Anemia as a Predictor of Cardiovascular Events in Patients with Elevated Serum Creatinine

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Patients with anemia and patients with chronic kidney disease have elevated risks for cardiovascular disease. Available studies have been too small to provide details about the relationship or to provide for extensive covariate control. In a large insurance database with linked laboratory values, records of women with serum creatinine >1.2 mg/dl and men with serum creatinine >1.4 mg/dl, identified from July 2000 through June 2003, were sought, and the insurance claims searches for hospitalizations that were associated with myocardial infarction, coronary revascularization, unstable angina, stroke, or congestive heart failure. New onset of dialysis also was sought. Multivariate Poisson regression was used to estimate rate ratios for these events at various hemoglobin (Hb) levels, with adjustment for patient characteristics and previous event history. Among 88,657 patients with high serum creatinine, the risk for hospitalization with myocardial infarction was two to five times higher in anemic (Hb <12 g/dl) patients than in people with Hb from 12.0 to 12.9 g/dl. A similar but less dramatic pattern of higher incidence of coronary revascularization was observed with lower Hb levels. Risks for hospitalization with congestive heart failure declined regularly with increasing Hb levels from a doubling of risk at Hb <10 g/dl to a 61% decrease at 15 g/dl, both relative to 12.0 to 12.9 g/dl. The risk for progression to dialysis was only slightly elevated (7 to 34%) in anemic patients. Anemia raises the risk for cardiovascular disease in patients with elevated serum creatinine.

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Chronic anemia seems to increase the risk for coronary artery disease. Women but not men in the Framingham Heart Study with low hematocrit at baseline showed increased cardiovascular risk during 34 yr of follow-up (1). More recent studies with shorter follow-up have been more persuasive. Over 6 yr, men with hemoglobin (Hb) values <13 g/dl and women with values <12 g/dl in the Atherosclerosis Risk in Communities (ARIC) project experienced a 41% increase in cardiovascular disease, by comparison with men and women with higher levels of Hb (2). In the Studies of Left Ventricular Dysfunction (SOLVD), lower hematocrit was an independent risk factor for mortality among individuals with left ventricular dysfunction (3). Anemia may exercise its effects through the remodeling of cardiac muscle and atrial walls (4).

A total of 8.3 million adults in the United States have chronic kidney disease (CKD) (5). Anemia is a common complication of CKD (6). In elderly patients with congestive heart failure (CHF) in Canada, anemia and renal dysfunction were correlated, and each independently predicted subsequent mortality, the relation holding both for anemia of chronic disease and for anemia unrelated to chronic disease (7). That kidney disease by itself increases the risk for cardiovascular disease is well established by ARIC and other community studies (8–12). Despite the known associations of both CKD and anemia with cardiovascular disease and of CKD with anemia, the association between anemia and cardiovascular disease within a CKD population has not been documented. The purpose of this study was to explore the relationship between anemia and cardiovascular disease in a large cohort of individuals who had CKD that had not progressed to dialysis. Using a large health insurance claims database linked to laboratory values, we conducted a retrospective, longitudinal analysis to determine the incidence of a variety of cardiovascular events and treatments in relation to Hb levels in patients with elevated serum creatinine.

Materials and Methods

Data Source

The population for this study was drawn from claims and administrative databases of UnitedHealthcare, one of the largest health insurers in the United States. The insured individuals receive coverage for nearly all inpatient and outpatient medical services, as well as prescription drugs. The providers of these services submit their claims for payment directly to the health plan. Each medical claim is associated with one or more diagnoses, coded according to the *International Classification of Diseases, Ninth Revision*. The database contains medical, pharmacy, and laboratory results data for approximately 20 million current and past members from July 2000 through June 2003. The database includes results of laboratory tests that were performed by two large national laboratories, which provide approximately half of the outpatient tests that are performed for members of commercial health plans. The data that were accessed for this study previously had been stripped of protected health information.

