

Anemia as a Risk Factor for Cardiovascular Disease and All-Cause Mortality in Diabetes: The Impact of Chronic Kidney Disease

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Anemia is a potential nontraditional risk factor for cardiovascular disease (CVD). This study evaluated whether anemia is a risk factor for adverse outcomes in people with diabetes and whether the risk is modified by the presence of chronic kidney disease (CKD). Persons with diabetes from four community-based studies were pooled: Atherosclerosis Risk in Communities, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study. Anemia was defined as a hematocrit <36% in women and <39% in men. CKD was defined as an estimated GFR of 15 to 60 ml/min per 1.73 m². Study outcomes included a composite of myocardial infarction (MI)/fatal coronary heart disease (CHD)/stroke/death and each outcome separately. Cox regression analysis was used to study the effect of anemia on the risk for outcomes after adjustment for potential confounders. The study population included 3015 individuals: 30.4% were black, 51.6% were women, 8.1% had anemia, and 13.8% had CKD. Median follow-up was 8.6 yr. There were 1215 composite events, 600 MI/fatal CHD outcomes, 300 strokes, and 857 deaths. In a model with a CKD-anemia interaction term, anemia was associated with the following hazard ratios (95% confidence intervals) in patients with CKD: 1.70 (1.24 to 2.34) for the composite outcome, 1.64 (1.03 to 2.61) for MI/fatal CHD, 1.81 (0.99 to 3.29) for stroke, and 1.88 (1.33 to 2.66) for all-cause mortality. Anemia was not a risk factor for any outcome in those without CKD ($P > 0.2$ for all outcomes). In persons with diabetes, anemia is primarily a risk factor for adverse outcomes in those who also have CKD.

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There are pathophysiologic reasons why the presence of anemia may lead to adverse cardiovascular consequences. Chronic anemia may increase preload, reduce afterload, and lead to increased cardiac output (1). In the long term, this may result in maladaptive left ventricular hypertrophy (LVH), which in turn is a well-recognized risk factor for CVD outcomes and all-cause mortality (2–4). In theory, the presence of anemia may also exacerbate cardiac ischemia as a result of decreased supply or increased demand for oxygen, such as in patients with underlying coronary disease or those with LVH, respectively.

Several studies in various populations have evaluated the importance of anemia as a risk factor for adverse outcomes. In patients with heart failure, anemia has for the most part been found to be associated with an increased risk for hospitalization and all-cause mortality (3,5–8). Similarly, in patients with chronic kidney disease (CKD), anemia has been shown to be a risk factor for adverse outcomes (9,10).

In patients with coronary disease, the relationship between

anemia and adverse outcomes has been less consistent, with some but not all studies demonstrating an adverse effect of anemia on CVD outcomes (11,12). Similarly, in the general population, the relationships have not been consistent. In the Atherosclerosis Risk in Communities study (ARIC), anemia was associated with CVD outcomes (13), and a significant interaction between anemia and the presence of CKD was noted, such that anemia was primarily a risk factor in those with CKD (4,14). However, in the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study, after adjustment for traditional CVD risk factors and other covariates, there was no significant association between anemia and coronary heart disease (CHD) mortality (15).

Diabetes is the leading cause of kidney disease and kidney failure in the United States (16). Anemia is often more severe and occurs at an earlier stage of CKD in individuals with diabetes compared with those with other causes of CKD (17,18). Furthermore, diabetes is a known risk factor for coronary artery disease and small vessel disease and may be a contributing factor to the development of LVH (19,20). The combination of anemia and CKD therefore may be particularly harmful in individuals with diabetes, who already have reduced oxygen supply and increased oxygen demand. In this study, we therefore evaluated anemia as a risk factor for CVD outcomes and all-cause mortality in a community-based cohort of patients

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with diabetes and whether this risk is modified by the presence of CKD.

