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Anemia and cardiovascular disease, hospitalization, end stage renal disease, and death in older patients with chronic kidney disease

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Abstract. *Background:* Large observational studies examining the association between anemia and "hard" clinical outcomes are rare in patients with chronic kidney disease (CKD). *Methods:* We used the General Medicare 5% Denominator Files to identify patients aged 67 years or more with CKD on December 31, 1999. Outcomes in the ensuing 2 years were compared in patients with and those without anemia (entry period, 1998–1999; follow-up period, 2000–2001). *Results:* Of 41,522 CKD patients identified, 49.0% had claims of anemia diagnosis. The factors associated ($p < 0.0001$) with anemia included older age, female gender, black race, and all 10 comorbid conditions studied; adjusted odds ratios (ORs) exceeded 1.5 for age 80 years old or older (OR, 1.54 compared to <70 years), for black race (OR, 1.52), and for co-existing diagnoses of congestive heart failure (OR, 1.64), gastrointestinal bleeding (OR, 3.65), and liver disease (OR, 2.16). During the follow-up period, outcome event rates (expressed per 1000 patient-years) were as follows: renal replacement therapy, 23.5; death, 186.4; congestive heart failure, 390.0; atherosclerotic vascular disease, 410.5; and first hospitalization, 552.6. Using proportional hazards modeling, the presence of anemia was associated ($p < 0.0001$) with the following adjusted hazards ratios: atherosclerotic vascular disease, 1.09; congestive heart failure, 1.14; renal replacement therapy, 2.61 and death, 1.40. *Conclusion:* A diagnosis of anemia is present in nearly half of all patients with CKD, aged 67 years or more, a group at very high risk of cardiovascular disease, hospitalization, end-stage renal disease, and death. Anemia is associated with each of these events.

Key Words: Anemia, Chronic kidney disease, Medicare, Outcomes

Introduction

Guidelines for treating the anemia of chronic kidney disease (CKD) have existed since 1997 [1]. The evidence supporting these guidelines has mostly come from studies of patients receiving hemodialysis, particularly from observational studies using mortality and hospitalization [2–4] as endpoints and controlled trials showing regression of left ventricular hypertrophy [5, 6] and better quality of life [7–12]. Recently, anemia has become an area of active research in both the general population and patients with congestive heart failure [13–23]. Anemia is a cardinal feature of CKD [24].

Current anemia guidelines are independent of the stage of CKD. The evidence supporting anemia treatment in non-dialysis-requiring CKD is less than clear cut. The controlled trials performed to date show that quality of life and exercise capacity is enhanced [25, 26]. The few observational studies available show that anemia is associated with the development of left ventricular hypertrophy [27, 28] and nonelective hospitalization [29]. Large observational studies examining the association between anemia and "hard" clinical outcomes, such as cardiovascular events, need for renal replacement therapy, hospitalization, and death, are rare. This study is an attempt to partly address this information gap.

Methods

Objectives

The main objectives of this study were to quantify the associations between the presence of anemia and the following outcomes in the general Medicare population: (1) atherosclerotic vascular disease, defined as acute myocardial infarction, cerebrovascular accident or transient ischemic attack, or peripheral vascular disease; (2) congestive heart failure; (3) renal replacement therapy; (4) death; and (5) the composite outcome of atherosclerotic vascular disease, congestive heart failure, renal replacement therapy, or death.

Design

This study was a retrospective cohort analysis, with two phases. The entry phase, which extended from January 1, 1998 to December 31, 1999, was used to determine cohort characteristics. The follow-up period, which extended from January 1, 2000 to December 31, 2001, was used to determine study outcomes.

Subjects

The study cohort was derived from the Centers for Medicare & Medicaid Services (CMS) Medicare 5% Denominator Files for 1998–2001 and included patients who were continuously enrolled in Medicare Parts A and B in 1998–1999, were alive and at least 67 years old on December 31, 1999, and resided in the 50 US states, the District of Columbia, Puerto Rico, or the territories. Excluded were patients enrolled in a managed care program (health maintenance organization) and those diagnosed with end-stage renal disease during the entry period. For the analysis of first-hospitalization rate, patients also were excluded if they were in the hospital at the beginning of the follow-up period.

Measurements

The CMS Medicare 5% Denominator Files, CMS Medicare 5% Standard Analytical Files, and the United States Renal Data System (USRDS) database were used.

