RESEARCH

Direct All-Cause Health Care Costs Associated With Chronic Kidney Disease in Patients With Diabetes and Hypertension: A Managed Care Perspective

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ABSTRACT

BACKGROUND: Diabetes and hypertension are the 2 major causes of end-stage renal disease. The rate of chronic kidney disease (CKD) secondary to diabetes and/or hypertension is on the rise, and the related health care costs represent a significant economic burden.

OBJECTIVE: To quantify from a health system perspective the incremental direct all-cause health care costs associated with a diagnosis of CKD in patients with diabetes and/or hypertension.

METHODS: An analysis was conducted of medical claims and laboratory data with dates of service between January 1, 2000, and February 28, 2006, from a managed care database for approximately 30 million members enrolled in 35 health plans. Each patient's observation period began on the date of the first diabetes or hypertension diagnosis (index date) and ended on the earlier of the health plan disenrollment date or February 28, 2006. Inclusion criteria were continuous insurance coverage in the 6 months prior to the index date and during the observation period, age at least 18 years, and at least 2 claims less than 90 days apart with a primary or secondary diagnosis for diabetes or hypertension. Exclusion criteria were cancer, lupus, or organ transplantation or chemotherapy at any time during the observation period. CKD was defined as at least 1 claim with a primary or secondary diagnosis for CKD and at least 2 glomerular filtration rate values of below 60 milliliters per minute per 1.73 square meters of body surface area (60 mL/min/1.73m^2) at any time during the observation period. Bivariate and Tobit regression analyses were conducted to compare patients who developed CKD versus those who did not for annualized (per patient per month [PPPM] multiplied by 12) direct, all-cause, health care costs, defined as standardized net provider payments after subtraction of member cost-share. These costs consisted of outpatient services, inpatient services, and pharmacy claims. A subset analysis of the post- versus pre-CKD medical costs was also conducted for cohorts of patients with at least 60 days of observation before and after the development of CKD; that analysis measured both all-cause costs and costs for services directly related to CKD treatment (i.e., claims with a primary or secondary diagnosis of CKD or claims for dialysis services).

RESULTS: 11,531 patients with diabetes, 74,759 patients with hypertension, and 4,779 patients with both conditions were identified, of whom 123 (1.1%), 1,137 (1.5%), and 712 (14.9%), respectively, developed CKD during the observation period. The CKD group was older than the no-CKD group in each cohort (mean ages for CKD vs. no-CKD were, respectively, diabetes only cohort: 60.7 vs. 49.9 years, $P<0.001$; hypertension only cohort: 63.6 vs. 53.6 years, $P<0.001$; diabetes and hypertension cohort: 63.4 vs. 61.8 years, $P<0.001$). CKD was associated with significantly higher total direct all-cause health care costs, with unadjusted annualized per patient mean [median] cost differences of $11,814 [$6,895], $8,412 [$4,115], and $10,625 [$7,203], respectively (diabetes: $18,444 [$11,025] vs. $6,631 [$4,131], $P<0.001$; hypertension: $14,638 [$7,817] vs. $6,226 [$3,703], $P<0.001$; diabetes and hypertension: $21,452 [$13,840] vs. $10,827 [$6,637], $P<0.001$). The largest driver of the all-cause mean cost difference associated with CKD for each cohort was hospitalization cost (diabetes: $6,410, $P<0.001$; hypertension: $5,498, $P<0.001$; diabetes and hypertension: $6,467, $P<0.001$). Among patients developing CKD, all-cause mean [median] annualized costs increased significantly following CKD onset (increases for patients with diabetes: $8,829 [$4,899], $P=0.026$; hypertension: $4,175 [$2,741], $P=0.004$; diabetes and hypertension: $9,397 [$7,240], $P<0.001$). In the post-CKD period, costs directly related to treatment of CKD accounted for 9%-19% of all-cause medical service costs—9.2% for patients with diabetes, 11.6% for patients with hypertension, and 18.8% for patients with both diabetes and hypertension.

CONCLUSION: CKD was associated with significantly higher all-cause health care costs in managed care patients with diabetes and/or hypertension.

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What is already known about this subject

- Diabetes and hypertension are 2 important causes of chronic kidney disease (CKD) and end-stage renal disease, according to the 2007 Annual Data Report from the United States Renal Data System.
- According to the American Diabetes Association, people with diabetes incur average expenditures of $11,744 per year ($979 per month), of which $6,649 ($554 per month) is attributed to diabetes.
- Although the rate of CKD secondary to diabetes or hypertension is on the rise, the cost burden of CKD in diabetic and/or hypertensive populations has not been quantified from a managed care perspective.

What this study adds

- For cohorts of patients with diabetes only, hypertension only, and diabetes and hypertension, CKD was associated with significantly higher total all-cause direct health care costs, with unadjusted annualized mean per patient costs differences of $11,814, $8,412, and $10,625, respectively ($P<0.001$ for all comparisons).
- After controlling for covariates, the adjusted annualized incremental all-cause health care costs associated with CKD were still pronounced and remained statistically significant (diabetes cohort: $7,190, $P<0.001$; hypertension cohort: $5,450, $P<0.001$; diabetes and hypertension cohort: $9,177, $P<0.001$).
- Among those patients who developed CKD during the study, the post-CKD phase was associated with a significant increase in direct all-cause health care costs: incremental annualized mean per patient costs of $8,829 ($P=0.026$), $4,175 ($P=0.004$), and $9,397 ($P<0.001$) relative to pre-CKD, for patients with diabetes only, hypertension only, and diabetes and hypertension, respectively.

Diabetes and hypertension are the 2 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%-50% of incident ESRD cases.[2] Diabetes or hypertension are found to be present in more than 70% of patients who begin therapy for ESRD, according to the 2007 Annual Data Report from the United States Renal Data System (USRDS).[1] Due to the increasing prevalence of both diabetes and hypertension, driven primarily by the aging population and increase in obesity, rates of CKD secondary to diabetes and/or hypertension are on the rise.[3,4] During the period from 1992 to 2006, the incidence of reported diabetic ESRD in the United States has doubled while the prevalence of CKD (stages 1 to 4) among non-ESRD Medicare beneficiaries diagnosed with diabetes tripled from 4.4% to 13.6%.[1]

CKD is a significant driver of health-related expenditures. The total health care spending for the treatment of ESRD patients in 2005 was approximately $32 billion. Medicare ESRD program expenditures grew from $5.8 billion in 1991 to $21 billion by 2005, accounting for 6.4% of the total 2005 Medicare budget.[1] Based on the Medicare population, the annual cost per dialysis patient was $68,585 in 2005.[1]

According to the American Diabetes Association, people with diabetes incurred average health care expenditures of $11,744 per year ($979 per month) in 2007, of which $6,649 ($554 per month) was attributed to diabetes.[5] Moreover, patients with both diabetes and hypertension incurred much higher annual health care costs than did patients with diabetes or hypertension alone ($13,446, $8,493, and $8,424, respectively).[6]

The rate of CKD secondary to diabetes and/or hypertension is on the rise, and the related health care costs represent a significant economic burden. Consequently, this topic has gained increased attention.[1,2] However, to the best of our knowledge, the cost burden of CKD in patients with diabetes and/or hypertension has not been documented from a managed care perspective. The purpose of the current analysis was to quantify the incremental health care costs associated with CKD in managed care cohorts with diabetes only, hypertension only, and both diabetes and hypertension.

