left Ventricular Hypertrophy on Cardiovascular Disease in Patients with Chronic Kidney Disease

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Left ventricular hypertrophy (LVH) and anemia are highly prevalent in moderate chronic kidney disease (CKD). Because anemia may potentiate the adverse effects of LVH on cardiovascular outcomes, the effect of both anemia and LVH on outcomes in CKD was examined. Data from four community-based longitudinal studies were pooled: Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study. Serum creatinine levels were calibrated indirectly across studies, and GFR was estimated using the Modification of Diet in Renal Disease equation. CKD was defined as GFR between 15 and 60 ml/min per 1.73 m^2. LVH was based on electrocardiogram criteria. Anemia was defined as hematocrit <36% in women and 39% in men. The primary outcome was a composite of myocardial infarction, stroke, and death; a secondary cardiac outcome included only myocardial infarction and fatal coronary heart disease. Among 2423 patients with CKD, 96% had electrocardiogram and anemia data. Median follow-up was 102 mo. In adjusted analysis, LVH was associated with increased risk for composite and cardiac outcomes (hazard ratio [HR], 1.67 [95% confidence interval (CI), 1.34 to 2.07] and 1.62 [95% CI, 1.18 to 2.24], respectively), whereas anemia was associated with increased risk for the only composite outcome (HR, 1.51 [95% CI, 1.27 to 1.81]). The combination of anemia and LVH was associated with an increased risk for both study outcomes compared with individuals with neither risk factor (HR, 4.15 [95% CI, 2.62 to 6.56] and 3.92 [95% CI, 2.05 to 7.48]; $P = 0.02$ and 0.01 for interaction term, respectively). The combination of anemia and LVH in CKD identifies a high-risk population.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). This increased risk begins during the earlier stages of CKD before the onset of kidney failure (1–3). Although much of the burden of cardiovascular disease in CKD may be due to atherosclerosis, patients with CKD also have frequent disorders of left ventricular structure and function (4).

Left ventricular hypertrophy (LVH) represents a physiologic adaptation to a long-term increase in myocardial work requirements as a result of either pressure or volume overload. Pressure overload results from increased cardiac afterload, whereas volume overload may be related to anemia, as the heart attempts to compensate for decreased peripheral oxygen delivery. As hypertrophy progresses, capillary density decreases and subendocardial perfusion is reduced. Myocardial fibrosis may ensue, and, with sustained maladaptive forces, myocyte death occurs (5). Both anemia and LVH are highly prevalent in stages 3 to 4 CKD. Between 20 and 50% of patients with moderate CKD have evidence of LVH on echocardiography (6,7), whereas 5% of the U.S. population with GFR between 30 and 59 and 44% with GFR between 15 and 29 ml/min per 1.73 m^2 are anemic (8).

Several studies have shown an association between anemia and CVD outcomes in CKD (9,10). Because LVH increases oxygen demand and anemia may limit supply, we hypothesized that the combination of these two risk factors may be particularly hazardous. In the current study, we examine the relationship between anemia and LVH, as well as their interaction, with CVD in a pooled cohort of patients with CKD.

Materials and Methods

Study Design

This study is a secondary evaluation of four community-based, longitudinal, public-use data sets designed to evaluate CVD: The Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), and the Framingham Offspring Study (Offspring).

Study Population

Between 1987 and 1989, ARIC enrolled 15,792 participants aged 45 to 64 yr from Jackson, MS; Forsyth County, NC; the northwestern suburbs

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of Minneapolis, MN; and Washington County, MD. The Mississippi cohort is entirely black and comprises >80% of the black individuals in ARIC. CHS is a population-based study of 5201 individuals who were 65 yr and older and randomly selected from Medicare eligibility files during 1989 and 1990 from four different communities: Sacramento County, CA; Washington County, MD; Forsyth County, NC; and Pittsburgh, PA. An additional 687 black individuals were recruited in 1992 and 1993. FHS began in 1948 with 5209 residents of Framingham, MA, aged 28 to 62 yr. Serum creatinine levels were initially assessed at the 15th biennial examination (1977 to 1979; $n = 2632$) in FHS. Offspring recruited 5124 of the children and the spouses of children of FHS participants in 1971, and serum creatinine was assessed at the second examination (1979 to 1983; $n = 3863$). Therefore, the 15th examination in FHS and the second examination in Offspring were considered to be the baseline period for our current analysis. Details of recruitment for all studies have been described elsewhere (11–14).