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Study Population

The studied population consisted of all plan members with a recorded Hb value and a serum creatinine level of >1.2 mg/dl for women or 1.4 mg/dl for men, identified at any time from July 2000 through June 2003. Insurance claims evidence of hemolytic anemia, aplastic anemia, neoplasm (not including neoplasm of skin), traumatic amputation, parasitic disease, or gastrointestinal hemorrhage resulted in exclusion. Patients became eligible for follow-up as of the latest of January 1, 2001, the passage of 6 mo since joining the health plan (to allow assessment of baseline variables), or the first laboratory result that met criteria for elevated serum creatinine. Follow-up continued through the earliest of termination of health plan membership, blood transfusion, dialysis, kidney transplant, or June 30, 2003.

Hb Values

All patients had at least one known Hb level. In addition, the insurance claims data sometimes indicated that a Hb test had been performed, although it was not from one of the collaborating national laboratories whose results we had. Rather than simply ignore the data from other laboratories, we performed two analyses: One restricted to periods after a Hb test with known results and the other in which we imputed the results from noncollaborating laboratories, on the basis of a very wide range of preceding aspects of health care utilization. We did the imputation by regression, as follows. For each test from a larger population that included the patients with elevated creatinine, we identified a large number of patient characteristics that might predict Hb level. We grouped all diagnoses, procedures, and drugs that were identified within 30 d of a Hb test according to the mean Hb levels that were associated with each. Taking known Hb values as the dependent variable, we conducted an ordinary least squares regression including as predictor variables age; gender; closest known creatinine, HbA_{1c}, and Hb results; groups of diagnoses, drugs, and procedures; and each of the population's 100 most common diagnostic codes (grouped at the three-digit *International Classification of Diseases, Ninth Revision* level). A stepwise procedure using $P = 0.01$ was implemented to create the prediction equation.

Outcome Events

We calculated crude and adjusted incidence rates by Hb category for hospitalizations that were associated with myocardial infarction (MI), CHF, coronary revascularization, stroke, and unstable angina. Each event was identified *via* the occurrence of a corresponding diagnostic or procedure code during an inpatient hospital admission. When ≥7 d passed between a hospital discharge and a subsequent admission for the same type of event, the later event was considered to be newly occurring. New-onset dialysis was identified from both inpatient and outpatient claims and by definition could only occur once.

Person-Time and Incidence Rates

The unit of observation was an interval that began at the time of a Hb record (observed or imputed) and continued until the occurrence of a new Hb record or until follow-up ended. A single individual's recorded experience typically would contain several such intervals during the observation period. The crude rate of events (per 1000 person-years) was calculated within Hb category for each type of outcome event. Crude incidence rates additionally were calculated at distinct levels of each of the covariates that were included in the multivariate analysis described next.

We estimated adjusted incidence rates for each event type *via* Poisson regression, which is a multivariate technique that assesses and adjusts for the influence of covariates on event occurrence and accounts for differing lengths of follow-up. Covariates included age categories, gender, an indicator representing whether the Hb result was observed or imputed, an indicator representing diabetes (defined by a diagnosis code for diabetes or dispensing of an antidiabetic medication at any time during follow-up), concurrent laboratory values, indicators for selected baseline characteristics, and indicators representing a previous cardiovascular event. Baseline characteristics were determined during the 6-mo interval that preceded cohort entry and included any claims evidence of the following: Lipid metabolism disorder, hypertension, nicotine addiction, cardiac dysrhythmia, and insulin dispensing. We included as a predictor attached to each interval the occurrence of similar events in the past. HbA_{1c} level and an indicator for serum creatinine level of ≥2.0 mg/dl within 90 d of the Hb interval start, plus indicators for missing values, were included to provide measurements of diabetic control and renal function that were time-linked to the Hb intervals. We accounted for within-patient correlations between intervals using generalized estimating equations, with robust standard errors for the Poisson regression used. To assess whether the imputation of unavailable Hb values affected the results, we performed all of the reported analyses in the subset of observation periods for which we had Hb results, and we compared the findings with those from the full data.