Materials and Methods

Study Design

Our study is a secondary analysis of four community-based, longitudinal, public-use data sets that were designed to evaluate CVD outcomes. The data sets that were used were ARIC, 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 of Minneapolis, MN; and Washington County, MD. The CHS is a population-based study of 5201 subjects who were 65 yr of age 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. The FHS began in 1948 with 5209 residents of Framingham, MA, who were between the ages of 28 and 62 yr. Serum creatinine levels were initially assessed at the 15th biennial examination (1977 to 1979, $n = 2632$) in the FHS. The Offspring Study 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 of the original FHS cohort and the second examination in Offspring were considered to be the baseline period for our analyses. For each of the four studies, the study design, rationale, details of recruitment, and procedures followed have been described previously (21–24).

Ascertainment of Level of Kidney Function

In ARIC, serum creatinine at baseline was obtained in 15,582 (99%) individuals using the modified kinetic Jaffe method (alkaline picrate). Serum creatinine in CHS was measured by the Kodak Ektachem 700 Analyzer (Rochester, NY), a colorimetric method, in 5716 (97%) individuals. In the FHS and Offspring studies, serum creatinine was measured using either an autoanalyzer technique or the creatinine amidohydrolase assay in 2536 (96%) and 3703 (96%) individuals, respectively.

Kidney function was assessed using GFR as estimated by 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 was measured in mg/dl, age was measured in years, and GFR was expressed in ml/min per 1.73 m² (25,26).

The MDRD Study equations for estimating GFR were derived by comparing GFR assessed by kidney clearance of iothalamate with demographic characteristics and laboratory values (25). Serum creatinine assays in the MDRD Study were performed at the Cleveland Clinic Foundation. Because serum creatinine assays vary among laboratories, use of the MDRD Study equation for our analyses requires calibration of the serum creatinine assays from each study laboratory with the Cleveland Clinic laboratory (27). We calibrated serum creatinine values from the various study laboratories indirectly using data from the Third National Health and Nutrition Examination Survey (NHANES III). Serum specimens from a subset of participants from NHANES III were previously analyzed at the Cleveland Clinic laboratory. Because both NHANES III and the studies used for our analyses were population based, we assumed that the mean serum creatinine in each study

for participants 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 values before estimation of GFR for these analyses.

Definition of CKD

CKD was defined on the basis of the Kidney Disease Outcomes and Quality Initiative guidelines, which use both GFR and the presence of markers of kidney damage such as proteinuria to define CKD (28). Participants were considered to have CKD when the estimated GFR was <60 ml/min per 1.73 m². Participants with a GFR <15 ml/min per 1.73 m² were excluded from our analysis to avoid confounding by kidney failure. Information on markers of kidney damage was not available for the studies included in this analysis.

Definition of Diabetes

For ARIC, CHS, and Offspring, participants were considered to have diabetes when they reported the use of insulin or oral hypoglycemic medications or when they had a fasting serum glucose level ≥ 126 mg/dl, thereby meeting American Diabetes Association criteria for the diagnosis of diabetes (29). In the FHS, serum glucose was not necessarily measured in a fasting state. For our analysis, diabetes in the FHS was also defined by the use of diabetes medications or the presence of a serum glucose ≥ 126 mg/dl. We, however, also performed the following sensitivity analyses for the FHS to verify the consistency of our results: (1) Diabetes defined as the presence of serum glucose ≥ 200 mg/dl or use of diabetes medications at visit 15 and (2) diabetes defined as any serum glucose ≥ 200 mg/dl or any use of diabetes medications at or before visit 15. The glucose cut point of ≥ 200 mg/dl was chosen on the basis of an alternative American Diabetes Association definition of diabetes: Casual (with respect to fasting) plasma glucose ≥ 200 mg/dl in the presence of symptoms of diabetes (29).

Definition of Anemia

Anemia was defined as a hematocrit $<36\%$ in women and $<39\%$ in men. These values were obtained by extrapolating from the World Health Organization definition, which defines anemia as hemoglobin <12 g/dl in women and <13 g/dl in men (30).

Covariates

Baseline characteristics that were collected in the original longitudinal studies included demographics (age, gender, race, and education level), lifestyle factors (smoking and alcohol intake), medical history (baseline CVD and hypertension), medication use (antihypertensive agents, lipid-lowering agents, and diabetes medications), physical examination findings (height, weight, body mass index [BMI], systolic and diastolic BP), LVH by electrocardiogram, and laboratory variables (total cholesterol, HDL cholesterol, creatinine, and glucose). The methods used to collect baseline data in each of these studies have been described previously (21–24).