Ascertainment of Level of Kidney Function

In the ARIC study, baseline serum creatinine levels were assessed in 15,582 (99%) individuals using the modified kinetic Jaffé method (alkaline picrate). Serum creatinine in CHS was assessed by the Kodak Ektachem 700 Analyzer, a colorimetric method, in 5716 (97%) individuals. Creatinine was assessed in the FHS and the Offspring cohorts using either an autoanalyzer technique or the creatinine imodohydrolase assay in 2536 (96%) and 3703 (96%) individuals, respectively.

Kidney function was quantified using estimated GFR derived from the four-variable Modification of Diet in Renal Disease (MDRD) study equation as follows: GFR = $186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212$ (if black) $\times$ 0.742 (if female). Serum creatinine is measured in mg/dl, age is measured in years, and GFR is expressed in ml/min per 1.73 m^2 (15). The MDRD Study equations for estimating GFR were derived by comparing GFR assessed by kidney clearance of iothalamate with demographic characteristics and laboratory values (16). Serum creatinine assays in the MDRD Study were performed at the Cleveland Clinic Foundation. Because serum creatinine assays vary across laboratories, use of the MDRD Study equation in these analyses requires calibration of the serum creatinine assays from each study laboratory with the Cleveland Clinic (17). We calibrated the study laboratories indirectly using the data from the Third National Health and Nutrition Examination Survey (NHANES III). Serum specimens from a subset of individuals from NHANES III were previously assayed at the Cleveland Clinic laboratory. Because both NHANES III and the studies used for these analyses were designed as population samples, we assumed that the mean serum creatinine in each study for individuals of a given age range, race, and gender should be comparable to NHANES III. A linear regression of data comparing each study individually with NHANES III showed that serum creatinine values were 0.24 mg/dl higher in ARIC, 0.11 mg/dl higher in CHS, 0.04 mg/dl higher in the CHS black cohort, 0.22 mg/dl higher in FHS, and 0.32 mg/dl higher in Offspring than among NHANES III participants. These values then were subtracted from measured creatinine levels before estimation of GFR for these analyses. Similar calibration corrections have been made by the CHS investigators to pool the two CHS cohorts and the Framingham investigators to pool data from the FHS and Offspring studies (18).

CKD was defined on the basis of the Kidney Disease Outcomes and Quality Initiative guidelines (19). Markers of kidney damage, such as proteinuria, were not available, so individuals were classified as having CKD when estimated GFR was <60 ml/min per 1.73 m^2. Individuals with a GFR of <15 ml/min per 1.73 m^2 were excluded from the study to avoid including individuals who may have been dialysis dependent or who were likely to require dialysis in the near future.

LVH

LVH was defined using resting 12-lead electrocardiogram in all studies. LVH criteria for individual studies are presented in Table 1. To

Table 1. Criteria for defining LVH in the various studies[a]

	CHS and ARIC	FHS and Offspring
Voltage criteria	R-wave amplitude >26 mm in V5 or V6	R-wave amplitude ≥25 mm in any deflection in precordial leads
	R-wave amplitude >20 mm in any of leads I, II, III, aVF	R-wave amplitude ≥20 mm in standard leads
	R amplitude >12 in aVL	R-wave amplitude ≥11 mm in augmented unipolar leads
	R-wave amplitude >15 but ≤20 mm in lead I	—
	R-wave amplitude in V5 or V6 plus S amplitude in V1 >35 mm	R-wave amplitude in V5 or V6 plus S amplitude in V1 or V2 ≥35 mm
S-T segment characteristics	S-T depression Minnesota Codes: anterolateral = 4–1–2, 4–2, 4–3 posterior = 4–2, 4–3, 4–12 anterior = 4–2, 4–3, 4–4–1, 4–1–2	"Depressed S-T segments"
T wave characteristics	Flattened to inverted T waves Minnesota Codes: anterolateral = 5–1, 5–2, 5–3 posterior = 5–2, 5–3 anterior = 5–1, 5–2, 5–3	"Flattened to inverted T waves"

[a]LVH, left ventricular hypertrophy; CHS, Cardiovascular Health Study; ARIC, Atherosclerosis Risk in Communities Study; FHS, Framingham Heart Study; Offspring, Framingham Offspring Study.

be classified as having LVH, individuals needed to meet voltage criteria and have either the S-T segment characteristics or T wave characteristics described in Table 1.

