

Impact of Anemia on Hospitalization Rates and Costs in a Diabetic and a Hypertensive Cohort of Chronic Kidney Disease Patients

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Summary

Diabetes and hypertension are the two major causes of chronic kidney disease (CKD) and the associated anemia. To quantify the economic burden of anemia in a diabetic and a hypertensive cohort, the current study evaluated the impact of untreated anemia on hospitalization rates and costs in CKD patients. Anemia of CKD was associated with statistically significant increased risk of hospitalization, which translated into significant inpatient cost burden in patients with diabetes or hypertension. Both univariate and multivariate analyses confirmed the study findings.

- Diabetes or hypertension is found to be present in more than 70 percent of patients who begin therapy for end-stage renal disease.
- CKD and the associated anemia, secondary to diabetes or hypertension, are on the rise primarily caused by the aging population and increase in obesity.
- Both unadjusted and adjusted results consistently indicated that anemia was associated with significant increases in hospitalization rates and costs compared to non-anemia.
- Cardiovascular disease-related hospitalizations were important drivers of the cost difference, with adjusted cost increases associated with anemia of 65 percent and 68 percent compared to non-anemia for the diabetic and/or the hypertensive cohorts, respectively.
- These results highlight the economic as well as clinical importance of early CKD-related anemia detection.

INTRODUCTION

Diabetes and hypertension are the two major causes of end-stage renal disease (ESRD – chronic kidney disease (CKD) stage 5 requiring dialysis).¹ In most Western countries, diabetes accounts for 40 to 50 percent of incident ESRD cases.² When combined with hypertension, one or both these conditions are found to be present in more than 70 percent of patients who initiate ESRD therapy.¹ Due to the increasing prevalence of diabetes and hypertension, primarily caused by the aging population and increase in obesity, rates of kidney disease secondary to these two conditions are on the rise.^{3,4} Within the past two decades, the incidence of ESRD secondary to diabetes in the United States has doubled while the prevalence of CKD (stages 1 to 4) among general Medicare patients diagnosed with both diabetes and hypertension has increased fourfold.²

Anemia is a common complication of CKD. It results from the inability of the diseased kidneys to produce an adequate amount of erythropoietin, a hormone that regulates the production of red blood cells. Anemia of CKD, defined as hemoglobin (Hb) <11 g/dL according to the National Kidney Foundation,⁵ becomes increasingly prevalent as kidney function declines.⁶⁻⁸ There is a growing body of literature establishing the complex association between anemia, renal disease, and cardiac disease, also known as the cardio-renal-anemia syndrome.⁹⁻¹¹ Numerous studies have shown that anemia of CKD is associated with cardiovascular and renal complications, resulting in increased hospitalizations and mortality.¹²⁻¹⁸ Throughout 1980 to 2005, approximately 10 million hospitalizations had kidney disease listed as a diagnosis.¹⁹ The annual number of hospitalizations with a recorded diagnosis of kidney

disease quadrupled during this period, from approximately 416,000 in 1980 to 1,646,000 in 2005.¹⁹ An increasing number of kidney disease hospital discharges are associated with a concomitant diagnosis of diabetes mellitus or hypertension.¹⁹

Cardiovascular diseases (CVDs) are the leading cause of mortality in the United States and their societal cost for 2007 was estimated at \$431.8 billion, including \$283.2 billion in direct health expenditures and \$148.6 billion in indirect lost productivity.²⁰ Between 1979 and 2004, the number of CVD-related inpatient discharges from short-stay hospitals increased by 30 percent to approximately 6.4 million discharges, ranking highest among all disease categories in hospital discharges.²⁰

CKD and the associated anemia, secondary to diabetes and/or hypertension, are on the rise. The related medical costs due to hospitalizations and adverse CVD events represent a significant economic burden. Consequently, this topic has gained increasing awareness. However, to the best of our knowledge, the impact of CKD-related anemia on hospitalization rates and costs has not been documented from a managed care population perspective in patients with diabetes and/or hypertension. The purpose of this study was to investigate whether anemia is associated with increased risks and costs of hospitalization in a diabetic and a hypertensive cohort of CKD patients.