Methods

Data Source

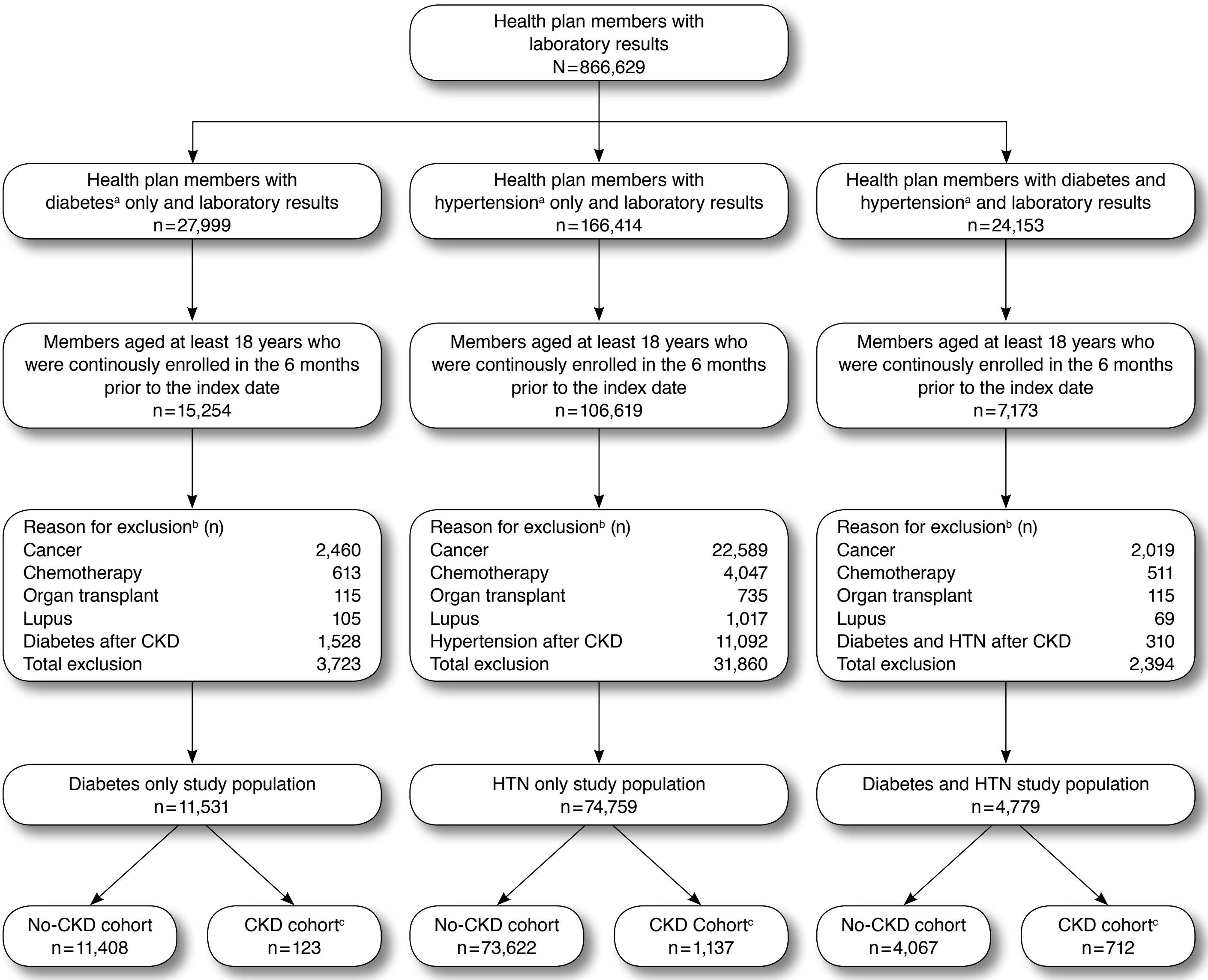
De-identified health care claims and laboratory data from the Integrated HealthCare Information Services (IHCIS) National Managed Care Benchmark Database with dates of service between January 1, 2000, and February 28, 2006, were used to conduct the analysis. The IHCIS database included complete medical and pharmacy claims for more than 30 million managed care members 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 claims, pharmacy dispensing claims, and laboratory results. Laboratory results from the IHCIS database are available for the subset of patients tested within a given carrier's laboratory network, representing approximately 10% of the IHCIS population. In order to develop a database that accounts for differences in provider contracting and other pricing variations, IHCIS developed several approaches (e.g., proprietary algorithms and multivariate models) for standardizing pricing for different service categories (inpatient facility, outpatient facility, professional services, ancillary services, and pharmacy claims) across health plans. The resulting cost figures are therefore comparable across health plans and reflect net provider payments after subtraction of member cost-share.

Study Design

A retrospective, parallel-group design was employed to compare patients who developed CKD versus those who did not in 3 distinct cohorts: patients with diabetes only, patients with hypertension only, and patients with both diabetes and hypertension (Figure 1). Each patient's observation period spanned from the date of the first diabetes or hypertension diagnosis (index date) until the end of health plan enrollment or the defined study end date of February 28, 2006, whichever occurred earlier. For those patients who developed CKD during the observation period, the pre- and post-CKD periods were defined based on the first CKD claim.

To be included in the study sample, patients were required to meet all of the following criteria: (a) continuous health plan coverage in the 6 months prior to the index date and during the observation period, (b) at least 2 claims less than 90 days apart with a primary or secondary diagnosis for diabetes (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes: 250.xx; diabetes cohort) and/or hypertension (ICD-9-CM codes: 401.xx-405.xx; hypertension cohort), and (c) at least 18 years of age on the index date. To be included in the CKD cohort, patients were required to have at least 1 claim with a primary or secondary diagnosis commonly associated with CKD (ICD-9-CM codes: 250.4x [diabetes with renal manifestations], 403.xx [hypertensive kidney disease], 404.xx [hypertensive heart and kidney disease], 585.xx [chronic kidney disease], 586.xx [renal failure, unspecified], or 588.xx [disorders resulting from impaired renal function]) *and* have at least 2 estimated glomerular filtration rate (eGFR) values of below 60 milliliters per minute per 1.73 square meters of body surface area (60 mL/min/1.73m^2) during the observation period. Patients were excluded from the study if they had received an organ transplant or had lupus, cancer, or received chemotherapy at any time during the observation period. The rationale behind these exclusion criteria is that these conditions generally result in substantial medical allowed charges, which are independent of CKD per se and would, therefore, potentially bias the estimation of the costs associated with CKD. We measured all-cause health care costs instead of costs specific to CKD for 2 main reasons: (a) we