Anemia

The presence or absence of anemia was based on measurement of hematocrit. Adapting the World Health Organization definition, which was based on hemoglobin levels of <12 g/dl in women and <13 g/dl in men, anemia was defined as hematocrit <36% in women and 39% in men (20).

Baseline Variables

Other baseline characteristics included demographics (age, gender, race, and education level), lifestyle (smoking and alcohol intake), medical history (baseline CVD, diabetes, and hypertension), medication use (antihypertensive agents, lipid-lowering agents, and diabetes medications), physical examination findings (height, weight, body mass index, systolic and diastolic BP), and laboratory variables (total cholesterol, HDL cholesterol, creatinine, and glucose). The methods used for collection of baseline data by each of these studies have been described previously (11–14).

Race was defined as white or black. The Framingham cohorts were assumed to be entirely white (21). Education level was dichotomized according to whether the individual graduated from high school. Cigarette smoking and alcohol use were dichotomized as current users and nonusers. For ARIC, CHS, and Offspring, diabetes was defined as either the use of insulin or oral hypoglycemic medications or a fasting glucose level ≥126 mg/dl. Although the measurement of serum glucose in FHS was based on a casual measurement with respect to fasting, for the analysis, diabetes was also defined by use of diabetes medications or serum glucose level ≥126 mg/dl. Hypertension was defined as systolic BP ≥140 mmHg, diastolic ≥90 mmHg, or use of an antihypertensive medication. Body mass index was calculated using the formula weight (kg)/height^2 (m).

Baseline CVD included a history of both recognized and silent myocardial infarction (MI), angina, stroke, transient ischemic attack, and intermittent claudication as defined by consensus committees for the respective studies. In addition, baseline CVD included a history of congestive heart failure in CHS, FHS, and Offspring (not coded in ARIC) and a history of angioplasty and coronary bypass procedures in ARIC and CHS (not available in the Framingham cohorts). The methods used for definitions of CVD outcomes by each of these studies have been described extensively elsewhere (11–14).

Study Sample

We excluded 575 individuals who had data missing on age, race, gender, or creatinine or were of nonwhite/nonblack race; 36 individuals with GFR <15 ml/min per 1.73 m^2; 93 individuals who did not provide permission to release data; three individuals without follow-up data; and 556 individuals with missing baseline CVD data. From the remaining 26,912 individuals, 2423 had CKD. A total of 87 (3.6%) individuals were missing either ECG or hematocrit data, and an additional three individuals were missing BP data and were excluded from analysis. The final study sample was composed of 2333 individuals (Figure 1).

A total of 180 individuals had missing single data points, such as total cholesterol; for these individuals, single imputation was performed on the basis of age-, gender-, and race-stratified means. Final models are based on the imputed results.

Follow-Up Time and Outcomes

Because only the Framingham cohorts reliably had >10 yr of follow-up data, we censored all individuals at 10 yr for follow-up times to be similar among the studies. The primary study outcome was a composite of MI, stroke, and all-cause mortality. MI was defined by