Race was defined as white or black. The Framingham cohorts were assumed to be entirely white (31). Education level was dichotomized according to whether the participant graduated from high school. Cigarette smoking and alcohol use were dichotomized as current users and nonusers. Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of an antihypertensive medication. BMI was calculated using the formula weight (kg)/height (m)².

Baseline CVD included a history of both recognized and silent myocardial infarction (MI), angina, stroke, transient ischemic attack, and intermittent claudication. Consensus committees for each of the respective studies defined these end points. 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 artery bypass procedures in ARIC and CHS (not available in the Framingham cohorts).

Study Sample

We excluded 651 individuals because of missing data needed to estimate GFR, 36 individuals with GFR <15 ml/min per 1.73 m², 99 individuals who did not provide permission to release data or who did not have follow-up data, 557 individuals with missing information required for the definition of diabetes, and 762 individuals with missing hematocrit values. The final cohort consisted of 3015 individuals with diabetes (Figure 1).

Follow-up Time and Outcomes

Because only the Framingham cohorts had >10 yr of follow-up data, we censored all participants at 10 yr so that follow-up times would be similar across the studies. Study outcomes included a composite end point of MI/fatal CHD/stroke/all-cause mortality, as well as components of the composite, including MI/fatal CHD, stroke, and all-cause mortality. MI was defined by both clinically recognized and silent infarctions. Stroke included both fatal and nonfatal events.

Statistical Analyses

Baseline characteristics of participants with and without anemia were compared using χ^2 tests for categorical data and *t* test for continuous data. Kaplan-Meier survival analysis was used to estimate event-free survival times among participants with anemia *versus* those without anemia. The log-rank test was used to test the significance of differ-

ences in long-term outcomes between these groups. Cox proportional hazards regression analysis was used to examine differences in study outcomes between the respective comparison groups while adjusting for other covariates. All models included traditional CVD risk factors described in the Framingham population, namely age, gender, smoking status, systolic BP, total cholesterol, HDL cholesterol, diabetes, and a history of hypertension. Other covariates including LVH, alcohol use, BMI, presence of CVD, and education status, and terms for original study were also included in all models. We tested for an interaction between anemia and CKD for each of the study outcomes. This was accomplished by including their cross-product in the multivariable regression model, given the *a priori* hypothesized relationship between these two risk factors. The proportional hazards assumption was tested using a time-varying coefficient model that tested for global and individual covariates, using an approximate score statistic that tests for linear correlation between the rank order of the failure times in the sample and Schoenfeld's partial residuals. Data were analyzed using SAS 8.2 (Cary, NC) and S-Plus 6.1 (Insightful Inc., Seattle, WA).

Sensitivity Analyses

We performed several sensitivity analyses. First, as described above, we used different definitions of diabetes in the FHS. Second, to account for differences among the original studies or study heterogeneity, in addition to including terms for original study in all of our multivariable models, we performed the following analyses: (1) Stratified Cox analyses by study to assess for paradoxical results related to study differences in baseline hazard rates, (2) 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 (3) subgroup analysis by study. We did not evaluate the Framingham studies separately because of the small number of participants with both anemia and CKD in these studies. Third, to ensure that participants with prevalent CVD were not responsible for our study results, we conducted a subgroup analysis to examine the anemia-CKD interaction in participants with and without a baseline history of CVD. Fourth, to determine whether our results are limited to individuals with diabetes, we examined the anemia-CKD interaction in the participants without diabetes (*n* = 24,229) in our pooled study cohort. Fifth, we reran the interaction models using continuous hematocrit (Hct) and continuous GFR rather than the dichotomous variables anemia and CKD.