According to a previously validated methodology for using Medicare claims to identify patients with diabetes [30], anemia and other comorbid conditions at baseline were identified from Medicare Part A institutional claims and Part B physician/supplier claims using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Physicians' Current Procedural Terminology (CPT) codes. Anemia was defined as the presence of ICD-9-CM diagnosis codes 280.XX (iron deficiency anemias), 281.XX (other deficiency anemias), 282.XX (hereditary hemolytic anemias), 283.XX (acquired hemolytic anemias), 284.XX (aplastic anemia), or 285.XX (other and unspecified anemias) from at least one Part A inpatient, home health, or skilled nursing facility claim, or at least two Part A outpatient claims on different dates, or at least two Part B claims on different dates. Comorbid conditions included acute myocardial infarction, congestive heart failure, cerebrovascular accident or transient ischemic attack, peripheral vascular disease, cancer, chronic obstructive pulmonary disease, diabetes mellitus, gastrointestinal bleeding, hypertension, and liver disease. Administration of renal replacement therapy was determined by linking the Medicare 5% Denominator Files to the USRDS database.

Analysis

The baseline characteristics of patients with and those without anemia were compared initially with the χ^2 test and subsequently with multivariate logistic regression. To determine outcomes, patients were followed up to 2 years starting January 1, 2000. For cardiovascular endpoints and hospitalization, follow up was censored at the earliest occurrence of death, renal replacement therapy, end of Medicare Part A or Part B entitlement, enrollment in a health maintenance organization, or December 31, 2001. For death, follow up was censored at renal replacement therapy or December 31, 2001. For renal replacement therapy, follow-up was censored at death or December 31, 2001.

Unadjusted event rates were estimated as the observed total number of events divided by total follow-up duration. A Poisson regression model was used to compare the differences in event rates between patients with and those without anemia. Cumulative event-free probabilities of the

composite outcome (atherosclerotic vascular disease, congestive heart failure, renal replacement therapy, or death) were graphed with Kaplan–Meier curves. Cox proportional hazards modeling was used to assess the association between presence of anemia and time to each endpoint, with adjustment for demographic characteristics and comorbid conditions. Finally, a supplemental analysis was performed, testing the association between anemia and the composite outcome in the subgroup without cardiovascular disease and gastrointestinal bleeding. All statistical analyses were performed under the SAS system for Windows, version 8.2 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 41,522 study subjects. Anemia was present in 49.0% of the overall study population. The mean age was 78.4 years; 52.4% of the patients were

Table 1. Baseline patient characteristics

Characteristic		Anemia status[a]			Odds Ratio for Anemia	
	All n = 41,522 (100.0%)	No anemia n = 21,163 (51.0%)	Anemia n = 20,359 (49.0%)	p Value[b]	OR (95% CI)	p Value[c]
Age (yr)				<0.0001		
67–69	4393 (10.6%)	2601 (12.3%)	1792 (8.8%)		1.00 (reference)	
70–74	9561 (23.0%)	5424 (25.6%)	4137 (20.3%)		1.06 (0.98, 1.14)	NS
75–79	10,485 (25.3%)	5480 (25.9%)	5005 (24.6%)		1.21 (1.12, 1.31)	<0.0001
≥80	17,083 (41.1%)	7658 (36.2%)	9425 (46.3%)		1.54 (1.44, 1.66)	<0.0001
Gender				<0.0001		
Male	19,780 (47.6%)	10,852 (51.3%)	8928 (43.9%)		0.74 (0.71, 0.77)	<0.0001
Female	21,742 (52.4%)	10,311 (48.7%)	11,431 (56.1%)		1.00 (reference)	
Race				<0.0001		
White	34,733 (83.6%)	18,226 (86.1%)	16,507 (81.1%)		1.00 (reference)	
Black	4790 (11.5%)	2020 (9.5%)	2770 (13.6%)		1.52 (1.42, 1.62)	<0.0001
Other	1999 (4.8%)	917 (4.3%)	1082 (5.3%)		1.38 (1.25, 1.52)	<0.0001
Comorbidity						
AMI	4141 (10.0%)	1585 (7.5%)	2556 (12.6%)	<0.0001	1.25 (1.17, 1.35)	<0.0001
Cancer	13,238 (31.9%)	6527 (30.8%)	6711 (33.0%)	<0.0001	1.28 (1.23, 1.34)	<0.0001
CHF	19,113 (46.0%)	7779 (36.8%)	11,334 (55.7%)	<0.0001	1.64 (1.56, 1.71)	<0.0001
COPD	12,524 (30.2%)	5415 (25.6%)	7109 (34.9%)	<0.0001	1.23 (1.17, 1.29)	<0.0001
CVA/TIA	11,745 (28.3%)	5022 (23.7%)	6723 (33.0%)	<0.0001	1.25 (1.19, 1.31)	<0.0001
Diabetes	17,949 (43.2%)	8662 (40.9%)	9287 (45.6%)	<0.0001	1.09 (1.04, 1.14)	<0.0001
GI bleeding	7084 (17.1%)	1642 (7.8%)	5442 (26.7%)	<0.0001	3.65 (3.44, 3.88)	<0.0001
Hypertension	34,502 (83.1%)	16,966 (80.2%)	17,536 (86.1%)	<0.0001	1.20 (1.13, 1.27)	<0.0001
Liver disease	1123 (2.7%)	348 (1.6%)	775 (3.8%)	<0.0001	2.16 (1.88, 2.47)	<0.0001
PVD	14,624 (35.2%)	6450 (30.5%)	8174 (40.1%)	<0.0001	1.23 (1.17, 1.28)	<0.0001