Results

Cohort Characteristics

A total of 88,657 people had one or more recorded Hb values, a qualifying creatinine level, and the absence of any of the excluded diagnoses or procedures. Table 1 presents baseline characteristics for the cohort members, separated out by average Hb level during observation. The cohort was 64% female, and the mean age at cohort entry was 58.0 yr (SD 14.5). Nearly 20% of the cohort also had diabetes. During the 6 mo before study entry, 17 and 39% had medical claims evidence of a lipid metabolism disorder and hypertension, respectively. One, 7, and 3%, respectively, had claims evidence of a nicotine addiction, cardiac dysrhythmia, and insulin dispensing during this 6-mo baseline period. Older patients tended to predominate among patients with lower Hb levels, as did patients with diabetes (especially insulin-dependent diabetes) and those with hypertension and cardiac rhythm disorders. Sixty-nine percent of the Hb intervals were based on recorded Hb results, whereas the remainder were based on imputed values. Nearly 5000 Hb intervals were among individuals who had one or more previous cardiovascular events since their initiation of follow-up.

Hb

The mean observed Hb value over 120,195 records in 88,657 patients was 13.5 g/dl (SD 1.6). Among these patients with at least one recorded Hb value, 53,870 (31%) tests lacked an available result, so the results for these tests were imputed. The R^2 of the prediction equation that was constructed to impute unknown Hb results was 0.46. The total of 174,065 tests characterized 67,852 patient-years in the database, giving an average of 4.7 mo of follow-up between tests.

Unadjusted Incidence

Table 2 presents the unadjusted incidence rates for each cardiovascular outcome and dialysis within categories of each of the baseline patient characteristics listed in Table 1, plus each

Table 1. Characteristics of the study population[a]

Patient Characteristics	Mean Observed Hb Level							
	<10.0	10.0 to 10.9	11.0 to 11.9	12.0 to 12.9	13.0 to 13.9	14.0 to 14.9	15.0+	Total
No. of patients	1398	2908	7599	16,989	24,473	19,974	15,316	88,657
Age at cohort entry (yr; %)								
<15	0.9	1.0	0.8	0.4	0.3	0.1	0.1	0.3
15 to 24	0.7	0.8	0.7	0.6	0.6	0.6	1.0	0.7
25 to 34	3.2	3.2	2.9	2.9	3.0	2.9	4.1	3.2
35 to 44	12.7	13.2	12.8	14.2	14.3	14.3	16.7	14.5
45 to 54	19.8	16.7	18.7	21.2	22.2	24.1	26.3	22.6
55 to 64	18.7	20.3	22.7	24.8	28.0	30.6	30.1	27.5
65 to 74	17.4	16.8	17.8	17.3	17.5	16.7	14.6	16.8
75+	26.7	28.1	23.6	18.5	14.1	10.8	7.2	14.5
Gender (%)								
female	71.2	77.1	81.5	84.0	78.0	53.7	20.3	63.9
male	28.8	22.9	18.5	16.0	22.0	46.3	79.8	36.2
Diabetes (%)	35.8	35.1	29.3	22.2	17.3	16.5	15.5	19.6
Baseline evidence of (%)								
lipid metabolism disorder	18.7	19.2	18.1	17.1	16.7	17.0	15.8	16.9
hypertension	60.8	58.9	52.7	42.7	36.1	34.0	32.7	38.9
nicotine addiction	1.0	1.5	1.1	0.9	1.1	1.3	1.3	1.2
cardiac dysrhythmia	15.6	13.2	10.3	7.1	5.7	5.4	5.5	6.7
insulin	11.9	10.3	6.6	3.7	2.1	1.8	1.4	3.0

[a]Hb, hemoglobin.

of the time-varying characteristics identified. Because many of the characteristics are dependent on age and are related to one another even for people of a given age, the values in Table 2 should be interpreted only as a general description of how events occur. For each, there was a decreasing trend with increasing Hb. This inverse relationship was greatest for MI, CHF, and new-onset dialysis. There was a general trend of increasing incidence with increasing age, and men exhibited higher incidence rates than women for each outcome. There was a regular tendency for Hb intervals that were initiated by an imputed result to have a much higher associated risk than intervals with a known result. All of the selected baseline characteristics and previous occurrence of a cardiovascular event during follow-up were associated with higher crude incidence rates.