Results

Baseline Characteristics

The baseline characteristics of the diabetic cohort are shown in Table 1, stratified by the presence or absence of anemia. Fifty-four percent of participants were from ARIC, 30% were from CHS, 11% were from FHS, and 5% were from Offspring. For the entire cohort, the mean age was 62.5 yr, 52% were female, 31% were black, 28% had a history of CVD, 71% had a history of hypertension, mean hematocrit was 42.7%, 245 (8.1%) patients had anemia, mean serum creatinine was 0.9 mg/dl, mean estimated GFR was 89.3 ml/min per 1.73 m², and 415 (13.8%) participants had CKD (data not shown). Participants with anemia had a higher prevalence of several CVD risk factors, including older age and hypertension. However, they were also less likely to be smokers and had lower total cholesterol and higher HDL cholesterol levels compared with participants without anemia.

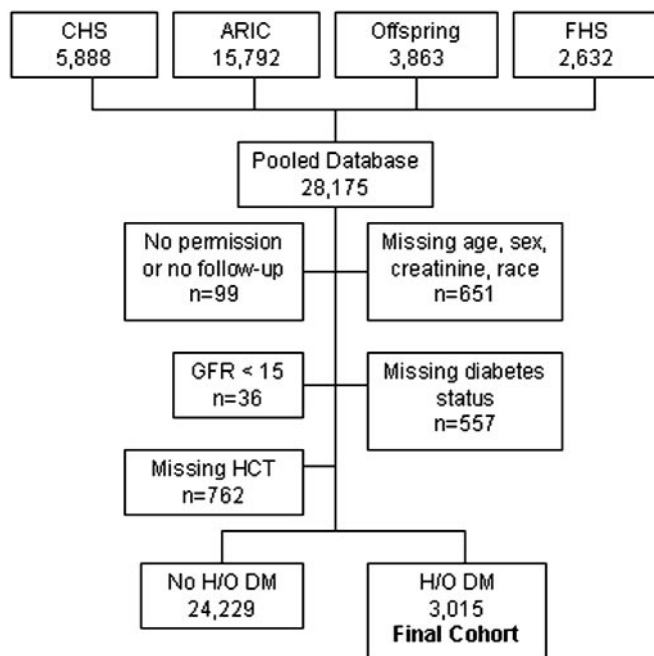


Figure 1. Derivation of the study cohort. Individuals could be excluded for more than one reason; therefore, the numbers are not additive.

Table 1. Baseline characteristics of the pooled diabetic cohort, stratified by the presence or absence of anemia^a

	No Anemia (n = 2770)	Anemia (n = 245)
Demographics (%)		
age (yr)	62.4 ± 10.2 ^b	63.9 ± 10.9 ^b
male	49.2	39.6
white	72.6	35.5
high school graduate	64.8	49.0
medical history (%)		
CVD	27.8 ^c	31.4 ^c
hypertension	69.6	80.8
Lifestyle (%)		
currently smokes	20.5	10.2
currently drinks	41.8	22.4
Physical characteristics		
BMI (kg/m ²)	29.9 ± 5.4 ^c	29.5 ± 5.6 ^c
systolic BP (mmHg)	134.2 ± 20.8	139.0 ± 25.3
diastolic BP (mmHg)	74.5 ± 11.8	71.7 ± 13.1
LVH (%)	4.2 ^c	6.6 ^c
Laboratory results		
creatinine, calibrated (mg/dl)	0.9 ± 0.3	1.1 ± 0.6
GFR (ml/min per 1.73 m ²)	90.0 ± 26.3	81.3 ± 31.8
total cholesterol (mg/dl)	219.0 ± 47.7	208.7 ± 49.4
HDL cholesterol (mg/dl)	44.8 ± 14.0 ^b	46.9 ± 14.9 ^b
hematocrit (% packed cell volume)	43.4 ± 3.8	34.8 ± 2.5
CKD (%)	12.4	29.0

^aData are presented as mean ± SD or %. CVD, cardiovascular disease; BMI, body mass index; LVH, left ventricular hypertrophy; CKD, chronic kidney disease.

Statistical tests of comparison are for no anemia *versus* anemia. All *P* values are <0.01 except as follows: ^b*P* = 0.02, ^c*P* > 0.05.

Outcomes

Clinical outcomes and follow-up time stratified by the presence or absence of anemia and outcomes stratified by the presence of anemia and CKD are shown in Tables 2 and 3, respectively.