PATIENTS AND METHODS

Data Source

Health claims and laboratory data from the Ingenix Impact National Managed Care (IMPACT) database between January 2000 and February 2006 were used to conduct the analysis. This large national database was designed to support benchmarking projects, health care outcomes research, and other research initiatives. In order to create the IMPACT database, Ingenix compiles data from a large number of health plans and places significant emphasis on the quality of the data. As part of this process, Ingenix utilizes a series of data evaluation and reconciliation steps to ensure the completeness, validity, and consistency of the data. Ingenix also standardizes the information across contributing health plans, which is critical for creating valid benchmarks.

The IMPACT database includes complete medical and pharmacy claims for more than 25 million managed care lives from over 35 health care plans, covering all census regions of the United States. Data elements used in the present analysis included enrollment records, patient demographics, inpatient and outpatient medical services, and laboratory re-

sults. Laboratory results are available for the subset of patients tested within a given carrier's laboratory network, representing approximately 10 percent of the IMPACT population.

Data included in the IMPACT database are completely de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) in order to preserve patients' confidentiality.

Study Design

A retrospective open-cohort design was employed to classify patients' observation periods into anemia (Hb <11 g/dL) and non-anemia based on their observed Hb values. The open-cohort approach was used to allow a patient's anemia status to change over time (Exhibit 1), as observed in actual patient experience.

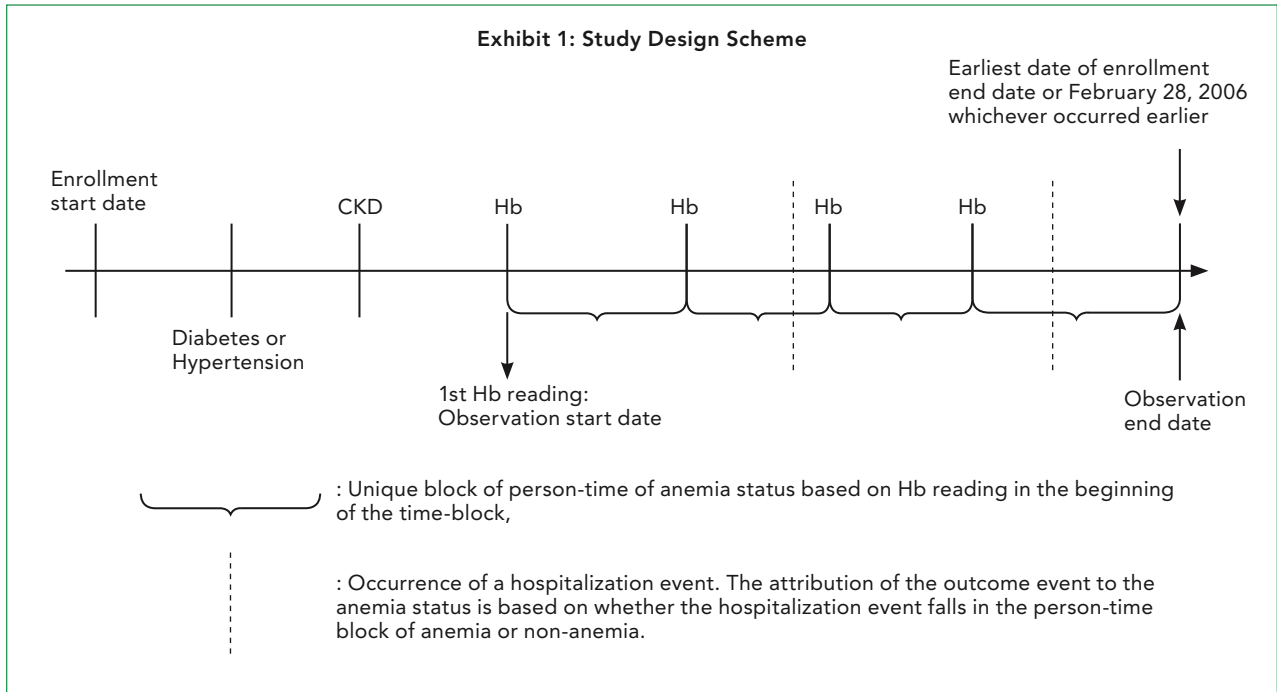
Patients with continuous health plan coverage and with ≥ 2 claims for diabetes (International Classification of Diseases 9th revision (ICD-9) codes: 250; diabetic cohort) or ≥ 2 claims for hypertension (ICD-9: 401 to 405; hypertensive cohort) within a 90-day period were included in the study. In addition, patients were required to have their first claim for CKD (ICD-9: 250.4, 585, 586, 588, 403, and 404) following diabetes or hypertension diagnosis, ≥ 2 estimated glomerular filtration rate (eGFR) value <60 mL/min/1.73 m², and ≥ 2 Hb readings. Patients with both diabetes and hypertension prior to the onset of CKD contributed to each cohort of our study and adjustments were made for the presence of both conditions in the multivariate analysis. Finally, at least 90 days of observation were imposed prior to the first diabetes or hypertension diagnosis (baseline period for patients' characteristics evaluation).