AMI: acute myocardial infarction; CHF: congestive heart failure; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CVA/TIA: cerebrovascular accident/transient ischemic attack; GI: gastrointestinal; NS: not statistically significant; OR: odds ratio; PVD: peripheral vascular disease.

[a]With the exception of italicized items, descriptive statistics are presented as number (percentage) of patients within all patients and by anemia status (columns add to 100%).

[b]Using the χ^2 test.

[c]Using the logistic regression model. The reference group has the following characteristics: age ≤69 years, female gender, white race, and no co-morbid conditions. An odds ratio >1 means a greater probability of being associated with anemia than the reference category. An odds ratio <1 means a lesser probability of being associated with anemia than the reference category.

female; and 83.6%, 11.5%, and 4.8% of the patients were white, black, and of other race, respectively. Unadjusted analyses showed that the presence of anemia was associated with older age, female gender, black and other race, and the presence of any comorbid condition studied. The associations were similar in a multivariate logistic regression model in which the presence or absence of anemia at baseline was the dependent variable. Adjusted odds ratios (ORs) exceeded 1.5 for age 80 years old or older, for black race, and for coexisting diagnoses of congestive heart failure, gastrointestinal bleeding, and liver disease.

Outcomes

The overall mean follow-up duration was 1.6 years. Table 2 shows unadjusted event rates per 1000 patient-years for all patients and also shows that these were associated with the presence of a previous anemia claim. Figure 1 provides Kaplan–Meier survival estimates of time to the combined endpoint of atherosclerotic vascular disease, congestive heart failure, renal replacement therapy, or death. The 1- and 2-year event-free survival probabilities in patients with anemia were 0.32 and 0.19, respectively, compared to 0.49 and 0.34 in those without anemia ($p < 0.0001$).

Figure 2 presents anemia-associated hazards ratios from Cox regression models with cardiovascular disease, renal replacement therapy, first hospitalization, and death as endpoints. Table 3 shows the hazards ratios associated with anemia and other covariates for the following outcomes: atherosclerotic vascular disease, congestive heart failure, death, and renal replacement therapy. Compared to nonanemic patients, anemic patients were 9% more likely to develop atherosclerotic vascular disease, 14% more likely to develop congestive heart failure, 40% more likely to die, and 161% more likely to need renal replacement therapy. Only 16% of the study population were

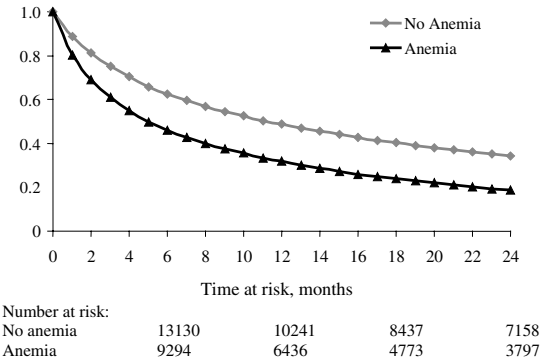

Figure 1. Kaplan–Meier survival estimates of time to the combined endpoint of atherosclerotic vascular disease, congestive heart failure, renal replacement therapy, or death. The numbers below the *x*-axis indicate the number of event-free patients under observation at 6, 12, 18, and 24 months. $p < 0.0001$ for comparison of patients with to those without anemia by log-rank test.