Table 2. Clinical outcomes and follow-up time stratified by the presence or absence of anemia^a

Clinical Outcomes (%)	No Anemia (n = 2770)	Anemia (n = 245)
MI/fatal CHD	19.9 ^b	19.6 ^b
Stroke	9.8 ^b	11.4 ^b
All-cause mortality	27.4	39.6
Composite	39.6	48.2
Follow-up time (mo)	94.8 ± 29.5	81.0 ± 32.9

^aContinuous variables are mean ± SD. Statistical tests of comparison are for no anemia *versus* anemia. MI, myocardial infarction; CHD, coronary heart disease.

All *P* values are <0.01 except ^b*P* > 0.05

tively. The median follow-up time was 8.6 yr for the entire cohort, and those with anemia had a shorter period of follow-up (Table 2). There were 1215 (40.3%) composite outcomes, 600 (19.9%) MI/fatal CHD outcomes, 300 (10.0%) strokes, and 857 (28.4%) deaths. Those with anemia had a higher percentage of composite events and all-cause mortality but no difference in MI/fatal CHD or stroke events. Unadjusted analyses demonstrated the following hazard ratios (HR) for anemia: 1.40 (95% confidence interval [CI], 1.16 to 1.70) for the composite outcome, 1.15 (95% CI, 0.85 to 1.54) for MI/fatal CHD, 1.35 (95% CI, 0.91 to 1.99) for stroke, and 1.74 (95% CI, 1.41 to 2.15) for all-cause mortality. In fully adjusted analyses, anemia was a significant risk factor for the composite outcome (HR, 1.24; 95% CI, 1.01 to 1.53) and for all-cause mortality (HR, 1.45; 95% CI, 1.15 to 1.83; Table 4).

Anemia and CKD Interaction Model

The anemia × CKD interaction term was significant for the composite (*P* = 0.02) and stroke (*P* = 0.03) outcomes and of borderline significance for the outcomes of MI/fatal CHD (*P* = 0.07) and all-cause mortality (*P* = 0.06).

Effect of Anemia in Participants with Diabetes and with and without CKD

In a fully adjusted model accounting for the interaction term, anemia was a significant risk factor in participants with CKD for all of the outcomes except for stroke (HR, 1.81; 95% CI, 0.99 to 3.29), for which it was of borderline significance. In contrast, in participants without CKD, anemia was not a significant risk factor for any of the outcomes (Table 4).

Risk of Outcomes by Anemia and CKD Status

Using participants with no anemia and no CKD as the referent group, participants with both anemia and CKD were at particularly high risk for all outcomes (Figure 2 and Table 5).

Sensitivity Analyses

There were no significant differences in the results when different definitions of diabetes in FHS were used to define the cohort. Both stratified Cox analyses to assess the impact of 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 CKD as well as their interactions with outcomes were in the same direction as the combined cohort. However, whereas the interaction between anemia and CKD was statistically significant for all outcomes except all-cause mortality in ARIC, this interaction was not significant and the magnitude was significantly smaller for all outcomes in CHS. Of note, when we examined the interaction between continuous Hct and GFR in CHS, the results were significant for the composite (*P* = 0.02) and all-cause mortality (*P* = 0.002) outcomes.

When participants with and without history of CVD at study baseline were compared, the interaction between ane-

Table 3. Clinical outcomes stratified by anemia and CKD^a

	+Anemia + CKD (n = 71)	+Anemia – CKD (n = 174)	–Anemia + CKD (n = 344)	–Anemia – CKD (n = 2426)
Composite outcome	55 (75%)	63 (36%)	208 (60%)	889 (37%)
MI/fatal CHD	25 (35%)	23 (13%)	102 (30%)	450 (19%)
Stroke	16 (23%)	12 (7%)	51 (15%)	221 (9%)
All-cause mortality	48 (68%)	49 (28)	179 (52%)	581 (24%)

^aData are presented as number of events, and in parentheses the percentage of participants within each anemia-CKD category who had each outcome. Because the composite outcome includes all of the other outcomes, the percentages in each column do not add to 100%.