Multivariate Adjustment

Table 3 presents fully adjusted incidence rate ratio estimates for each cardiovascular outcome and dialysis, according to Hb level, with adjustment for all of the factors listed in Table 2. There is strong evidence of increased incidence of MI during periods for which Hb levels were <12 g/dl, with a five-fold elevation in incidence at the lowest levels of Hb. Hb groups >12 g/dl showed little variation in the associated MI incidence rate. Rates of coronary revascularization showed a similar but less dramatic pattern, with elevations <12 g/dl and no variation above that level. Hospitalizations with CHF, by contrast, decreased regularly with increasing Hb. The rates of hospitalization with stroke or unstable angina varied little across the various Hb levels. The covariate adjustment in Table 3 essentially eliminates the apparent association between Hb levels and the incidence of new-onset dialysis seen in Table 2. The effect is due almost entirely to a strong correlation between low Hb and high creatinine, which was, as expected, a potent predictor of patients who started on dialysis. An analysis that omitted all intervals with imputed Hb values produced results that were qualitatively identical to those reported in Table 3.

Discussion

Among patients with elevated serum creatinine, the risk for hospitalization with MI was five times higher in very anemic patients than in people with normal Hb levels. Coronary revascularization showed a similar but less dramatic pattern of higher risk with lower Hb levels. Risks for hospitalization with CHF declined regularly with increasing Hb levels.

Demographic and health characteristics of patients all followed the anticipated patterns in their relation to risks for the various outcome events. Risks increased with age, were higher in men than in women, and were higher in each of the groups that were flagged at the onset of the study as having an expected higher risk for cardiovascular events. These were patients with diabetes, lipid elevations, hypertension, nicotine addiction, previous dysrhythmias, and previous occurrence of each of the outcome events. Notably, the risk relations that were associated with previous events were relatively specific, in that the risk gradient for MI was greatest in relation to previous MI, for CHF in relation to previous CHF, for stroke in

Table 2. Crude event incidence rates in relation to population characteristics[a]