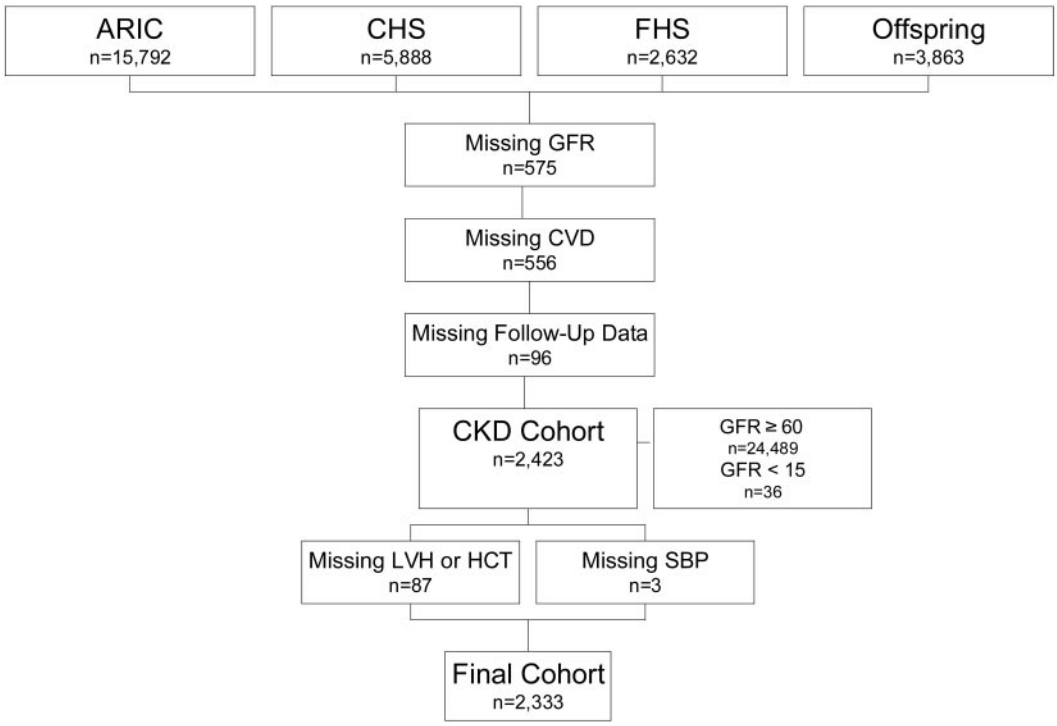

Figure 1. Derivation of the final study cohort.

both clinically recognized and silent infarctions. The secondary outcome comprised cardiac events (fatal coronary heart disease and MI); stroke and all-cause mortality were also analyzed.

Statistical Analyses

The goal of our analysis was to determine whether anemia and LVH were associated with adverse events in individuals with CKD and whether there was an interaction between these risk factors. Data were stratified into groups on the basis of anemia and LVH status. χ^2 tests and ANOVA were used to compare baseline data between individuals with and without anemia and with and without LVH.

Kaplan-Meier survival analysis was used to compare survival times without study outcomes among patients with anemia *versus* those without anemia and among those with LVH *versus* those without LVH. Cox proportional hazards regression was used to examine the differences in the primary study outcome between the respective comparison groups while adjusting for covariates. Candidate variables included traditional CVD risk factors described in the Framingham population, namely age, gender, smoking status, systolic BP, total cholesterol, HDL cholesterol, diabetes, and history of hypertension, as well as LVH, alcohol use, body mass index, and education status. Stepwise selection was performed, and variables were retained when $P < 0.05$. Terms for original study were included in the models. We also tested for interactions among the variables described previously. We specifically examined for an interaction between anemia and LVH given the hypothesized relationship between these two risk factors. Further analyses were performed for the cardiac outcome as well as the individual outcomes of stroke and all-cause mortality using covariates that were significant in the fully adjusted model for the composite outcome.

Several sensitivity analyses were performed: (*1*) Comparing the model with imputed data with that without imputed data; (*2*) removing systolic BP from the model to investigate for overcorrection for factors that may be in the pathway between anemia, LVH, and CVD; (*3*) evaluating in exploratory analyses whether the anemia and LVH interaction for the composite outcome was different in individuals with and without CVD; and (*4*) exploring whether the relationship between LVH and anemia with outcomes was different in each of the studies using (*a*) stratified Cox analyses by study to assess for paradoxic results related to study differences in baseline hazard rates, (*b*) additional models with a robust sandwich estimator with the four studies entered as clusters to explore the impact of potential study clustering and between-study heterogeneity, and (*c*) subgroup analysis by study. We did not evaluate the Framingham studies separately because of the small number of individuals with anemia and LVH in these studies. Data were analyzed using SAS Version 8.2.

Results

Baseline Characteristics

Mean (median, SD) GFR for the CKD cohort was 51.0 ml/min per 1.73 m^2 (53.1, 8.3). Mean (median, SD) calibrated serum creatinine was 1.3 mg/dl (1.3, 0.3). Individuals with CKD had a mean age of 69.4 yr, and 38.3% were male; 759 (31.3%) individuals had a history of CVD, whereas 17.1% had diabetes and 69.1% had a history of hypertension. Mean hematocrit for men was 43.8% and for women was 41.1%. A total of 275 (11.8%) individuals had anemia; anemia was more frequently present in black individuals (31.0 *versus* 6.8%). A total of 130 (5.6%) individuals had LVH by ECG criteria. Individuals with LVH had significantly higher systolic BP and were more likely to be anemic. A total of 25 (1.1%) individuals had both anemia and LVH. The baseline characteristics of the 2423 individuals who were eligible for analysis are shown in Table 2.

Primary Outcome

The median duration of follow-up was 102 mo for the pooled database; median follow-up for ARIC was 107 mo, for CHS was 99 mo, for FHS was 120 mo, and for Offspring was 120 mo. The composite outcome occurred in 1019 (43.7%) individuals. There were 422 (18.1%) cardiac events, 251 (10.8%) strokes, and 819 (35.1%) deaths (Table 2). The distribution of events by anemia and LVH subgroup is presented in Table 3.