Patients with cancer or lupus, who had received organ transplantation or chemotherapy or who were treated for anemia with blood transfusion or erythropoiesis stimulating agents (ESAs), were excluded. Patients were observed starting on the index date, i.e. the first Hb reading following CKD diagnosis, and ending at the enrollment end date or the defined study end date of February 28, 2006, whichever occurred earlier.

Definition of Anemia

Patients' observation periods of anemia and non-anemia were determined based on laboratory Hb values and were formulated as a dichotomous variable. Anemia was defined as Hb <11 g/dL, the lower limit for treatment recommended by The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) guide-

Exhibit 1: Study Design Scheme



lines.5 Patients' observations were assigned to each group (anemia versus non-anemia) based on their subsequent Hb readings after the index date reading (Exhibit 1).

Definition of CKD based on eGFR

Estimated glomerular filtration rate values were calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated equation,²¹ based on serum creatinine value, age, gender, and ethnicity:

$$eGFR = 186(SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African-American})$$

where SCr = serum creatinine value. Because the patient ethnicity variable was not available in the database, non-African American race was assumed in the eGFR calculation. Chronic kidney disease was defined as an eGFR value <60 mL/min/1.73 m² (i.e., stages 3 to 5).

Statistical Analysis

Both univariate and multivariate analyses were conducted to compare the incidence rates of hospitalization and the corresponding costs by anemia status. Two definitions for hospitalization were used: (1) all hospitalization events (number of inpatient visits or services) and (2) first hospitalization event (censored observation at the first event). In addition, hospitalizations were stratified into: (i) any kind of hospitalization and (ii) CVD-related hospitalizations, defined as any one of the following admitting diagnoses: acute myocardial infarction

(AMI – ICD-9: 410 to 412), angina (ICD-9: 413), cardiac arrest (ICD-9: 427.5), cardiac arrhythmia (ICD-9: 427 (excluding 427.5), 785.0, and 785.1), congestive heart failure (ICD-9: 428), coronary artery disease (ICD-9: 414), stroke (ICD-9: 430 to 437), and left ventricular hypertrophy (LVH – ICD-9: 429.3 and 402.9).

Descriptive statistics were used to compare periods of anemia and non-anemia for incidence rates of hospitalization (number of events divided by the person-years of observation). Incidence rate difference (IRD), defined as the difference between the incidence rates of anemia and non-anemia, and incidence rate ratio (IRR), defined as the incidence rate during anemia periods divided by the incidence rate during non-anemia periods, were used for the univariate analysis. For the cost analysis, the incremental yearly hospitalization cost of anemia relative to non-anemia was calculated using cost difference and cost ratio metrics.

Multivariate regression analyses also were used to isolate the impact of anemia relative to non-anemia on the risk of hospitalization by adjusting for differences in patient characteristics and observation periods. The covariates for adjustment in the multivariate regression models included age, gender, eGFR value at baseline, previous hospitalization related to CVDs, presence of concomitant hypertension [for diabetes cohort] or presence of concomitant diabetes [for hypertension cohort], AMI, angina, cardiac arrhythmia, congestive heart failure, coronary artery disease, stroke, and LVH. The adjusted risk of

hospitalization associated with anemia was estimated using Poisson regression models to account for the person-time design and to appropriately model the outcome variable (hospitalization events). This model offsets observation duration by weighting subjects by how long they were observed.

Multivariate analyses also were conducted to adjust for potential confounding factors in estimating the incremental cost burden of anemia. Because of the non-normality of the inpatient cost outcome variables, which are truncated at zero and positively skewed, a Tobit regression model was used to estimate the adjusted incremental costs of anemia using the same covariates as previously defined.