FIGURE 1 Patient Selection



[a]*At least 2 primary or secondary diagnoses for diabetes and/or hypertension less than 90 days apart. The first claim marked the beginning of the observation period (index date).*

[b]*Categories are not mutually exclusive.*

[c]*At least 1 primary or secondary diagnosis for CKD and at least 2 glomerular filtration rate values of less than 60 milliliters per minute per 1.73 square meters of body surface area during the observation period.*

CKD=chronic kidney disease; HTN=hypertension.

conducted the current study from the managed care perspective; therefore, our objective was to quantify the overall cost change associated with a diagnosis of CKD, since health plans are paying for all charges, not the CKD-related charges only; and (b) we wanted to contrast our results with recent findings from the USRDS report, which reported all-cause medical costs.

We imposed a minimum of 6 months of insurance coverage prior to the index date to assess the baseline characteristics of the study population in order to appropriately control for confounding factors in the multivariate analysis. No further minimum follow-up time was imposed during the observation period to avoid introducing potential bias such as survival or observation bias. However, for the analysis that compared pre-CKD costs with post-CKD costs in the subgroup of patients who developed CKD during the study period, we required at least 60 days of observation in each of the 2 time periods to mitigate the effects of very short observation periods on study results.

Definition of CKD based on eGFR

Estimated GFR values were calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula,[7] based on serum creatinine value, age, gender, and ethnicity:

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

where S_{Cr} = serum creatinine value. Because the patient ethnicity variable was not available in the database, non-African American race was assumed in the eGFR calculation. CKD was defined as an eGFR value below 60 mL/min/1.73m^2 (i.e., stages 3 to 5).

Outcome Measures

The outcome measures for the analyses were annualized (per patient per month [PPPM] multiplied by 12) direct all-cause standardized health care costs, which consisted of 3 mutually exclusive components: (a) outpatient services, (b) inpatient services, and (c) pharmacy costs. Outpatient services were identified from the IHCIS *Medical Claims* table, containing medical claims for professional and outpatient services, such as outpatient surgery, laboratory, and radiology. This table contains claim line information specific to professional claims (coded with Current Procedural Terminology, Fourth Edition [CPT-4] or Healthcare Common Procedure Coding System [HCPCS] procedure codes) and outpatient facility claims. Included within this table are revenue codes, procedure codes, ICD-9-CM diagnosis codes, type of provider, place of service, and type of service.

Inpatient services were obtained from the IHCIS *Inpatient Confinement* table, which provides a summarized record for each inpatient episode with a length of stay of at least 1 day from an acute care hospitalization or skilled nursing facility setting. The database includes a single record for every hospitalization observed during the data period. Included in the record are the admitting and discharge dates; length of inpatient stay; ICD-9-CM codes for admitting diagnosis, up to 5 "other" diagnoses, and discharge diagnosis; and total standardized cost amount for the inpatient stay, including the costs of drugs used during the stay. The IHCIS inpatient record excludes professional services that have been rendered and billed separately during the confinement period; these are reported in the *Medical Claims* (professional and noninpatient) table. Finally, the IHCIS *Pharmacy Claims* table summarizing claims submitted by pharmacies for outpatient drugs was used to measure pharmacy costs.

Statistical Analysis

Both descriptive and multivariate analyses were conducted to determine the incremental all-cause costs associated with CKD relative to no-CKD in cohorts of patients with diabetes only, hypertension only, and both diabetes and hypertension. For each cohort, descriptive bivariate statistics were used to compare groups of CKD and no-CKD for medical costs, and cost differences were assessed as both incremental costs and cost ratios. Incremental cost was defined as the weighted average annualized per patient cost of the CKD group minus the weighted average annualized per patient cost of the no-CKD group. Because the observation period of each patient was used as the weight, the annualized per patient cost represents the mathematical equivalent of a standard PPPM value (aggregated costs divided by aggregated months, with both values summed across all patients) multiplied by 12 but produces a value for each patient, allowing for statistical testing. Costs for CKD patients were divided by costs for patients without CKD to obtain the cost ratio.

Cost differences were also used to compare annualized direct health care costs between the pre-CKD and post-CKD periods among patients who developed CKD, weighted by the lengths of the pre-CKD and post-CKD observation periods. A minimum of 60 days of observation pre- and post-CKD was imposed for the analysis evaluating the change in all-cause health care costs following a diagnosis of CKD. We also reported the cost of treating CKD, that is, costs for claims with a primary or secondary CKD diagnosis and claims for dialysis services for the post-CKD period. In addition, PPPM costs for each of the 12 months before and after the first CKD diagnosis were calculated and plotted over time to illustrate the cost impact of CKD development.

Multivariate analyses were also conducted to adjust for potential confounding factors (that may otherwise contribute to increased costs) in estimating the incremental cost burden of CKD. Because of the non-normality of the health cost outcome variables, which are truncated at zero and positively skewed, a Tobit regression model was used to estimate the adjusted annualized incremental costs associated with CKD, as measured by the marginal effect for the CKD group after controlling for other covariates. Covariates used for adjustment in the regression models were age, gender, and diagnoses representing additional baseline comorbidities. These diagnoses included acute myocardial infarction, other acute and subacute forms of ischemic heart disease, and old myocardial infarction (ICD-9-CM: 410.xx, 411.xx, and 412.xx, respectively); angina pectoris (ICD-9-CM: 413.xx); cardiac dysrhythmias, tachycardia unspecified, and palpitations (ICD-9-CM: 427.xx, 785.0, and 785.1, respectively); heart failure (ICD-9-CM: 428.xx); other forms of chronic ischemic heart disease (ICD-9-CM: 414.xx); unspecified hypertensive heart disease (ICD-9-CM: 402.9x); cardiomegaly (ICD-9-CM: 429.3); and cerebrovascular disease (ICD-9-CM: 430.xx-437.xx).