Unadjusted analysis showed a hazard ratio (HR) of 2.13 (95% confidence interval [CI], 1.81 to 2.50) for anemia and an HR of 2.69 (95% CI, 2.18 to 3.32) for LVH for the composite outcome. In fully adjusted analysis, the hazard was significantly increased in individuals with anemia when compared with those without anemia (HR, 1.51; 95% CI, 1.27 to 1.81) and in individuals with LVH when compared with those without LVH (HR, 1.67; 95% CI, 1.34 to 2.07; Table 4). After adjustment for an interaction between blacks in CHS and ARIC (whereby blacks in CHS were at less risk than blacks in ARIC after adjustment for age and comorbid conditions), terms for the individual studies were not statistically significant (Wald statistic, $P > 0.10$).

Secondary Outcomes

LVH was an independent risk factor for cardiac events, stroke, and death. Anemia was an independent risk factor for all-cause mortality, and there was a higher but not statistically significant risk for both cardiac events and stroke (Table 4).

Interaction of Anemia and LVH with Outcomes

Primary Outcome. The interaction term LVH × anemia was statistically significant ($P = 0.02$; Table 4). Individuals with both anemia and LVH had a nearly four-fold increased risk (HR, 4.15; 95% CI, 2.62 to 6.56) for the composite outcome compared with individuals with neither anemia nor LVH. Anemia without LVH and LVH without anemia both increased the risk for composite outcomes by approximately 40% compared with the risk in individuals with neither anemia nor LVH.

Secondary and Other Outcomes. The interaction term LVH × anemia was significant for the secondary (cardiac) outcome and stroke but not all-cause mortality ($P = 0.01$, 0.04, and >0.20, respectively). Individuals with both anemia and LVH had a nearly four-fold increase in risk (HR, 3.92; 95% CI, 2.05 to 7.48) for the cardiac outcome compared with individuals with neither anemia nor LVH (Figure 2, Table 4). However, in individuals who had LVH and did not have anemia and in individuals who had anemia and did not have LVH, there was no significant increase in the risk for cardiac outcomes (Table 4).

Sensitivity Analyses

HR in models without imputed data and in models in which systolic BP was removed were not appreciably different from models with these data. Exploratory analyses for the composite outcome demonstrated that the interaction between anemia and LVH may be stronger in those with CVD. In individuals with CVD, the HR for those with both anemia and LVH *versus*

Table 2. Baseline characteristics and outcomes of individuals stratified by anemia and LVH status[a]

	LVH		Anemia	
	Absent (n = 2228)	Present (n = 131)	Absent (n = 2112)	Present (n = 287)
Demographics (%)				
age (yr)	69.0 ± 11.0	73.1 ± 9.0	69.1 ± 10.8	72.1 ± 11.2
male	37.9[b]	43.5[b]	37.5	46.0
white	91.1	77.1	93.2	69.0
high school graduate	68.2[c]	58.9[c]	68.9	60.0
Medical history (%)				
CVD	29.3	59.5	30.8[c]	36.9[c]
diabetes	16.8[b]	20.6[b]	16.2	24.7
hypertension	67.4	93.1	67.9	78.0
currently smokes	15.2[b]	16.0[b]	15.9	9.4
currently drinks	50.0[b]	50.0[b]	51.0	38.9
Physical characteristics				
BMI (kg/m^2)	27.1 ± 4.6	25.9 ± 3.6	27.1 ± 4.5[c]	26.4 ± 5.0[c]
systolic BP	134.6 ± 22.3	150.6 ± 26.7	135.1 ± 22.6	139.9 ± 25.6
diastolic BP	72.9 ± 11.7[b]	73.8 ± 13.8[b]	73.2 ± 11.6	71.0 ± 13.4
LVH (%)	—	—	5.1[c]	8.7[c]
Laboratory results				
creatinine, calibrated (mg/dl)	1.3 ± 0.3	1.5 ± 0.5	1.3 ± 0.3	1.6 ± 0.6
GFR (ml/min per 1.73 m^2)	51.2 ± 8.1	47.5 ± 10.6	51.7 ± 7.5	45.9 ± 11.5
total cholesterol (mg/dl)	222.3 ± 45.9[b]	218.5 ± 44.0[b]	223.2 ± 45.0	211.5 ± 50.4
HDL cholesterol (mg/dl)	50.4 ± 15.8[b]	49.4 ± 16.8[b]	50.2 ± 15.5[b]	51.5 ± 17.8[b]
HCT (% packed cell volume)	42.2 ± 4.6[c]	41.3 ± 5.1[c]	43.2 ± 3.8	34.6 ± 2.9
anemia (%)	11.4[c]	18.5[c]	—	—
Clinical outcomes (%)				
cardiac	17.2	34.4	17.5[c]	23.3[c]
stroke	10.0	22.9	10.5[d]	14.3[d]
mortality	33.3	65.6	32.6	56.4
composite	41.9	74.0	41.4	63.1
Follow-up (mo)	91.9 ± 31.5	68.0 ± 37.3	93.1 ± 30.8	69.1 ± 35.9