A two-sided alpha error of 0.05 was used to declare statistical significance. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Characteristics of the Study Populations

A total of 708 diabetic and 1,889 hypertensive patients with CKD met the entry criteria and formed the study populations. Exhibit 2 presents the baseline characteristics of the study populations. Mean age was 65.0 and 65.3 years for the diabetic and the hypertensive cohorts, and women represented 43.6 and 44.4 percent, respectively. On average, patients were observed 2.5 years in the diabetic group (anemia period: 0.8 year; non-anemia periods:

2.3 years) and 2.6 years in the hypertensive group (anemia period: 0.8 year; non-anemia periods: 2.5 years), respectively.

Hypertension at baseline was common among the diabetic population (59.7 percent), while fewer hypertensive patients had a diagnosis of diabetes (35.0 percent). In the two groups, the most predominant cardiovascular medical histories were coronary artery disease (diabetic: 27.0 percent; hypertensive: 23.9 percent), cardiac arrhythmia (diabetic: 16.9 percent; hypertensive: 16.5 percent), and congestive heart failure (diabetic: 14.7 percent; hypertensive: 11.8 percent).

Unadjusted Incidence Rates of Hospitalization

Unadjusted incidence rates of hospitalization between the anemia and non-anemia periods are reported in Exhibit 3. In both populations, anemia was associated with a significant increase in hospitalization rates. The incidence rates of any hospitalizations for diabetic patients were 139.4 and 55.2 per 100 person-years of observation for periods of anemia and non-anemia, respectively (IRD: 84.2, IRR: 2.53, 95 percent CI: 2.20 to 2.90, $p < .001$). For hypertensive patients, the incidence rates of any hospitalizations were 150.8 and 51.0 per 100 person-years for periods of anemia and non-anemia, respectively (IRD: 99.8, IRR: 2.96, 95 percent CI: 2.70 to 3.23, $p < .001$). When considering only the first hospitalization, anemia increased the risk of hospi-

Exhibit 2: Baseline Characteristics of the Study Population

VARIABLE	DIABETIC Cohort (N=708)	HYPERTENSIVE Cohort (N=1,889)
Women, n (%)	309 (43.6)	838 (44.4)
Age, year, mean (SD)	65.0 (10.9)	65.3 (11.6)
Health plan eligibility period, years, mean (SD)	2.5 (1.3)	2.6 (1.3)
Mean duration of non-anemia observation periods per patient	2.3 (1.3)	2.5 (1.3)
Mean duration of anemia observation periods per patient	0.8 (0.8)	0.8 (0.8)
Baseline eGFR, mL/min/1.73m ² , mean (SD)	47.0 (13.7)	45.7 (13.6)
Cardiovascular medical history [†] , n (%)		
Acute Myocardial Infarction	65 (9.2)	156 (8.3)
Angina	45 (6.4)	108 (5.7)
Cardiac Arrest	0 (0.0)	1 (0.1)
Cardiac Arrhythmia	120 (16.9)	311 (16.5)
Congestive Heart Failure	104 (14.7)	223 (11.8)
Coronary Artery Disease	191 (27.0)	452 (23.9)
Left Ventricular Hypertrophy	48 (6.8)	126 (6.7)
Stroke	59 (8.3)	156 (8.3)
Previous CVD-related hospitalizations [†] , n (%)	74 (10.5)	213 (11.3)
Medical history of hypertension [†] , n (%)	423 (59.7)	n/a
Medical history of diabetes [†] , n (%)	n/a	662 (35.0)

[†] Based on a 180-day period prior to baseline.