Table 2. Unadjusted event rates in patients with and without anemia

Event	Anemia status			
	All	No anemia	Anemia	*p* Value[a]
AMI	51.5 (0.9)	41.5 (1.1)	63.4 (1.5)	<0.0001
ASVD	410.5 (2.9)	342.5 (3.6)	499.8 (4.9)	<0.0001
CHF	390.0 (2.9)	290.6 (3.2)	528.9 (5.1)	<0.0001
CVA/TIA	188.6 (1.8)	160.6 (2.3)	223.6 (3.0)	<0.0001
PVD	226.4 (2.0)	188.4 (2.5)	274.6 (3.4)	<0.0001
RRT	23.5 (0.6)	13.8 (0.6)	35.1 (1.1)	<0.0001
First hospitalization	552.6 (3.6)	443.1 (4.2)	703.5 (6.2)	<0.0001
All-cause mortality	186.4 (1.7)	134.5 (1.9)	248.6 (2.9)	<0.0001
Combined endpoint[b]	805.5 (4.6)	618.8 (5.3)	1079.9 (8.4)	<0.0001

AMI: acute myocardial infarction; ASVD: atherosclerotic vascular disease; CHF: congestive heart failure; CVA/TIA: cerebrovascular accident/transient ischemic attack; PVD: peripheral vascular disease; RRT: renal replacement therapy.
[a]Using the Poisson regression model to test for differences in event rates between patients with and those without anemia. Event rates are per 1000 patient-years, with standard errors in parentheses.
[b]Including ASVD, CHF, RRT, and all-cause mortality.

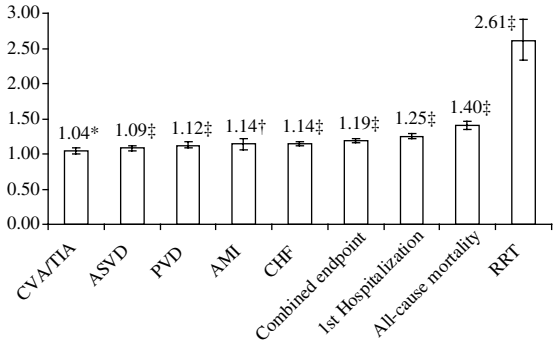

Figure 2. Anemia-associated Cox regression hazards ratios (and 95% confidence intervals) of cardiovascular disease, first hospitalization, RRT, all-cause mortality, and combined endpoint (ASVD, CHF, RRT, or death). Non-anemia was the reference category. Adjustment was made for age, gender, race, and presence of AMI, cancer, CHF, chronic obstructive pulmonary disease, CVA/TIA, diabetes, gastrointestinal bleeding, hypertension, liver disease, and PVD. *$p < 0.05$. †$p < 0.001$. ‡$p < 0.0001$. AMI: acute myocardial infarction; ASVD: atherosclerotic vascular disease; CHF: congestive heart failure; CVA/TIA: cerebrovascular accident/transient ischemic attack; PVD: peripheral vascular disease; RRT: renal replacement therapy.

free from cardiovascular and gastrointestinal bleeding claims during the study entry period. In this subgroup, anemia was associated with an adjusted hazards ratio of 1.55 (95% confidence interval, 1.43–1.69; $p < 0.0001$) for the combined endpoint described in the preceding paragraph.

Discussion

We found that a diagnosis of anemia was present in nearly half of all CKD patients aged 67 years or more. Older CKD patients were at a very high risk of cardiovascular disease, hospitalization, renal replacement therapy, and death. A diagnosis of anemia was associated with a higher risk of each of these adverse events.