[a]Continuous variables are mean ± SD. CVD, cardiovascular disease; BMI, body mass index; HCT, hematocrit.
All P values are <0.01 when compared within the LVH or anemia status except as follows: [b]$P > 0.05$, [c]$P < 0.05$, and [d]$P = 0.05$.

Table 3. Distribution of events by anemia and LVH status[a]

	Composite (n = 1022)	Cardiac (n = 423)	Stroke (n = 252)	Mortality (n = 821)
+LVH, +anemia (n = 25)	22 (88.0%)	11 (44.0%)	9 (36.0%)	20 (80.0%)
+LVH, −anemia (n = 130)	74 (56.9%)	33 (25.4%)	21 (16.2%)	65 (50.0%)
−LVH, +anemia (n = 250)	152 (60.8%)	52 (20.8%)	30 (12.0%)	135 (54.0%)
−LVH, −anemia (n = 1928)	774 (40.1%)	327 (17.0%)	192 (10.0%)	601 (31.2%)

[a]The number of individuals with the composite event is smaller than the total of cardiac, stroke, and mortality because some patients have more than one outcome, and, for the composite outcome, each patient is counted only once.

those with neither anemia nor LVH was 5.78 ($P < 0.001$ for the LVH × anemia interaction term), whereas for those without CVD, the HR was 2.17 ($P > 0.20$ for the interaction term).

Both stratified Cox analyses to assess the impact of the individual studies and models using a robust sandwich estimator with the four studies entered as clusters demonstrated essentially the same results as above (data not shown). In subgroup analyses in which ARIC and CHS were evaluated individually, we noted that the direction of the relationships between anemia and LVH as well as their interactions with outcomes were in the same direction as the combined cohort; however, we did note that the interaction

Table 4. Hazard ratios and confidence intervals from fully adjusted multivariate analysis for primary and secondary outcomes in individuals with CKD[a]

	Composite[b]	Cardiac[b]	Stroke[b]	Mortality[c]
Without interaction				
LVH	1.67 (1.34 to 2.07)	1.62 (1.18 to 2.24)	1.78 (1.20 to 2.65)	1.74 (1.38 to 2.20)
anemia	1.51 (1.27 to 1.81)	1.21 (0.90 to 1.61)	1.30 (0.89 to 1.89)	1.68 (1.39 to 2.04)
With interaction				
+LVH, +anemia	4.15 (2.62 to 6.56)	3.92 (2.05 to 7.48)	4.24 (2.00 to 8.99)	3.30 (2.04 to 5.34)
+LVH, −anemia	1.43 (1.18 to 1.72)	1.36 (0.94 to 1.97)	1.47 (0.92 to 2.34)	1.68 (1.29 to 2.18)
−LVH, +anemia	1.48 (1.16 to 1.89)	1.08 (0.79 to 1.48)	1.14 (0.75 to 1.71)	1.65 (1.35 to 2.02)
−LVH, −anemia	Reference	Reference	Reference	Reference

[a]Cardiac events included recognized and silent myocardial infarction and fatal coronary heart disease. Stroke includes both fatal and nonfatal events. All models were adjusted for age; gender; race; history of CVD, hypertension, and diabetes; current smoking; alcohol use; high school graduation status; systolic BP, total cholesterol; HDL cholesterol; GFR; and study terms.

[b]$P < 0.05$ for the interaction between anemia and LVH.

[c]The interaction term for anemia and LVH with mortality was not statistically significant ($P > 0.20$).