Abbreviations: SD=standard deviation; eGFR=estimated glomerular filtration rate; CVD-cardiovascular disease

Exhibit 3: Unadjusted Impact of Anemia on Hospitalization Rate

DIABETIC COHORT

	Incidence Rate (# of events per 100 person-years)		Univariate Analysis			
	Anemia	Non-Anemia	IRD	IRR	95% CI	p-value
All Services						
Any hospitalization	139.4	55.2	84.2	2.53	(2.20 - 2.90)	<0.001
CVD-related hospitalizations	77.8	31.8	46.1	2.45	(2.03 - 2.95)	<0.001
First Event						
Any hospitalization	63.3	30.0	33.3	2.11	(1.64-2.71)	<0.001
CVD-related hospitalizations	37.4	16.9	20.5	2.21	(1.63-3.01)	<0.001

HYPERTENSIVE COHORT

	Incidence Rate (# of events per 100 person-years)		Univariate Analysis			
	Anemia	Non-Anemia	IRD	IRR	95% CI	p-value
All Services						
Any hospitalization	150.8	51.0	99.8	2.96	(2.70-3.23)	<0.001
CVD-related hospitalizations	78.8	27.2	51.6	2.90	(2.56-3.28)	<0.001
First Event						
Any hospitalization	68.8	26.7	42.1	2.58	(2.18-3.04)	<0.001
CVD-related hospitalizations	36.7	13.9	22.8	2.65	(2.15-3.26)	<0.001

Abbreviations: IRD=incidence rate difference; IRR=incidence rate ratio; CI=confidence interval; CVD=cardiovascular disease

talization in diabetic and hypertensive patients by 2.11 times (95 percent CI: 1.64 to 2.71, p<.001) and 2.58 times (95 percent CI: 2.18 to 3.04, p<.001) respectively compared to non-anemia.

The majority of hospitalizations were CVD-related, with anemia increasing the risk of CVD-related hospitalizations and first CVD hospitalization in diabetic patients by 2.45 times (95 percent CI: 2.03 to 2.95, p<.001) and 2.21 times (95 percent CI: 1.63 to 3.01, p<.001), respectively compared to non-anemia. Similarly, in patients with hypertension, the risk of CVD-related hospitalizations and first CVD hospitalization during anemia periods was increased by 2.90 times (95 percent CI: 2.56 to 3.28, p<.001) and 2.65 times (95 percent CI: 2.15 to 3.26, p<.001), respectively.

Adjusted Incidence Rate of Hospitalization

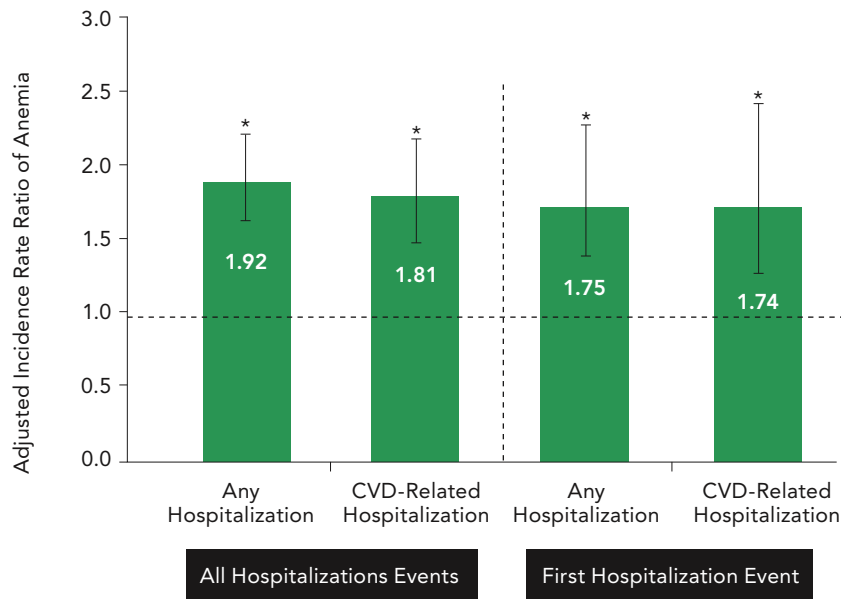
After controlling for covariates and duration of observation period, anemia was still associated with significantly higher adjusted risk of hospitalization for both the diabetic and the hypertensive cohorts (Exhibits 4a and 4b). Anemia increased the risk of any hospitalizations and first hospitalizations by approximately two fold compared to non-anemia (ad-

justed IRR - diabetic: 1.92, 95 percent CI: 1.66 to 2.23, p<.001 and 1.75, 95 percent CI: 1.34 to 2.30, p<.001; hypertensive: 2.14, 95 percent CI: 1.95 to 2.36, p<.001 and 2.00, 95 percent CI: 1.68 to 2.38, p<.001). Similar results were observed when considering the adjusted risk of CVD-related hospitalizations between anemia and non-anemia periods. Higher age, lower baseline eGFR value, and baseline history of CVD-related hospitalization, hypertension, or diabetes, coronary artery disease, congestive heart failure, and cardiac arrhythmia also were positively statistically associated with increased risk of hospitalizations.