Table 4. Effect of anemia versus no anemia in the fully adjusted model^a

	Composite	MI/Fatal CHD	Stroke	All-Cause Mortality
Model without anemia-CKD interaction (main effect)				
anemia	1.24 (1.01 to 1.53)	1.17 (0.85 to 1.61)	1.05 (0.69 to 1.59)	1.45 (1.15 to 1.83)
Model with anemia-CKD interaction				
anemia in CKD	1.70 (1.24 to 2.34)	1.64 (1.03 to 2.61)	1.81 (0.99 to 3.29)	1.88 (1.33 to 2.66)
anemia in non-CKD	1.03 (0.79 to 1.35)	0.93 (0.60 to 1.43)	0.71 (0.39 to 1.28)	1.21 (0.89 to 1.65)
<i>P</i> for anemia-CKD interaction term	0.02	0.07	0.03	0.06

^aData are presented as hazard ratios (95% confidence interval [CI]). All analyses are adjusted for age, gender, race, history of CVD, history of hypertension, LVH, smoking, alcohol use, education, systolic BP, total cholesterol, HDL cholesterol, BMI, and original study.

mia and CKD was stronger for all outcomes, with the exception of stroke, in participants without a history of CVD at baseline compared with those with CVD at baseline (data not shown).

The interaction between anemia and CKD did not seem to be as strong in participants without diabetes compared with those with diabetes. That is, in patients without diabetes, the *P* value for the interaction term between anemia and CKD (HR [95% CI] in CKD, HR [95% CI] in non-CKD with interaction term included) were 0.03 (1.66 [1.36 to 2.03] and 1.26 [1.10 to 1.45]) for the composite outcome, 0.30 (1.32 [0.93 to 1.86] and 1.06 [0.83 to 1.35]) for MI/fatal CHD, 0.24 (1.27 [0.81 to 1.98] and 0.91 [0.66 to 1.26]) for stroke, and 0.10 (1.85 [1.49 to 2.30] and 1.48 [1.26 to 1.74]) for all-cause mortality. This was despite that there was more power to detect a significant interaction in those without diabetes. For example, there were 24,229 nondiabetic participants in the cohort, with 3977 composite outcomes, 1646 MI/fatal CHD outcomes, 891 stroke outcomes, and 2609 all-cause mortality outcomes.

When we examined the interaction between continuous Hct and continuous GFR in diabetic participants, the interaction term in the fully adjusted models was statistically significant for all outcomes (*P* < 0.001) except for stroke (*P* = 0.63). With the exception of the stroke outcome, these results were stronger than those shown in Table 4 (anemia and CKD both as dichotomous variables).

Discussion

In this pooled analysis of individuals with diabetes, we found that anemia is a risk factor for adverse CVD and all-cause mortality outcomes primarily in participants who also have CKD. The combination of anemia and CKD confers a particularly high-risk group for adverse outcomes.

Several but not all studies have suggested that anemia may be a risk factor for adverse outcomes in different populations and that the risk may be modified by the presence of CKD (3,4,14). For example, in ARIC, anemia was an independent risk factor for CVD outcomes (13), and the combination of anemia and CKD conferred a synergistic risk for stroke and coronary disease compared with each risk factor alone (4,14). Similarly, in a secondary analysis of the Studies of Left Ventricular Dysfunction (SOLVD), a randomized controlled trial that enrolled patients with an LV ejection fraction ≤35%, lower GFR, and lower Hct were independent risk factors for all-cause mortality; however, the combination conferred a synergistic risk (3). In contrast, anemia and CKD were independent risk factors for all-cause mortality in a random sample of patients who were admitted to the hospital with acute MI and heart failure; however, in both studies, there was no interaction between anemia and CKD (32,33). Finally, the NHANES II study showed no significant relationship between anemia and CVD mortality, although analyses that were stratified by the presence of CKD were not performed (15).