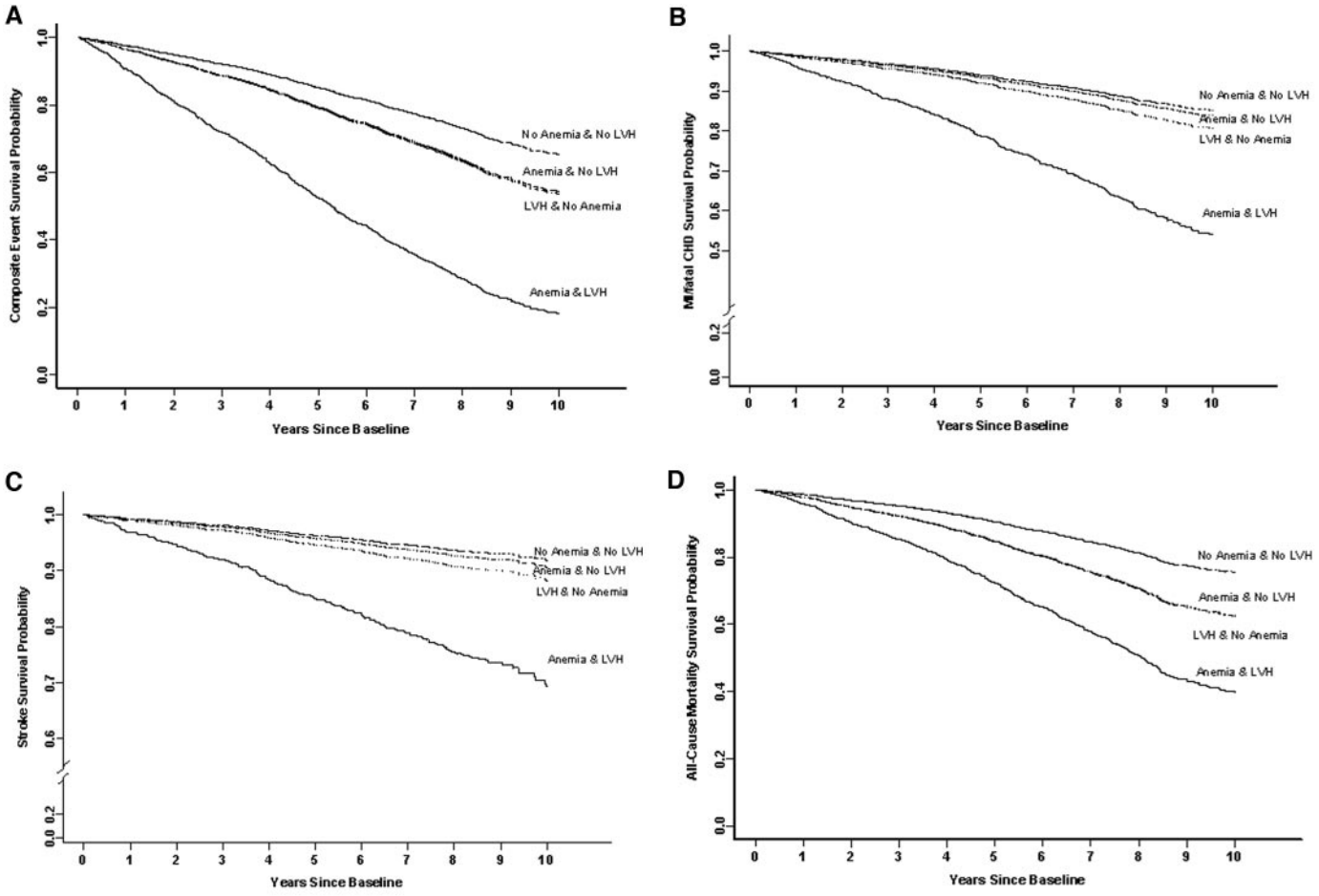

Figure 2. Graphical representation of the differing effect of the presence *versus* absence of anemia and left ventricular hypertrophy (LVH) in subjects with chronic kidney disease on study outcomes in fully adjusted analyses. Plots are based on models that contain an interaction term for anemia and LVH. Continuous variables were set at their median values, and binary covariates were set at their median value.

for the composite outcome between anemia and LVH was significant only in ARIC. We cannot be sure whether this is a true difference *versus* a lack of statistical power in CHS.

Discussion

In this study, we extend observations in the general population and in kidney failure to patients in the earlier stages of CKD, demonstrating that LVH is a risk factor for adverse cardiovascular outcomes. Furthermore, our results suggest that patients with both LVH and anemia may be at particularly increased risk for adverse outcomes.