Hospitalization Cost Burden Associated with Anemia

Unadjusted inpatient cost differences between anemia and non-anemia periods are reported in Exhibit 5. The higher incidence rate of hospitalization associated with anemia translated in higher inpatient costs: the unadjusted yearly hospitalization cost differences between periods of anemia and non-anemia were respectively \$17,072 and \$16,441 for the diabetic and hypertensive cohorts (diabetic: \$25,342 vs. \$8,270, p<.0001; hypertensive: \$23,694 vs. \$7,253,

Exhibit 4a
Multivariate Analysis: Adjusted Impact of Anemia on Hospitalization Rate in Diabetic Patients¹



Notes:

¹ Covariates for adjustment were: age, gender, baseline eGFR value, previous CVD-related hospitalization, and medical history of hypertension, AMI, angina, cardiac arrhythmia, congestive heart failure, coronary artery disease, stroke, and LVH.

*Indicates that the incidence rate ratio was statistically significantly different from 1.0 at p<.001. Error bars represent 95% confidence limits.

p<.0001). The corresponding cost ratios of anemia versus non-anemia for the diabetic and hypertensive cohorts were 3.1 and 3.3 respectively. When considering only CVD-related hospitalizations, anemia was associated with inpatient cost increase of \$8,647 in diabetic patients and \$8,426 in hypertensive patients (diabetic: \$13,723 vs. \$5,076, p<.0001; hypertensive: \$12,657 vs. \$4,231, p<.0001).

After controlling for covariates, the adjusted cost ratios of anemia versus non-anemia were less pronounced but remained statistically significant for both the diabetic and the hypertensive cohorts (any hospitalizations - diabetic: 2.0, p<.001; hypertensive: 2.1, p<.001; CVD-related hospitalizations - diabetic: 1.6, p=0.038, hypertensive: 1.7, p=0.002; Exhibit 7).

Discussion

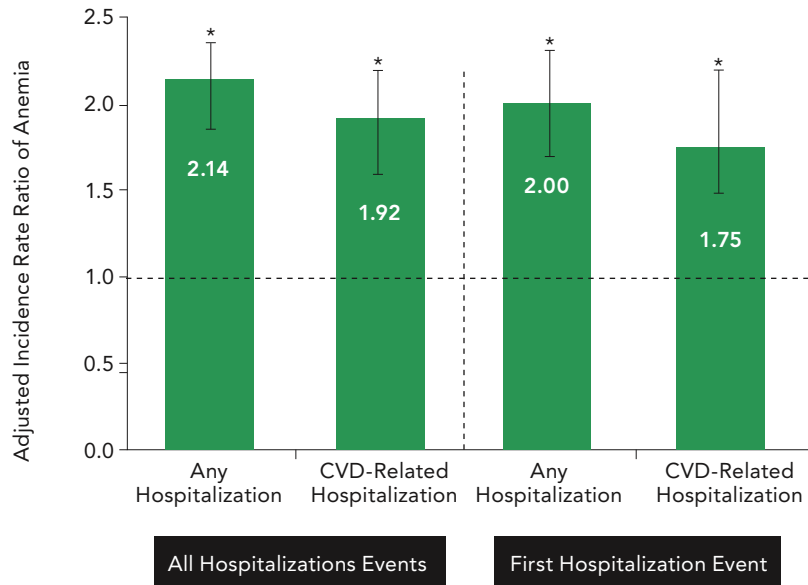
We conducted this retrospective study to assess the hospitalization rates and cost burden associated with anemia in CKD patients who were diabetic and/or hypertensive. The analysis was based on administrative medical claims data coupled with laboratory results. During the period from January 2000 to February 2006, a total of 708 diabetic and 1,889 hypertensive patients developing CKD were studied. Both unadjusted and adjusted results consistently indicated that anemia was associated with

significant increases in hospitalization rates and costs compared to non-anemia. Cardiovascular disease-related hospitalizations were important drivers of the cost difference, with adjusted cost increases associated with anemia of 65 and 68 percent compared to non-anemia for the diabetic and/or the hypertensive cohorts, respectively.