There is a paucity of published data from controlled trials relating anemia and outcomes in patients with CKD. In one study, 83 CKD patients with hematocrit values of 26.8% were randomly assigned to receive either epoetin alfa or no anemia treatment for 48 weeks. The intervention was successful in achieving hematocrit values greater than 36% and was associated with improvements in energy level, physical function, and cognitive function [26]. Similarly, there is a paucity of published data from observational studies relating anemia to "hard" clinical outcomes. In contrast, several recent studies have suggested that anemia, CKD, and congestive heart failure tend to cosegregate; in addition, these studies suggest that anemia is a marker of short survival in patients with congestive heart failure [15–20].

We found associations between anemia and several categories of clinical outcome, including congestive heart failure, atherosclerotic vascular disease, and more rapid progression to need for renal replacement therapy. Anemia is a classic cause of a hyperdynamic circulatory system. Sustained anemia is known to cause vasodilation, increased venous return, cardiac enlargement, and increased cardiac output. In the long term, sustained activation of these compensatory physiological mechanisms may cause harm, possibly by accelerating rates of cardiac myocyte apoptosis [31–33]. Moderate degrees of anemia have been associated with progressive cardiac enlargement in patients with CKD [28].

Biological hypotheses explaining the association between anemia and atherosclerotic outcomes are more speculative. It is conceivable that anemia could augment the severity of symptoms associated with a given atherosclerotic lesion. It is less clear, however, how anemia could contribute to the pathogenesis of a given atherosclerotic lesion. Chronic kidney disease may be a state of oxidative stress [34]. Erythrocytes constitute a major antioxidant system, mediated via the glutathione system, enzymes like superoxide dismutase and catalase, and cellular proteins that react with reactive oxygen species, such as low-molecular-weight proteins of the erythrocyte membrane, vitamin E, and coenzyme Q. In addition, erythrocytes can regenerate redox equivalents through the pentose phosphate pathway [35, 36]. It is noteworthy that randomized trials of *N*-acetylcysteine and vitamin E have found that antioxidant therapy reduces thrombovascular events in dialysis patients [37, 38]. It has been speculated that similar mechanisms underlie the association between anemia and more rapid progression of established renal disease [36]. Two randomized trials have examined the effect of epoetin on glomerular filtration rates in anemic patients with CKD. One of these found no effect [39]; the other demonstrated slower loss of renal function and improved renal survival in the

Table 3. Results of Cox proportional hazards model of atherosclerotic vascular disease, congestive heart failure, all-cause mortality, and renal replacement therapy