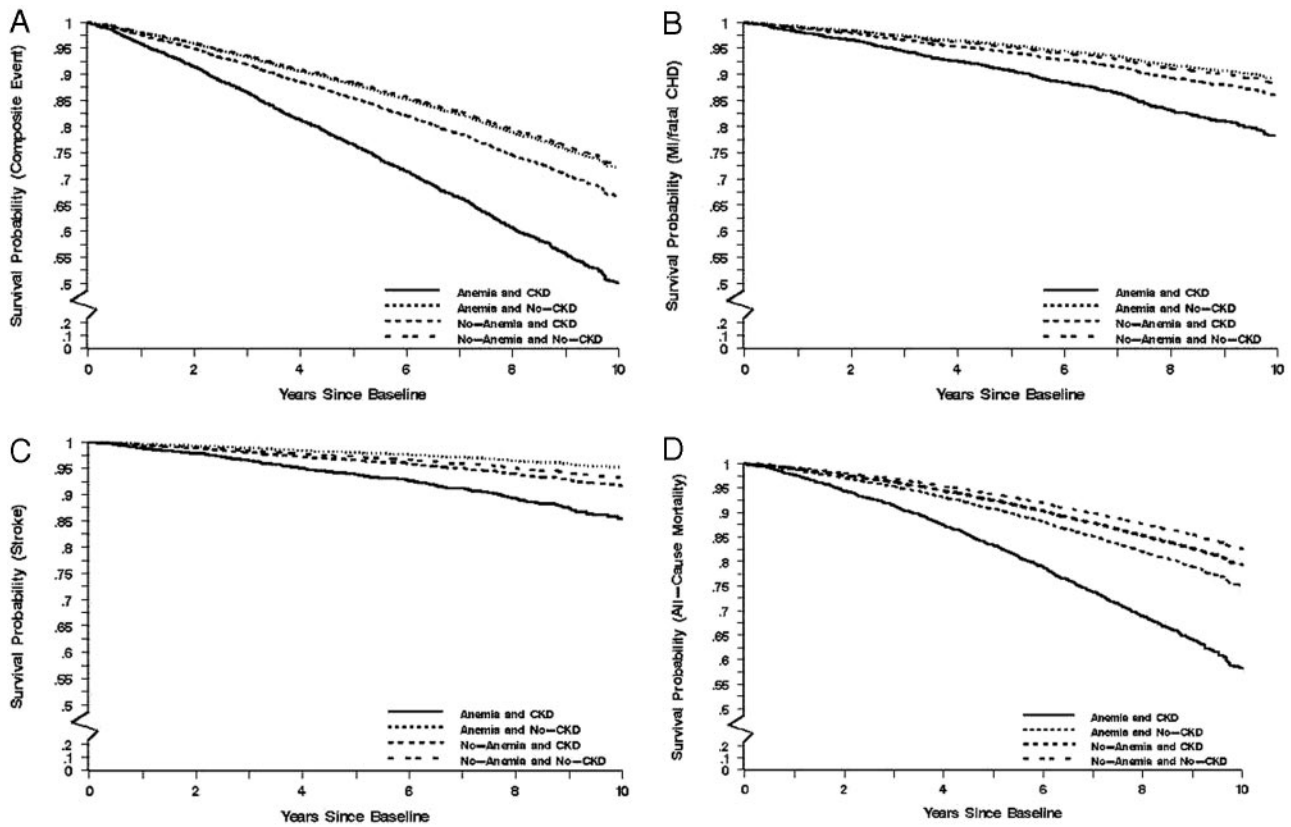


Figure 2. (A) Survival curves for the composite outcome by anemia and chronic kidney disease (CKD) status. (B) Survival curves for myocardial infarction (MI)/fatal coronary heart disease (CHD) by anemia and CKD status. (C) Survival curves for stroke by anemia and CKD status. (D) Survival curves for all-cause mortality by anemia and CKD status. Curves are based on fully adjusted models that contained an anemia \times CKD interaction term. Continuous covariates were set at their median values, and binary covariates were set at their median value.

Table 5. Outcomes by anemia and CKD status^a

	N per Group	Composite	MI/Fatal CHD	Stroke	All-Cause Mortality
+Anemia + CKD	71	2.18 (1.62 to 2.92)	2.00 (1.30 to 3.09)	2.24 (1.30 to 3.85)	2.84 (2.05 to 3.91)
+Anemia – CKD	174	1.03 (0.79 to 1.35)	0.93 (0.60 to 1.43)	0.71 (0.39 to 1.28)	1.21 (0.89 to 1.65)
–Anemia + CKD	344	1.28 (1.08 to 1.51)	1.22 (0.96 to 1.55)	1.24 (0.88 to 1.74)	1.51 (1.25 to 1.82)
–Anemia – CKD	2426	Reference	Reference	Reference	Reference

^aData are presented as hazard ratios (95% CI). All analyses are adjusted for age, gender, race, history of CVD, history of hypertension, LVH, smoking, alcohol use, education, systolic BP, total cholesterol, HDL cholesterol, BMI, and original study.