Relatively few prospective studies of which we are aware have evaluated the importance of anemia and LVH during the earlier stages of CKD. In the Studies of LV Dysfunction database, an investigation of patients with ejection fraction <35%, decreased GFR and anemia acted synergistically to increase the risk for all-cause mortality (22). Similarly, an evaluation of the ARIC cohort noted an interaction between anemia and CKD with regard to stroke and coronary outcomes, such that patients with both conditions were at particularly increased risk (9,10). Finally, a study of kidney transplant recipients noted that the presence of anemia but not LVH was an independent risk factor for all-cause mortality after adjustment for other comorbid conditions (23).

The synergistic relationship between anemia and LVH is consistent with the pathophysiology of LVH in CKD. LVH may become maladaptive and be associated with decreased capillary density, reduced subendocardial perfusion, and myocardial fibrosis (24,25). Under these conditions, reduced oxygen delivery, in the presence of anemia, may result in further maladaptive remodeling as well as subendocardial ischemia. The latter in turn may increase susceptibility to cardiac events. We acknowledge, however, that the presence of anemia and LVH may also be markers of the duration and severity of CKD, such that their dual presence identifies a particularly high-risk individual. The observational nature of our study cannot distinguish between these two possibilities.

Our study is predominantly composed of individuals with stage 3 CKD (estimated GFR 30 to 60 ml/min per 1.73 m^2) and therefore may be generalizable to the majority of patients with CKD in the United States. In fact, individuals in NHANES III with estimated GFR of 30 to 60 ml/min per 1.73 m^2 were very similar to our study population in distribution of gender (38% male for both NHANES III and our study), race (8 *versus* 10% black for NHANES III and our study, respectively), mean age (72 *versus* 69 yr, respectively), and the percentage of individuals with hypertension (73 *versus* 69%, respectively) and diabetes (both 17%) (26,27). Other strengths of the current study include the use of GFR-estimating equations based on calibrated creatinine values rather than serum creatinine alone to estimate true level of kidney function. In addition, there was rigid ascertainment of cardiovascular events in each of the original studies, with adjudication committees reviewing all possible CVD outcomes. Finally, this is one of only a few studies of which we are aware that has evaluated the role of either anemia or LVH in a large, community-based population composed solely of individuals with CKD.

Our study also has several limitations. First, the serum creatinine used to define CKD was assessed at only a single visit. However, given that patients were free of acute illnesses at the time of enrollment, the creatinine is likely a reflection of stable level of kidney function. Second, only 25 individuals had both anemia and LVH. Notably, despite the relatively low numbers, the interaction between anemia and LVH was statistically significant for cardiac, stroke, and composite outcomes. Third, there was a difference in the relationship between black individuals in CHS and ARIC with regard to the composite and mortality outcomes. Although we do not know the explanation for this finding, we do not believe that it changes the interpretation of our results with regard to the relationship between anemia and LVH as we adjust for this factor in our models. Fourth, as a corollary to one of the strengths of the study, the results are primarily generalizable to stage 3 CKD, as relatively few individuals had GFR values of <30 ml/min per 1.73 m^2. Fifth, we *a priori* used both individuals with and without baseline CVD and adjusted for baseline CVD status in our pooled analyses because of a limited number of events in those without baseline CVD, and therefore limited power to evaluate interactions further. Sixth, we used ECG criteria to diagnose LVH. Although ECG is less sensitive than echocardiogram for the diagnosis of LVH and is unable to identify patterns of hypertrophy that may be discriminate between volume and pressure overload, ECG remains a frequently used and inexpensive tool in medical practice. Use of echocardiography to diagnose LVH, however, may identify a larger at-risk population. Finally, because heart failure was not ascertained in all studies, we were unable to evaluate whether it mediates the relationship between anemia and LVH with the outcomes of interest.

This study has clinical implications because as many as 8 million individuals in the United States have reduced kidney function, and rates of CVD in this population are significantly higher than rates in the general population (27–29). Identification of potentially modifiable risk factors is important to potentially reduce CVD in the earlier stages of CKD before kidney failure.

In conclusion, this study demonstrates that LVH is an independent risk factor for CVD outcomes in individuals during the earlier stages of CKD and that individuals who have both anemia and LVH are at particularly increased risk. Additional studies, particularly those that use echocardiography to ascertain LVH, are needed to confirm this finding. If reproduced in future studies, individuals who have CKD and both LVH and anemia may be an important group for intervention studies.

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