	ASVD 19371/47190 (410.5 per 1000)[a]		CHF 18721/47999 (390.0 per 1000)[a]		All-cause mortality 12462/66845 (186.4 per 1000)[a]		RRT 1571/66845 (23.5 per 1000)[a]	
	HR (95% CI)[a]	*p* value	HR (95% CI)[b]	*p* value	HR (95% CI)[b]	*p* value	HR (95% CI)[b]	*p* value
Anemia	1.09 (1.05, 1.12)	<0.0001	1.14 (1.11, 1.18)	<0.0001	1.40 (1.35, 1.46)	<0.0001	2.61 (2.33, 2.91)	<0.0001
Age (yr)								
70–74	1.04 (0.99, 1.10)	NS	1.09 (1.02, 1.15)	0.0074	1.13 (1.04, 1.23)	0.0037	0.85 (0.73, 0.98)	0.0263
75–79	1.14 (1.08, 1.21)	<0.0001	1.20 (1.13, 1.27)	<0.0001	1.46 (1.34, 1.58)	<0.0001	0.61 (0.52, 0.71)	<0.0001
≥80	1.33 (1.27, 1.41)	<0.0001	1.52 1.44, 1.61)	<0.0001	2.32 (2.15, 2.50)	<0.0001	0.44 (0.38, 0.52)	<0.0001
Gender								
Male	1.03 (1.01, 1.06)	0.0207	1.01 (0.98, 1.04)	NS	1.09 (1.05. 1.13)	<0.0001	1.39 (1.26, 1.54)	<0.0001
Race								
Black	1.11 (1.07, 1.16)	<0.0001	0.99 (0.95, 1.03)	NS	1.06 (1.01, 1.12)	0.0296	1.76 (1.55, 1.99)	<0.0001
Other	0.93 (0.87, 0.99)	0.0301	0.94 (0.88, 1.01)	NS	0.88 (0.80, 0.96)	0.0058	1.14 (0.92, 1.41)	NS
Comorbidity								
AMI	1.19 (1.14, 1.24)	<0.0001	1.18 (1.13, 1.23)	<0.0001	1.12 (1.06, 1.18)	<0.0001	0.80 (0.67, 0.95)	0.0107
Cancer	0.93 (0.91, 0.96)	<0.0001	0.94 0.91, 0.97)	<0.0001	1.25 (1.20, 1.30)	<0.0001	0.94 (0.84, 1.05)	NS
CHF	1.23 1.19, 1.27)	<0.0001	5.76 (5.55, 5.97)	<0.0001	1.90 (1.82, 1.98)	<0.0001	1.43 (1.29, 1.60)	<0.0001
COPD	1.08 (1.05, 1.12)	<0.0001	1.29 (1.26, 1.33)	<0.0001	1.28 (1.23, 1.33)	<0.0001	0.70 (0.62, 0.78)	<0.0001
CVA/TIA	2.17 (2.11, 2.24)	<0.0001	1.07 (1.03, 1.10)	<0.0001	1.24 (1.20, 1.29)	<0.0001	0.79 (0.70, 0.89)	<0.0001
Diabetes	1.20 (1.16, 1.23)	<0.0001	1.36 (1.32, 1.40)	<0.0001	1.12 (1.08, 1.16)	<0.0001	1.64 (1.48, 1.82)	<0.0001
GI bleeding	1.05 (1.02, 1.09)	0.0051	1.07 (1.03, 1.11)	<0.0001	1.16 (1.11, 1.21)	<0.0001	0.90 (0.79, 1.03)	NS
Hypertension	1.16 (1.11, 1.21)	<0.0001	1.14 (1.09, 1.19)	<0.0001	0.75 (0.72. 0.79)	<0.0001	2.52 (2.04, 3.11)	<0.0001
Liver disease	0.99 (0.91, 1.08)	NS	0.99 (0.91, 1.08)	NS	1.28 (1.16, 1.41)	<0.0001	0.39 (0.26, 0.60)	<0.0001
PVD	2.47 (2.40, 2.54)	<0.0001	1.10 (1.07, 1.13)	<0.0001	1.13 (1.09, 1.17)	<0.0001	0.96 (0.86, 1.07)	NS

AMI: acute myocardial infarction; ASVD: atherosclerotic vascular disease; CHF: congestive heart failure; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CVA/TIA: cerebrovascular accident/transient ischemic attack; GI: gastrointestinal; HR: hazards ratio; NS: not statistically significant; PVD: peripheral vascular disease; RRT: renal replacement therapy.

[a]Events per patient-years at risk (rate per 1000 patient-years).

[b]The reference group has the following characteristics: no anemia, age 69 years, female gender, white race, and no comorbid conditions. A hazards ratio >1 means a greater probability of being associated with the outcome being studied than the reference category. A hazards ratio <1 means a lesser probability of being associated with the outcome being studied than the reference category.

epoetin arm [40]. The design of the latter study does not allow one to determine the relative contributions of higher erythrocyte mass and epoetin therapy *per se*.

The inverse association between hemoglobin levels and adverse outcome in this observational study does not imply causality, as declining hemoglobin levels could as easily be caused by illness, as vice versa. This study also has other limitations. This was a retrospective analysis and used claims to define the study subjects and their outcomes. Thus, CKD and anemia were not identified by a random process. Presumably, however, clinical events were a prerequisite to diagnosis in most subjects, and it is possible that these events account for some of the associations observed. The definitions of anemia and CKD were qualitative, being based on diagnostic codes. Approximately 1% of the Medicare population had a diagnosis, by claims, of CKD. Random sampling of the general population, using quantitative estimates of kidney function, suggests that the expected burden of CKD is at least one order of magnitude higher [41]. It is equally likely that the labels "chronic kidney disease" and "anemia" in this study mostly represent the moderate to severe end of the disease spectrum. In addition, the findings of this study can be generalized only to older CKD patients, as only subjects aged 67 years or more were studied.

Despite its limitations, we believe that this study has useful features. The sample size is relatively large. The results suggest that CKD patients with anemia are at increased risk of adverse outcomes. In most patients with CKD, anemia is a treatable condition; this study therefore advances a testable hypothesis, namely, that treating anemia is beneficial in patients with CKD. Randomized, controlled, clinical trials are needed to clearly the define the risks and benefits of anemia treatment in patients with CKD.

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