TABLE 1 Baseline Characteristics of the Study Populations

	Diabetes Only Cohort			Hypertension Only Cohort			Diabetes and HTN Cohort		
	No-CKD	CKD	All	No-CKD	CKD	All	No-CKD	CKD	All
Number (n) of patients	**11,408**	**123**	**11,531**	**73,622**	**1,137**	**74,759**	**4,067**	**712**	**4,779**
Women, n (%)	5,078 (44.5)	56 (45.5)	5,134 (44.5)	39,286 (53.4)	529 (46.5)[a]	39,815 (53.3)	2,167 (53.3)	287 (40.3)[a]	2,454 (51.3)
Mean [SD] age in years	49.9 [12.7]	60.7 [12.9][a]	50.0 [12.7]	53.6 [12.6]	63.6 [12.4][a]	53.7 [12.6]	61.8 [10.7]	63.4 [10.5][a]	62.1 [10.6]
Observation period in days Mean [SD] median	906 [583] 801	1,232 [588] 1,288[a]	910 [584] 805	1,068 [600] 1,009	1,466 [536] 1,516[a]	1,074 [601] 1,017	1,429 [550] 1,471	1,490 [535] 1,556[a]	1,438 [548] 1,485
Observation period. n (%)									
< 6 Months	920 (8.1)	3 (2.4)[a]	923 (8.0)	3,806 (5.2)	5 (0.4)[a]	3,811 (5.1)	25 (0.6)	2 (0.3)	27 (0.6)
6-11 months	1,466 (12.9)	7 (5.7)[a]	1,473 (12.8)	6,313 (8.6)	25 (2.2)[a]	6,338 (8.5)	102 (2.5)	11 (1.5)	113 (2.4)
12 months or more	9,022 (79.1)	113 (91.9)[a]	9,135 (79.2)	63,503 (86.3)	1,107 (97.4)[a]	64,610 (86.4)	3,940 (96.9)	699 (98.2)	4,639 (97.1)
Cardiovascular disease,[b] n (%)									
Acute myocardial infarction[c]	145 (1.3)	4 (3.3)	149 (1.3)	1,144 (1.6)	29 (2.6)[a]	1,173 (1.6)	84 (2.1)	28 (3.9)[a]	112 (2.3)
Angina[d]	137 (1.2)	3 (2.4)	140 (1.2)	1,209 (1.6)	31 (2.7)[a]	1,240 (1.7)	96 (2.4)	30 (4.2)[a]	126 (2.6)
Cardiac arrhythmia[e]	565 (5.0)	16 (13.0)[a]	581 (5.0)	4,902 (6.7)	97 (8.5)[a]	4,999 (6.7)	258 (6.3)	52 (7.3)	310 (6.5)
Heart failure[f]	108 (0.9)	8 (6.5)[a]	116 (1.0)	642 (0.9)	51 (4.5)[a]	693 (0.9)	92 (2.3)	43 (6.0)[a]	135 (2.8)
Coronary artery disease[g]	570 (5.0)	21 (17.1)[a]	591 (5.1)	4,058 (5.5)	130 (11.4)[a]	4,188 (5.6)	331 (8.1)	82 (11.5)[a]	413 (8.6)
Left ventricular hypertrophy[h]	56 (0.5)	1 (0.8)	57 (0.5)	362 (0.5)	8 (0.7)	370 (0.5)	23 (0.6)	8 (1.1)	31 (0.6)
Cerebrovascular disease[i]	149 (1.3)	6 (4.9)[a]	155 (1.3)	1,239 (1.7)	31 (2.7)[a]	1,270 (1.7)	88 (2.2)	25 (3.5)[a]	113 (2.4)
Previous hospitalization related to CVD,[b] n (%)	104 (0.9)	4 (3.3)[a]	108 (0.9)	978 (1.3)	34 (3.0)[a]	1,012 (1.4)	69 (1.7)	23 (3.2)[a]	92 (1.9)

[a]*Denotes statistically significant comparison (P<0.05) of No-CKD versus CKD using a Pearson chi-square test for comparisons of categorical variables and a Student's t-test for the comparison of age and observation period.*

[b]*Measured during 180 days prior to index date.*

[c]*Acute myocardial infarction, other acute and subacute forms of ischemic heart disease, and old myocardial infarction (ICD-9-CM: 410.xx, 411.xx, and 412.xx, respectively).*

[d]*Angina pectoris (ICD-9-CM: 413.xx).*

[e]*Cardiac dysrhythmias, tachycardia unspecified, and palpitations (ICD-9-CM: 427.xx, 785.0, and 785.1, respectively).*

[f]*Heart failure (ICD-9-CM: 428.xx).*

[g]*Other forms of chronic ischemic heart disease (ICD-9-CM: 414.xx).*

[h]*Since there are no specific ICD-9-CM codes for identifying left ventricular hypertrophy, we used unspecified hypertensive heart disease (ICD-9-CM: 402.9) and cardiomegaly (ICD-9-CM: 429.3) codes to identify left ventricular hypertrophy.*

[i]*Cerebrovascular disease (ICD-9-CM: 430.xx-437.xx).*

CKD = chronic kidney disease; CVD = cardiovascular disease; HTN = hypertension; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

All comorbidities were identified through claims with a primary or secondary diagnosis in the 6 months prior to the index date. The models also included a covariate for hospitalization with an admitting diagnosis of cardiovascular disease (CVD) in the 6-month baseline period.

Statistical comparisons between cohorts of patients were conducted using the Pearson chi-square test for categorical variables and the 2-sided Student's t-test for continuous variables. In both cases, a 2-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 11,531 patients with diabetes (123 CKD and 11,408 no-CKD), 74,759 patients with hypertension (1,137 CKD and 73,622 no-CKD), and 4,779 patients with both conditions (712 CKD and 4,067 no-CKD) met the entry criteria and formed the study populations (Table 1). The CKD group was older than the no-CKD group in each cohort (mean [SD] age—diabetes only cohort: 60.7 [12.9] vs. 49.9 [12.7] years, $P<0.001$; hypertension only cohort: 63.6 [12.4] vs. 53.6 [12.6] years, $P<0.001$; diabetes and hypertension cohort: 63.4 [10.5] vs. 61.8 [10.7] years, $P<0.001$). The proportion of women was lower in the CKD group than in the no-CKD group in the hypertension only cohort (46.5% vs. 53.4%, $P<0.001$) and the diabetes and hypertension cohort (40.3% vs. 53.3%, $P<0.001$).

Overall, the CKD group had a higher rate of CVD during the 180 days prior to the index date than did the no-CKD group, with predominance of coronary artery disease (diabetes: 17.1% vs. 5.0%, $P<0.001$; hypertension: 11.4% vs. 5.5%, $P<0.001$; diabetes and hypertension: 11.5% vs. 8.1%, $P<0.001$) and cardiac arrhythmia (diabetes: 13.0% vs. 5.0%, $P<0.001$; hypertension: 8.5% vs. 6.7%, $P=0.012$; diabetes and hypertension: 7.3% vs. 6.3%, $P=0.338$).