Diabetes is the leading cause of kidney failure in the United States and a primary cause of CVD in all patient populations (16). Therefore, evaluation of anemia as a risk factor for adverse outcomes is of particular importance in individuals with diabetes. There is also evidence that anemia is more severe and occurs at an earlier stage of kidney disease in patients with diabetic compared with nondiabetic CKD (17,34). Consequently, the effect of anemia and CKD on outcomes may be different in patients with and without diabetes.

There are several potential explanations for our results, which demonstrate that anemia is primarily a risk factor in those with CKD. First, patients with CKD have evidence of damage to at least one organ from diabetes; thus, they may be

more likely to have damage to other organs, including the heart. These patients may have microvascular and/or macrovascular disease of the coronary circulation or more severe LVH and therefore be more susceptible to ischemia induced by anemia. Second, the pathophysiology of anemia is different in patients with CKD, whereby erythropoietin (EPO) deficiency is of primary importance, compared with those without CKD, for whom other processes such as occult blood loss may be the cause of anemia. EPO has been shown *in vitro* and *in vivo* in animal studies to have several potential beneficial effects on the cardiovascular system independent of anemia correction, including reduction in myocardial damage, and pro-angiogenic and antiapoptotic effects on endothelial cells (35,36). If EPO

indeed has beneficial effects on the cardiovascular system, then EPO deficiency rather than low Hct itself may be the mechanism relating anemia to adverse outcomes in CKD. Third, unmeasured confounding from nontraditional cardiac risk factors may be important. For example, the presence of anemia in CKD may be a proxy for factors, such as inflammation, that were not measured in our study. Finally, residual confounding from factors that have been measured imperfectly may also be important. For example, participants with anemia and CKD may have had more severe hypertension or a longer exposure to diabetes, compared with those with anemia in the absence of CKD.

Strengths and Limitations

Our study has several strengths. First, there was rigid and systematic ascertainment of risk factors as well as outcomes in each of the original studies, with adjudication committees reviewing each outcome. Second, the studies involved several large community-based populations, and therefore the results may be generalizable to a large group of individuals with diabetes in the general population.

Our study also has several limitations. First, we defined CKD using estimated GFR from a single visit, whereas the National Kidney Foundation's Kidney Disease Outcomes and Quality Initiative guidelines require two estimates of GFR three or more months apart to classify a patient as having CKD (28). However, because study participants should have been free of acute illness at the time of enrollment, the serum creatinine likely was obtained in a steady state. Therefore, the GFR estimated from a single serum creatinine measurement likely would have reflected accurately the participants' level of kidney function. Second, the interaction results are primarily generalizable to patients with diabetes and stage 3 CKD (estimated GFR of 30 to 60 ml/min per 1.73 m²), as relatively few patients had GFR <30 ml/min per 1.73 m². Third, the number of patients with both anemia and diabetes was small ($n = 71$). Fourth, the anemia-CKD interaction terms achieved modest or borderline significance for all outcomes (Table 4), raising the possibility that some of our results were due to chance. However, we note that the interactions were stronger in the continuous analysis (Hct \times GFR) for all outcomes except stroke, making the possibility of a chance finding less likely. Fifth, we were unable to assess for differences across the studies related to period effects, including differences in diagnostic and therapeutic modalities.

Conclusions

In patients with diabetes, anemia is primarily a risk factor for CVD outcomes and all-cause mortality in those who also have CKD. Furthermore, the presence of anemia and CKD confers a particularly high-risk group. Prospective studies are currently under way to determine whether correction of anemia in patients with diabetes and CKD leads to a reduction in the risk for CVD outcomes and all-cause mortality.

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