	Rate per 1000 Person-Years						Person-Years
	MI (n = 341)	CHF (n = 436)	Coronary Revascularization (n = 469)	Stroke (n = 272)	Unstable Angina (n = 418)	Dialysis (n = 972)	
Hb level							
<10.0	27.14	23.27	11.63	5.82	5.82	257.87	515.77
10.0 to 10.9	9.99	19.27	13.56	9.28	13.56	99.19	1401.29
11.0 to 11.9	9.62	14.66	8.53	6.34	7.00	36.53	4571.64
12.0 to 12.9	5.17	8.78	6.83	4.88	5.91	10.85	17,419.84
13.0 to 13.9	4.63	6.12	7.94	3.30	7.40	9.80	18,775.83
14.0 to 14.9	3.98	2.88	5.83	3.57	5.15	6.66	14,569.48
15+	3.21	1.89	4.91	2.64	4.43	5.95	10,597.97
Age at cohort entry							
<15	0.00	0.00	0.00	0.00	0.00	21.21	235.71
15 to 24	0.00	0.00	0.00	0.00	0.00	22.97	478.94
25 to 34	0.45	0.90	0.45	0.45	0.00	25.98	2232.53
35 to 44	0.65	1.30	0.47	0.56	1.21	12.19	10,747.59
45 to 54	2.80	2.86	2.86	1.58	3.47	14.20	16,408.67
55 to 64	4.13	5.87	7.93	2.51	7.82	15.31	17,898.26
65 to 74	7.87	9.15	13.64	6.04	9.80	13.00	10,923.35
75+	14.23	18.82	14.00	14.34	11.31	13.22	8926.77
Gender							
female	3.78	5.57	4.01	3.74	4.58	10.06	44,141.56
male	7.34	8.01	12.32	4.51	9.11	22.27	23,710.28
Hb value							
observed	2.82	3.54	3.99	2.71	3.51	11.20	54,179.69
imputed	13.75	17.85	18.50	9.14	16.68	26.70	13,672.15
Diabetes							
no	3.90	3.89	5.13	3.27	4.51	10.70	56,352.29
yes	10.52	18.87	15.65	7.65	14.26	32.09	11,499.54
Lipid metabolism disorder							
no	4.48	5.61	5.21	3.83	4.72	13.92	57,416.47
yes	8.05	10.92	16.29	4.98	14.09	16.58	10,435.36
Hypertension							
no	3.21	3.35	3.94	2.53	3.67	8.89	43,884.51
yes	8.34	12.06	12.35	6.72	10.72	24.28	23,967.32
Insulin							
no	4.79	5.73	6.54	3.70	5.85	12.16	66,174.38
yes	14.31	33.98	21.46	16.10	18.48	99.56	1677.45
Nicotine addiction							
no	4.93	6.34	6.72	3.95	5.96	14.25	67,077.80
yes	12.92	14.21	23.26	9.04	23.26	20.67	774.03
Cardiac dysrhythmia							
no	4.42	4.62	5.62	3.40	5.67	13.02	64,054.63
yes	15.27	36.87	28.71	14.22	14.48	36.34	3797.20
High HbA_{1c} (8.0+)							
no	8.92	11.23	13.21	9.58	16.18	28.73	3,028.22
yes	6.97	22.08	19.75	8.13	15.10	16.27	860.67
missing	4.82	5.99	6.44	3.69	5.57	13.62	63,962.94
High creatinine (2.0+)							
no	3.87	4.95	5.88	3.51	5.48	5.00	54,971.46
yes	15.91	24.69	13.17	8.78	9.88	320.46	1822.36
missing	8.95	10.76	11.03	5.70	8.95	10.22	11,058.01

Table 2. Continued

	Rate per 1000 Person-Years						Person-Years
	MI ($n = 341$)	CHF ($n = 436$)	Coronary Revascularization ($n = 469$)	Stroke ($n = 272$)	Unstable Angina ($n = 418$)	Dialysis ($n = 972$)	
Previous MI							
no	4.76	6.22	6.70	3.93	5.97	14.31	67,659.97
yes	99.03	78.18	83.39	31.27	72.97	20.85	191.86
Previous CHF							
no	4.93	6.21	6.88	4.02	6.08	14.29	67,603.73
yes	32.25	64.49	16.12	0.00	28.21	24.18	248.10
Previous coronary revascularization							
no	4.99	6.26	6.56	3.95	5.95	14.33	67,556.21
yes	13.53	43.98	87.95	16.91	54.12	13.53	295.62
Previous stroke							
no	5.02	6.38	6.88	3.93	6.13	14.32	67,687.66
yes	6.09	24.37	18.27	36.55	18.27	18.27	164.17
Previous unstable angina							
no	4.99	6.29	6.57	4.01	5.83	14.25	67,581.14
yes	14.78	40.64	92.36	3.69	88.66	33.25	270.69

[a]CHF, congestive heart failure; MI, myocardial infarction.

relation to previous stroke, and for unstable angina in relation to previous unstable angina. The regularity with which all of the expected epidemiologic relations have been reproduced in these data provides substantial assurance that events and risk factors have been captured and documented adequately.

Although it was not possible to separate out an anemia of chronic disease in these data *per se*, the ability to identify and control for the effects of all chronic illnesses that require regular medical attention, inherent in insurance claims data, provides some assurance that the effects seen are not the product of concomitant identifiable poor health. Because the commercially insured population does not include recipients of Medicare, the proportion of individuals who were older than 65 yr in the source data was small, and the results may not be generalizable to older patients. The relatively young age of the study population also resulted in a lower prevalence of chronic illness of all forms than among people with CKD in the general US population.