TABLE 2 Annualized Per Patient All-Cause Health Care Costs[a] and Observation Period for Patients With and Without CKD

	No-CKD Group [A]			CKD Group [B]			Cost difference [B]-[A]			Cost ratio [B]/[A]	*P* value
Diabetes Only Cohort (n = 11,408 no-CKD; n = 123 CKD)											
Observation period in days, mean [SD] median	906	[583]	801	1,232	[588]	1,288					< 0.001
Costs: All patients, mean [SD] median											
Outpatient services	$3,362	[8,021]	2,158	$7,672	[15,405]	5,121	$4,310	[8,136]	2,964	2.3	< 0.001
Inpatient services	$1,425	[9,925]	0	$7,835	[24,513]	1,110	$6,410	[10,192]	1,110	5.5	< 0.001
Pharmacy claims	$1,843	[5,082]	1,153	$2,937	[7,113]	1,879	$1,094	[5,108]	726	1.6	0.002
Total costs	$6,631	[16,455]	4,131	$18,444	[38,124]	11,025	$11,814	[16,835]	6,895	2.8	< 0.001
Total costs for patients with < 12 months of observation (n = 2,386 no-CKD; n = 10 CKD)	$11,035	[18,507]	4,866	$30,874	[25,299]	13,410	$19,839	[18,548]	8,544	2.8	0.086
Total costs for patients with ≥ 12 months of observation (n = 9,022 no-CKD; n = 113 CKD)	$6,405	[15,769]	4,100	$18,239	[38,936]	11,025	$ 11,835	[16,261]	6,925	2.8	< 0.001
Hypertension Only Cohort (n = 73,622 no-CKD; n = 1,137 CKD)											
Observation period in days, mean [SD] median	1,068	[600]	1,009	1,466	[536]	1,516					< 0.001
Costs: All patients, mean [SD] median											
Outpatient services	$3,263	[6,534]	2,270	$5,961	[17,730]	3,880	$2,699	[6,843]	1,610	1.8	< 0.001
Inpatient services	$1,655	[10,491]	0	$7,153	[32,639]	1,538	$5,498	[11,162]	1,538	4.3	< 0.001
Pharmacy claims	$1,309	[3,518]	782	$1,523	[3,800]	1,002	$214	[3,523]	220	1.2	< 0.001
Total costs	$6,226	[15,713]	3,703	$14,638	[44,039]	7,817	$8,412	[16,512]	4,115	2.4	< 0.001
Total costs for patients with < 12 months of observation (n = 10,119 no-CKD; n = 30 CKD)	$11,139	[19,127]	4,498	$42,563	[41,294]	20,654	$31,424	[19,233]	16,156	3.8	0.002
Total costs for patients with ≥ 12 months of observation (n = 63,503 no-CKD; n = 1,107 CKD)	$6,086	[15,021]	3,687	$14,504	[43,937]	7,803	$8,418	[15,964]	4,116	2.4	< 0.001
Diabetes and Hypertension Cohort (n = 4,067 no-CKD; n = 712 CKD)											
Observation period in days, mean [SD] median	1,429	[550]	1,471	1,490	[535]	1,556					0.007
Costs: All patients, mean [SD] median											
Outpatient services	$4,492	[9,076]	3,325	$8,140	[23,423]	5,262	$3,648	[12,325]	1,938	1.8	< 0.001
Inpatient services	$4,343	[20,215]	0	$10,810	[36,867]	4,075	$6,467	[23,462]	4,075	2.5	< 0.001
Pharmacy claims	$1,992	[4,393]	1,430	$2,501	[5,138]	1,706	$509	[4,512]	276	1.3	< 0.001
Total costs	$10,827	[27,203]	6,637	$21,452	[52,691]	13,840	$10,625	[32,308]	7,203	2.0	< 0.001
Total costs for patients with < 12 months of observation (n = 127 no-CKD; n = 13 CKD)	$25,636	[34,309]	11,855	$98,630	[89,911]	61,143	$72,995	[42,951]	49,288	3.8	0.032
Total costs for patients with ≥ 12 months of observation (n = 3,940 no-CKD; n = 699 CKD)	$10,743	[26,849]	6,623	$21,191	[50,932]	13,817	$10,448	[31,679]	7,194	2.0	< 0.001

[a]*Cost per patient per month for each month of insurance eligibility following the index date, multiplied by 12.*
CKD = chronic kidney disease.

Unadjusted All-Cause Health Care Cost Difference: CKD Versus No-CKD

In all 3 cohorts, CKD was associated with significantly higher total direct all-cause health care costs (Table 2), with unadjusted annualized per patient mean [median] cost differences of $11,814 [$6,895], $8,412 [$4,115], and $10,625 [$7,203], respectively (diabetes only cohort: $18,444 [$11,025] vs. $6,631 [$4,131], $P<0.001$; hypertension only cohort: $14,638 [$7,817] vs. $6,226 [$3,703], $P<0.001$; diabetes and hypertension cohort: $21,452 [$13,840] vs. $10,827 [$6,637], $P<0.001$). The corresponding cost ratios for the CKD diabetes, hypertension, and diabetes and hypertension cohorts relative to no-CKD groups were 2.8:1, 2.4:1, and 2.0:1, respectively. The largest driver of the all-cause mean cost difference associated with CKD for each cohort was hospitalization cost (diabetes: $6,410, $P<0.001$; hypertension: $5,498, $P<0.001$; diabetes and hypertension: $6,467, $P<0.001$). Stratified analyses by duration of observation period (subsets of patients with < 12 months of observation and ≥ 12 months of observation) produced similar findings; however, both total annualized costs and the incremental annualized cost differences were much higher for patients with shorter observation periods.

Adjusted Cost Burden of CKD Relative to No-CKD

After controlling for covariates, the adjusted annualized incremental all-cause health care costs associated with CKD were

TABLE 3 Tobit Regression Analysis Results: Annualized Per Patient Incremental All-Cause Health Care Costs Associated With CKD

Factor	Diabetes Only Cohort[a]				Hypertension Only Cohort[b]				Diabetes and Hypertension Cohort[c]			
	β[d]	Marginal Effects[e]			β[d]	Marginal Effects[e]			β[d]	Marginal Effects[e]		
		Incremental All-Cause Cost	95% CI ($)	*P* value		Incremental All-Cause Cost	95% CI ($)	*P* value		Incremental All-Cause Cost	95% CI ($)	*P* value
CKD[f]	10,577	$7,190	5,057–9,322	<0.001	7,989	$5,450	4,818–6,083	<0.001	12,273	$9,177	7,895–10,459	<0.001
Age[g]	19	$13	-4–31	0.144	86	$59	52–65	<0.001	79	$59	15–102	0.008
Female	1,758	$1,195	753–1,637	<0.001	-124	-$84	-240–71	0.288	-244	-$183	-1,102–736	0.697
Diagnoses												
Acute myocardial infarction[h]	2,034	$1,383	-838–3,604	0.222	2,584	$1,763	1,041–2,485	<0.001	2,746	$2,053	-1,326–5,432	0.234
Angina[i]	2,999	$2,039	-29–4,106	0.053	1,438	$981	349–1,613	0.002	-1,501	-$1,122	-4,087–1,843	0.458
Cardiac arrhythmia[j]	2,057	$1,398	371–2,425	0.008	2,644	$1,804	1,485–2,123	<0.001	3,142	$2,349	422–4,276	0.017
Heart failure[k]	6,921	$4,704	2,333–7,076	<0.001	8,790	$5,997	5,154–6,840	<0.001	12,358	$9,240	6,300–12,181	<0.001
Coronary artery disease[l]	4,275	$2,906	1,811–4,001	<0.001	3,790	$2,586	2,213–2,958	<0.001	2,120	$1,585	-184–3,355	0.079
Cerebrovascular disease[m]	5,810	$3,950	2,018–5,881	<0.001	5,158	$3,519	2,906–4,132	<0.001	4,690	$3,507	473–6,541	0.023
LVH[n]	-1,664	-$1,131	-4,308–2,046	0.485	5,186	$3,538	2,428–4,649	<0.001	15,350	$11,477	5,680–17,275	<0.001
CVD-related hospitalization	7,407	$5,035	2,265–7,804	<0.001	4,517	$3,082	2,279–3,884	<0.001	2,388	$1,786	-2,143–5,714	0.373