These results highlight the economic as well as clinical importance of early CKD-related anemia detection. An analysis of the prevalence of anemia in CKD patients in the United States reported that 46.7 percent had Hb levels below 11g/dL and 26.3 percent had Hb levels below 10 g/dL.²² Nevertheless, only 31.3 percent of these anemic patients were treated despite the condition's high prevalence.²² There is still a lack of awareness of the potential benefit of treating anemia of CKD and concern about accelerating the progression of kidney disease with treatment, however there is virtually no evidence of accelerating the progression of kidney disease when the treatment goals are within the currently recommended Hb range.^{5,23} Moreover, since a large percentage of people with kidney disease have diabetes and/or hypertension (the two major causes of kidney failure), early profiling and active management of these patients could prevent or delay progression to more advanced stages of CKD including ESRD.²⁴ Early screening for anemia in patients with CKD

Exhibit 4b

Multivariate Analysis: Adjusted Impact of Anemia on Hospitalization Rate in Hypertensive Patients¹



Notes:

¹ Covariates for adjustment were: age, gender, baseline eGFR value, previous CVD-related hospitalization, and medical history of hypertension, AMI, angina, cardiac arrhythmia, congestive heart failure, coronary artery disease, stroke, and LVH.

*Indicates that the incidence rate ratio was statistically significantly different from 1.0 at p<.001. Error bars represent 95% confidence limits.

Exhibit 5: Unadjusted Hospitalization Cost Burden of Anemia Relative to Non-Anemia

DIABETIC COHORT

	Anemia	Non-Anemia	Unadjusted Cost Ratio	Unadjusted Cost Difference	p-value
Yearly healthcare costs (\$)					
Any Hospitalization	25,342	8,270	3.1	17,072	<.0001
CVD-Related Hospitalizations	13,723	5,076	2.7	8,647	<.0001

HYPERTENSIVE COHORT

	Anemia	Non-Anemia	Unadjusted Cost Ratio	Unadjusted Cost Difference	p-value
Yearly healthcare costs (\$)					
Any Hospitalization	23,694	7,253	3.3	16,441	<.0001
CVD-Related Hospitalizations	12,657	4,231	3.0	8,426	<.0001

Abbreviation: CVD-cardiovascular disease

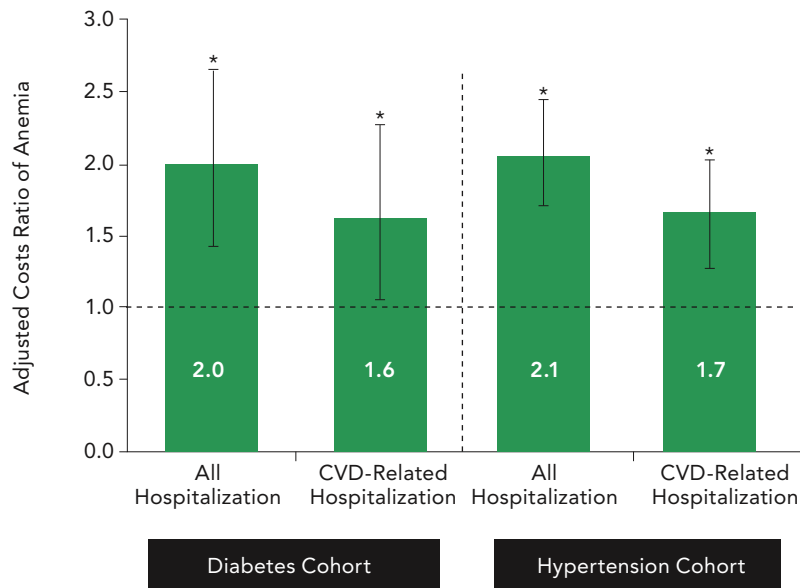
due diabetes may be particularly important, as the prevalence of anemia is higher in this population as compared to other populations with similar levels of renal function and iron stores.²⁵

To our knowledge, the present study was the first to investigate the hospitalization rates and cost impact

of anemia in diabetic and/or hypertensive patients developing CKD from a managed-care perspective. Anemia of CKD is associated with cardiovascular and renal complications, resulting in increased hospitalizations and mortality rates. Results from the Atherosclerosis Risk in Communities (ARIC) study

Exhibit 6:

Multivariate Analysis: Adjusted Hospitalization Costs Ratio of Anemia Relative to Non-Anemia¹



Notes:

¹ Covariates for adjustment were: age, gender, baseline eGFR value, previous CVD-related hospitalization, and medical history of hypertension, AMI, angina, cardiac arrhythmia, congestive heart failure, coronary artery disease, stroke, and LVH.