The risks for stroke, unstable angina, and dialysis were unrelated to Hb levels. Unstable angina is less reliably coded in insurance claims than is MI, because the key features of the diagnosis are based on patient history rather than objective criteria. Misclassification of unstable angina may have led to an underestimation of the true association with Hb levels. The absence of association between anemia and either stroke or new-onset dialysis probably is a more reliable negative finding.

We estimated GFR in the study population on the basis of the available serum creatinine values, using the Modification of Diet in Renal Disease formula (13). All but 0.1% of patients in this study had a GFR of <60 ml/min. A single elevated creatinine level does not reliably indicate CKD, and it is probable that the study population includes some people with transient

Table 3. Adjusted relative incidence rates in relation to Hb level[a]

Hb Level	MI		CHF		Coronary Revascularization		Stroke		Unstable Angina		New-Onset Dialysis	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
<10.0	5.23	2.78 to 9.83	1.99	1.09 to 3.62	1.63	0.71 to 3.77	0.98	0.31 to 3.12	1.07	0.34 to 3.38	1.34	1.01 to 1.80
10.0 to 10.9	1.80	1.01 to 3.20	1.51	0.99 to 2.32	1.64	1.00 to 2.68	1.48	0.80 to 2.74	1.96	1.15 to 3.33	1.11	0.85 to 1.45
11.0 to 11.9	2.00	1.34 to 2.98	1.44	1.06 to 1.94	1.14	0.78 to 1.66	1.24	0.80 to 1.93	1.18	0.78 to 1.78	1.07	0.83 to 1.38
12.0 to 12.9	Reference group		Reference group		Reference group		Reference group		Reference group		Reference group	
13.0 to 13.9	0.93	0.65 to 1.35	0.71	0.54 to 0.93	0.85	0.64 to 1.12	0.92	0.62 to 1.35	1.35	1.00 to 1.83	1.10	0.85 to 1.44
14.0 to 14.9	1.23	0.82 to 1.86	0.50	0.34 to 0.73	0.86	0.61 to 1.20	1.43	0.91 to 2.24	1.30	0.89 to 1.90	0.75	0.52 to 1.09
15+	1.18	0.72 to 1.94	0.39	0.23 to 0.65	0.79	0.52 to 1.20	1.32	0.74 to 2.36	1.33	0.83 to 2.11	0.72	0.46 to 1.11

[a]All incidence rate ratios are adjusted for all the covariates listed in Table 2. CI, confidence interval; IRR, incidence rate ratio.

creatinine elevations. If the relationship between anemia and cardiovascular risk is present only in people with CKD, then these patients without CKD will have attenuated the apparent risk gradients. If the finding is not specific to CKD, then the results are unaffected by this misclassification.

Although the study findings held completely when the analysis was restricted to intervals that were characterized by a known rather than an imputed Hb level, the high risk that is associated with imputed intervals deserves comment. The availability of laboratory results is linked to the use of two large national clinical laboratory services. We believe that the values that are not captured more often will be those that are done in hospital-based laboratories, whereas those that are captured will tend to be routine outpatient tests. Therefore, it may be that the missing values are selectively associated with emergency clinic care that is provided in large facilities and mark periods of higher risk for a variety of events. We adjusted for this tendency in the multivariate analysis and confirmed the findings in the analysis that omits intervals with imputed values.

It is a truism of observational studies that correlations do not demonstrate causality, and the reservations should be doubly valid when the key exposure assessment is done not per protocol but only at the request of a treating physician who is responding to a patient's health needs. Nonetheless, the opportunity to control for the distorting influence of many patient factors in this study, the ability to address "reverse causality" by assessing and controlling for previous occurrence of any of the outcome events, and the closeness of the result to the outcome patterns seen in smaller studies all combine to provide substantial evidence that an empirical relationship exists between cardiovascular pathology and anemia among patients with elevated creatinine and that the relationship is not simply the byproduct of other, widely known risk relations.

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S.R. and D.P. were employed by Amgen during the study. The study, however, is focused entirely on disease epidemiology and does not discuss any drugs produced by Amgen or any other pharmaceutical company.

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