[a]*N of cases: 11,531; Log-likelihood: -129,044; likelihood-ratio chi-square(11)=275; P value<0.001; σ: 17,537; ϕ: 0.36; Φ: 0.68; λ: 0.53.*
[b]*N of cases: 74,759; Log-likelihood: -828,497; likelihood-ratio chi-square(11)=2,639; P value<0.001: σ: 15,730; ϕ: 0.36; Φ: 0.68; λ: 0.52.*
[c]*N of cases: 4,779; Log-likelihood: -54,393; likelihood-ratio chi-square(11)=360; P value<0.001: σ:21,219; ϕ: 0.32; Φ: 0.75; λ: 0.43.*
[d]*Tobit regression coefficient.*
[e]$\frac{\partial E[y_i|x_i]}{\partial x_i} = \beta\Phi\left(\frac{\beta' x_i}{\sigma}\right)$
[f]*Relative to no CKD.*
[g]*Represents each 1 year increase in age.*
[h]*Acute myocardial infarction, other acute and subacute forms of ischemic heart disease, and old myocardial infarction (ICD-9-CM: 410.xx, 411.xx, and 412.xx, respectively).*
[i]*Angina pectoris (ICD-9-CM: 413.xx).*
[j]*Cardiac dysrhythmias, tachycardia unspecified, and palpitations (ICD-9-CM: 427.xx, 785.0, and 785.1, respectively).*
[k]*Heart failure (ICD-9-CM: 428.xx).*
[l]*Other forms of chronic ischemic heart disease (ICD-9-CM: 414.xx).*
[m]*Cerebrovascular disease (ICD-9-CM: 430.xx-437.xx).*
[n]*Since there are no specific ICD-9-CM codes for identifying LVH, we used unspecified hypertensive heart disease (ICD-9-CM: 402.9) and cardiomegaly (ICD-9-CM: 429.3) codes to identify LVH.*
CI=confidence interval; CKD=chronic kidney disease; CVD=cardiovascular disease; LVH=left ventricular hypertrophy.

still pronounced and remained statistically significant (diabetes cohort: $7,190, *P*<0.001; hypertension cohort: $5,450, *P*<0.001; diabetes and hypertension cohort: $9,177, *P*<0.001; Table 3). Among other statistically significant variables for most cost components were age, gender, and baseline history of coronary artery disease. As in the unadjusted results, regression analysis by cost category revealed that the largest driver of the adjusted incremental cost associated with CKD was cost of hospitalizations (diabetes cohort: $4,331, *P*<0.001; hypertension cohort: $3,605, *P*<0.001; diabetes and hypertension cohort: $6,225, *P*<0.001; data not shown).

Change in All-Cause Health Care Costs Following a Diagnosis of CKD

Among patients who developed CKD during the observation period and who had at least 60 days of observation both pre-CKD and post-CKD, the post-CKD phase was associated with a significant increase in total direct all-cause health care costs (Table 4), with mean incremental annualized per patient costs of $8,829, $4,175, and $9,397 relative to pre-CKD, respectively (diabetes cohort: $22,062 vs. $13,233, *P*=0.026; hypertension cohort: $15,540 vs. $11,365, *P*=0.004; diabetes and hypertension cohort: $24,171 vs. $14,774, *P*<0.001). The corresponding cost ratios for the post-CKD diabetes, hypertension, and diabetes and

TABLE 4 Annualized All-Cause and CKD-Related Mean [SD] Median Per Patient Costs[a] Before and After Developing CKD

	Pre-CKD Period[b] [A]	Post-CKD Period[b] [B]	Cost difference [B]-[A]	Cost ratio [B]/[A]	*P* Value[c]
Diabetes Only Cohort (n = 100)					
All-cause medical services cost	$10,252 [20,754] 3,568	$19,038 [46,200] 6,477	$8,787 [35,994] 2,910	1.9	0.024
All-cause pharmacy claims cost	$2,981 [5,674] 1,460	$3,023 [5,626] 1,857	$42 [5,678] 397	1.0	0.945
Total costs	$13,233 [21,856] 5,738	$22,062 [46,580] 10,637	$8,829 [36,566] 4,899	1.7	0.026
CKD-related medical services cost[d]	–	$1,746 [10,695] 141			
Observation period in days, mean [SD] median	520 [341] 456	837 [450] 806			< 0.001
Hypertension Only Cohort (n = 885)					
All-cause medical services cost	$10,185 [42,005] 3,114	$13,880 [42,122] 5,784	$3,695 [42,087] 2,671	1.4	0.012
All-cause pharmacy claims cost	$1,180 [1,791] 752	$1,660 [3,681] 1,102	$480 [2,896] 350	1.4	< 0.001
Total costs	$11,365 [42,081] 4,672	$15,540 [42,422] 7,413	$4,175 [42,276] 2,741	1.4	0.004
CKD-related medical services cost[d]	–	$1,616 [12,070] 97			
Observation period in days, mean [SD] median	503 [355] 397	1,078 [477] 1,062			< 0.001
Diabetes and Hypertension Cohort (n = 582)					
All-cause medical services cost	$12,819 [32,347] 4,464	$21,547 [54,380] 10,616	$8,729 [44,779] 6,152	1.7	< 0.001
All-cause pharmacy claims cost	$1,955 [2,518] 1,324	$2,624 [4,806] 1,846	$669 [3,840] 522	1.3	< 0.001
Total costs	$14,774 [32,618] 6,540	$24,171 [54,940] 13,780	$9,397 [45,218] 7,240	1.6	< 0.001
CKD-related medical services cost[d]	–	4,057 [29,946] 186			
Observation period in days, mean [SD] median	515 [355] 427	1,080 [472] 1,070			< 0.001

[a]*Costs per patient per month for each month of insurance eligibility before (pre-CKD) and after (post-CKD) the CKD diagnosis, multiplied by 12.*
[b]*A minimum of 60 days of observation pre- and post-CKD was imposed.*
[c]*Paired t-tests were used to evaluate the statistical significance of the differences between the 2 repeated measures (i.e., post-CKD vs. pre-CKD period)*
[d]*Costs for claims with primary or secondary CKD diagnoses or claims for dialysis services.*
CKD = chronic kidney disease.

hypertension cohorts relative to pre-CKD were 1.7:1, 1.4:1, and 1.6:1. CKD-related combined outpatient and inpatient services (i.e., medical claims with a primary or secondary CKD diagnosis or claims for dialysis services) accounted for 9% to 19% of all-cause medical services costs during the post-CKD period (diabetes cohort: $1,746, 9.2%; hypertension cohort: $1,616, 11.6%; diabetes and hypertension cohort: $4,057, 18.8%).