*Indicates that the incidence rate ratio was statistically significantly different from 1.0 at $p < .001$. Error bars represent 95% confidence limits.

showed that anemia independently predicted coronary heart disease in CKD patients (relative risk = 2.74, $p < 0.001$).¹⁵ Also, in a study by Levin et al., for each decrease in hemoglobin of 0.5 g/dL in patients with kidney disease, the risk of left ventricular growth increased by 32 percent ($p = 0.004$).¹⁶ These results are comparable to the IRR of CVD-related hospitalizations reported in the present study.

The increase in CVD events associated with anemia of CKD also lead to higher costs burden. Nissen et al. evaluated the cost of anemia among 4,834 adult patients with CKD from commercially insured and Medicare plans and found that anemia was associated with an annualized cost increase of \$28,757 per patient with CKD.²⁶ However, their study did not differentiate between treated and untreated anemia. Similarly, in elderly CKD patients, untreated anemia was associated with a significant increase in medical costs with an incremental monthly cost of \$1,089 (\$2,529 versus \$1,439; $p < 0.001$) compared to non-anemia.²⁷ In a study by Moyneur and colleagues, focusing on pre-dialysis CKD patients with anemia, incremental direct cost savings for ESA-treated patients was \$1,443 ($p < 0.001$) per member per month compared to non-ESA-treated patients.²⁸ These results are consistent with the hospitalization cost burden associated with

anemia reported in the present study for diabetic and hypertensive patients.

This study has several limitations. First, claims data sometime have inaccuracies in the recorded information (diagnoses, costs) and laboratory results are often missing. However, although not rare, it would be unlikely that these inaccuracies have significantly impacted our results considering the large sample size. Second, because the patient ethnicity was not available in our database, eGFR values for African-American patients were under-estimated by a small increment because of the omission of this factor for the calculation. The measurement errors of the eGFR values affected the subset of African-Americans estimated at about 10 percent of the total employed population.²⁹ Third, the study evaluated only the direct medical costs. Information to determine the indirect costs of anemia, such as work productivity loss and reduced quality of life, was not available. Fourth, the observational design was susceptible to various biases. We attempted to control for these potential biases by conducting multivariate regression analysis to control for potential confounding factors. However, such methodology only controls for inter-cohorts biases and does not account for potential selection biases that might arise from the population selection. The current study also may

suffer from detection bias. Indeed, because laboratory results and diagnoses were not collected at pre-specified intervals as in randomized clinical trials, false negatives of anemia could have occurred in patients who did not seek care (especially those who did not have symptomatic manifestations). Finally, our database excluded information from long-term nursing home care and consequently the impact of anemia may be under-estimated.

Despite these limitations, the current research has several advantages including the important advantage of relying on real-world data, a relatively large sample size, availability of laboratory results to ascertain with a relative accuracy the presence of CKD through eGFR and anemia through Hb values, and multivariate adjustments to control for confounders. Previous studies have demonstrated the detrimental health effects and cost burden associated with anemia of CKD-related complication such as CVDs.^{11;15-17;26-28} The current study showed increase rates of hospitalization and adverse economic impact of anemia of CKD in diabetic and/or hypertensive patients. Early identification and assessment of anemia among these populations may have the potential to improve patients' clinical outcomes and may reduce the utilization of health care resources.

Conclusion

This large observational study demonstrated that anemia was associated with statistically significant increased risks of any hospitalizations and CVD-related hospitalizations in CKD patients with diabetes and/or hypertension. The higher risks of hospitalization associated with periods of anemia also translated in a significant inpatient cost burden. These results suggest that timely evaluation and appropriate treatment of anemia may have the potential to improve patients' clinical outcomes (especially those related to CVDs) and reduce the utilization of inpatient services.

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