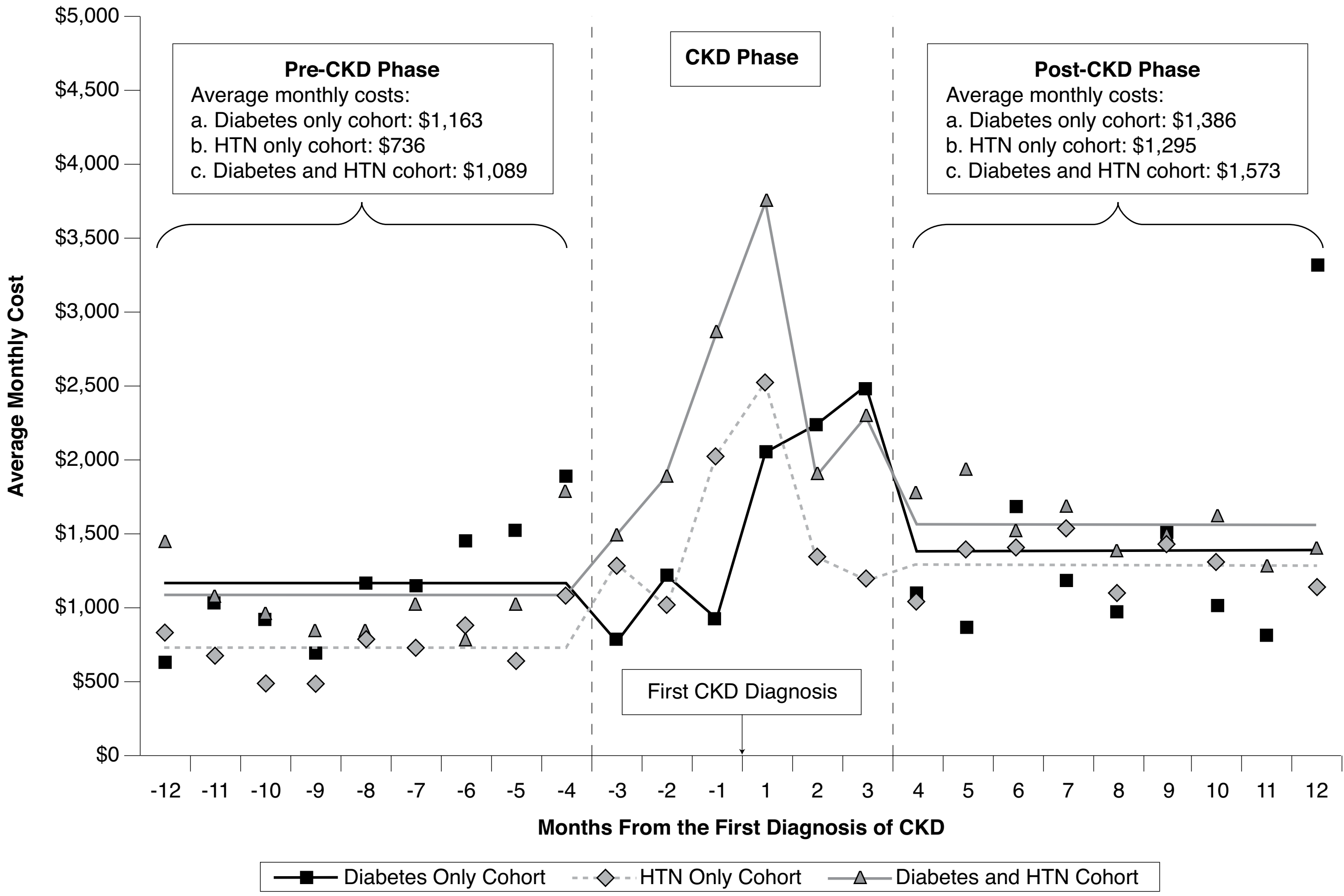
For each cohort, all-cause medical costs were at their highest level during the first 3 months following the first CKD diagnosis (Figure 2). Mean PPPM costs for the diabetes cohort were $1,163 and $1,386 during the 9-month periods preceding and following CKD onset, respectively, while they were $736 and $1,295 for the hypertension cohort, and $1,089 and $1,573 for the diabetes and hypertension cohort during the same corresponding CKD phases.

Discussion

We conducted this retrospective parallel-group study to assess the cost burden of CKD in cohorts of patients with diabetes only, hypertension only, and diabetes and hypertension. The analysis was based on administrative medical and pharmacy claims data coupled with laboratory results. From January 2000 to February 2006, a total of 11,531 patients with diabetes, 74,759 patients with hypertension, and 4,779 patients with both conditions were studied. Both unadjusted and adjusted results consistently indicated that CKD was associated with significantly higher all-cause health care costs in patients with diabetes, hypertension, and both conditions (mean annualized unadjusted differences of $11,814, $8,412, and $10,625, respectively). The largest driver of health care cost differences between the CKD and no-CKD groups was cost of hospitalizations. Among patients who developed CKD, the post-CKD phase was also associated with significantly higher health care costs, with cost increases of approximately 67%, 37%, and 64% compared with the pre-CKD period for the diabetes, hypertension, and diabetes and hypertension cohorts, respectively. For patients who developed CKD, approximately 9%-19% of all-cause health care costs were directly attributable to treatment of CKD.

Since a large percentage of people with kidney disease have diabetes and/or hypertension (the major causes of kidney failure), it is possible that early profiling and active management of patients with CKD might prevent or delay progression to more advanced costly stages of CKD including ESRD and the associated complications. Patients with a decline in renal function will generally notice no symptoms until their kidney function is reduced by 50%-75%.[8] By screening at-risk patients regularly, referring those with early abnormal kidney test results to nephrologists, and having an organized system for recall and

FIGURE 2 Monthly All-Cause Health Care Costs Before and After Developing Chronic Kidney Disease



Lines for pre-CKD and post-CKD periods represent mean per patient per month costs.
CKD = chronic kidney disease; HTN = hypertension.

monitoring, primary care providers could make a significant difference to their patients long before they experience the first symptoms.[8]

The present study was the first to investigate the costs associated with the development of CKD in patients with diabetes and/or hypertension in a managed care population. The USRDS reported that PPPM all-cause combined inpatient and outpatient costs for CKD patients reached $1,294 in 2005.[1] This figure is an average of the monthly cost of $2,113 for those CKD patients with diabetes and congestive heart failure (CHF), $831 for CKD patients with diabetes alone, and $780 for CKD patients with neither diabetes nor CHF. The estimated post-CKD monthly costs of $1,386 for the diabetic group, $1,295 for the hypertensive group, and $1,573 for the diabetic and hypertensive group reported in the current study are fairly comparable with the USRDS estimates, considering that we imposed no exclusion criteria for patients who developed CHF, which typically involves higher medical costs, and that our estimates also include pharmacy costs.

The present study had the advantages of a large sample size and the availability of laboratory results data, which enabled us to ascertain CKD status based on the eGFR measurement. CKD patients had higher morbidity at baseline, as reflected by more comorbidities and a greater proportion of patients with previous hospitalization related to CVDs. In addition, patients with CKD were more likely to use medical services in general due to their older age. Multivariate analyses, which controlled for these confounding factors, revealed that CKD was independently associated with increased medical costs.

Limitations

First, claims databases may contain inaccuracies or omissions in coded procedures or diagnoses, costs, or laboratory results.

Second, because patient ethnicity data were not available in our database, eGFR values for African-American patients were underestimated by a small increment because of the omission of this factor for the calculation. The measurement errors of the eGFR values affected the estimated subset of African-Americans, about 10% of the total employed population.[9] The consequence of this omission is that some African-Americans may have been included in the CKD group, although they should not have been considered CKD patients. Considering that CKD patients incur higher medical costs, this subset of patients would have lowered the average costs of the CKD group. Therefore, from this perspective, we can qualify our estimate of the cost burden due to CKD as conservative.

Third, the study evaluated only direct medical costs. Information to determine the indirect costs of CKD, such as work productivity loss and reduced quality of life, was not available. Despite our attempt to control for measured covariates through multivariate analyses, we do not know the extent to which unmeasured confounding factors influenced the total all-cause cost differences observed in the current study.

Fourth, the observational design was susceptible to various biases. We recognize that a randomized trial may be the ideal way of addressing this question; however, it is impossible to randomize patients to develop CKD. It would be possible, on the other hand, to randomize patients to a program of early and intensive intervention versus standard care to evaluate the effects of early profiling and active management on the progression of CKD. Future research studies that address this issue are warranted. In the absence of such randomized trials, well-designed observational studies with appropriate statistical techniques adjusting for confounding factors provide valuable information with real-life scenarios and high generalizability. In the current analysis, we tried to identify the cost increase associated with CKD by comparing the costs in the CKD group with the costs in a reference no-CKD group. A subset analysis was conducted to compare the pre- versus post-CKD all-cause costs for patients developing CKD.

Fifth, the current study may also 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 CKD could have occurred in patients who did not seek care (especially those who did not have symptomatic manifestations). Furthermore, since laboratory results are available only for a subset of beneficiaries tested within a given carrier's laboratory network, representing approximately 10% of the IHCIS population, it is possible that we are under-estimating the prevalence of CKD development. Finally, our database excluded information about long-term nursing home care.

Previous studies have demonstrated the detrimental health effects and associated costs of CKD-related complications such as anemia.[10-14] The current study reported an adverse economic association between CKD and all-cause health care costs in patients with diabetes and/or hypertension. Early identification and assessment of CKD among diabetic and/or hypertensive patients may have the potential to reduce the utilization of health care resources and may also improve patient and clinical outcomes by delaying progression to more advanced costly stages of CKD.

Conclusion

Despite limitations associated with a retrospective observational design, this large study demonstrated that CKD was associated with a significant increase in all-cause health care costs in patients with diabetes and/or hypertension. The cost difference associated with CKD remained significant after adjusting for important comorbidities that may otherwise contribute to the increased costs. Among patients who developed CKD, costs directly attributable to CKD treatment represented 9%-19% of total all-cause medical service costs. Further studies are warranted to evaluate whether earlier identification of CKD could prevent cost escalations in patients with diabetes and/or hypertension.

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DISCLOSURES

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Study concept and design and data interpretation were primarily the work of Bookhart and Lefebvre, with assistance from the other authors. Laliberté performed the data collection with the assistance of Vekeman and Lefebvre. Writing of the manuscript was shared by Laliberté, Vekeman, Duh, and Lefebvre. Revision of the manuscript was shared by Bookhart, Corral, Bailey, and Piech.

REFERENCES

1. United States Renal Data System. 2007 Annual data report. Available at: http://www.usrds.org/reference.htm. Accessed April 9, 2009.

2. Kramer H, Molitch ME. Screening for kidney disease in adults with diabetes. *Diabetes Care*. 2005;28(7):1813-16.

3. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298(17):2038-47.

4. Grossman E, Messerli FH. Hypertension and diabetes. *Adv Cardiol*. 2008;45:82-106.

5. American Diabetes Association. Economic costs of diabetes in the U.S. in 2007. *Diabetes Care*. 2008;31(3):596-615.

6. Amin SP, Mullins CD, Duncan BS, et al. Direct health care costs for treatment of diabetes mellitus and hypertension in an IPA-group-model HMO. *Am J Health Syst Pharm*. 1999;56(15):1515-20.

7. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139(2):137-47.

8. Craven N. Management of chronic kidney disease in the primary care setting. *BC Medical Journal*. 2005;47(6):296-99. Available at: http://www.bcmj.org/management-chronic-kidney-disease-primary-care-setting. Accessed April 9, 2009.

9. U.S. Census Bureau. Current population survey, racial statistics branch. Available at: http://www.census.gov/population/socdemo/race/black/ppl-164/tab11.pdf. Accessed April 9, 2009.

10. Penninx B, Pahor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc.* 2004;52(5):719-24.

11. Dharmarajan T, Norkus E. Mild anemia and the risk of falls in older adults from nursing homes and the community. *J Am Med Dir Assoc.* 2004;5(6):395-400.

12. Cesari M, Pahor M, Lauretani F, et al. Bone density and hemoglobin levels in older persons: results from the InCHIANTI study. *Osteoporos Int.* 2005;16(6):691-99.

13. Chaves P, Mody S, Blasi M, et al. Healthcare costs and resource utilization associated with chronic anemia in older adults. *J Manag Care Med.* 2005;8(2):13-20. Available at: http://www.namcp.org/JMCM_V8N2.pdf. Accessed April 9, 2009.

14. Lefebvre P, Duh M, Buteau S, et al. Medical costs of untreated anemia in elderly patients with predialysis chronic kidney disease. *J Am Soc Nephrol.* 2006;17(12):497-502.