

All-Cause Costs Increase Exponentially with Increased Chronic Kidney Disease Stage

HIGHLIGHTS

- › Cost as it Relates to Stages of Chronic Kidney Disease
- › Economic Burden of Chronic Kidney Disease
- › Readmission as Cost Driver

All-Cause Costs Increase Exponentially with Increased Chronic Kidney Disease Stage

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OVERVIEW

This supplement to *The American Journal of Managed Care*[®] evaluates the cost of chronic kidney disease on US health plans, and how the economic burden increases with each stage of chronic kidney disease.

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All-Cause Costs Increase Exponentially with Increased Chronic Kidney Disease Stage

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Chronic kidney disease (CKD) is a common disorder and has become a major public health concern in the United States, affecting an estimated 13.6% of the adult population.^{1,2} Simulation models predict that CKD prevalence in adults aged ≥ 30 years will increase to 14.4% by 2020 and 16.7% by 2030.³ CKD patients, even in early disease stages, carry a disproportionate burden of cardiovascular morbidity, mortality, healthcare utilization, and costs.⁴⁻¹⁰

The economic burden of CKD is substantial. According to the US Renal Data System, in 2013 among fee-for-service Medicare patients, total medical costs were \$50.4 billion for CKD (excluding end-stage renal disease [ESRD]), and another \$30.9 billion for the ESRD patient population.² In multiple studies, costs for CKD patients were higher than for those without CKD, matched for age and comorbidity, with costs increasing by disease stage and presence of comorbid diabetes mellitus (DM).¹¹⁻¹⁴ Data from commercial insurance databases show that both inpatient (IP) and outpatient (OP) costs contribute significantly to total CKD costs.¹¹

Clinical practice guidelines published by the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative, and more recently by Kidney Disease: Improving Global Outcomes, classify CKD by its stage of severity and provide specific therapeutic recommendations for reducing disease progression.¹⁵⁻¹⁷ Several interventions addressing potentially modifiable risk factors have been associated with decreased healthcare utilization in the CKD population, including use of renin-angiotensin-aldosterone inhibitors (RAASi), correction of volume overload, and proper nutrition.^{12,18} However, rates of attainment of recommended blood pressure targets and other treatment goals remain low.^{19,20}

In this study, we used a large electronic medical records (EMR) database to evaluate all-cause costs, as well as factors contributing to costs, at progressive CKD stages. We hypothesized that all-cause costs increase by CKD stage, and we hoped to identify major cost drivers to recognize opportunities for cost reductions. We further hypothesized that other factors, such as hyperkalemia, may contribute to cost independently through increased and repeated laboratory testing, more frequent provider office visits, as well as subsequent hospitalizations.

ABSTRACT

Objective: To evaluate the economic impact of chronic kidney disease (CKD) on US health plans.

Study Design: A retrospective analysis identified patients with a renin-angiotensin-aldosterone system inhibitor (RAASi) prescription from an electronic medical record (EMR) database (Humedical); those with ≥ 90 days in ≥ 1 CKD stage were selected based on estimated glomerular filtration rate or diagnosis code, and a cohort on RAASi medications without CKD was selected. Costs for specific services obtained from OptumInsight were applied to services in EMR data of patients aged < 65 years (commercial) and ≥ 65 years (Medicare). Dialysis costs were excluded.

Results: The study included 106,050 patients with CKD and 56,761 no-CKD controls (90,302 commercial and 72,509 Medicare overall). Mean annualized all-cause costs increased exponentially with advancing stage, from \$7537 (no CKD) to \$76,969 (CKD stages 4-5) in the commercial group, and \$8091 (no CKD) to \$46,178 (CKD stages 4-5) in the Medicare group ($P < .001$; all comparisons with preceding disease stage). Mean costs for end-stage renal disease (ESRD) patients were \$121,948 and \$87,339 in the commercial and Medicare groups, respectively. Inpatient costs were the largest contributor to total costs, and their relative contribution increased with advancing CKD.

Conclusions: Cost to US health plans increases exponentially with each CKD stage progression. ESRD costs are even higher. Because readmissions lead to higher costs, efforts to reduce readmissions would result in cost reductions. Furthermore, healthcare reengineering paradigms that manage increasing comorbidities with advancing CKD, including heart failure, diabetes, and hyperkalemia, should offer additional potential for cost reductions.

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For author information and disclosures, see end of text.

METHODS

Study Population and Cohorts

We queried the Humedica (Boston, Massachusetts) database EMRs covering approximately 7 million patients during 2007 to 2012 and selected patients with ≥ 1 RAASi prescription before July 1, 2009 (index date).²¹ Study patients were persons receiving care from providers in integrated health delivery networks across the United States, including those insured by private insurance, Medicare, Medicaid, other health insurance, or uninsured. The data were inclusive of services provided in hospitals as well as office and OP care. Medication data included written prescriptions and medication administrations that occurred in-clinic and/or in-hospital. We required postindex evidence of new, sustained, or progressive CKD (stages 2, 3a, 3b, or 4-5) or ESRD identified by estimated glomerular filtration rate (eGFR) or diagnosis code (definitions in [Supplementary Item S1](#)). Patients were included in the analysis of each postindex CKD stage lasting ≥ 90 days. Additionally, patients without evidence of CKD or ESRD during the study period (2007-2012) and with ≥ 90 days of postindex data were included as a no-CKD comparison group. Patients with ESRD before the index date and those receiving the above-recommended RAASi dosing at index were excluded from the current analyses.

Demographic and clinical characteristics (with the exception of sex, race, and region) were evaluated for each patient at the onset of each included CKD stage. Comorbidities were identified by single occurrence of any indicator in pre-stage data using diagnosis codes, laboratory values, or hypoglycemic medications ([Supplementary Item S2](#)). RAASi prescriptions were classified by dose level at the beginning of each CKD stage as “maximum” (recommended labeled dose; see [Supplementary Item S3](#)), “submaximum” (any lesser amount), or “discontinued” (> 390 days elapsed since most recent prescription). OP diuretic therapy during the 12-month period before the stage start date was categorized hierarchically as loop diuretic, other diuretic, or none. Visit frequency was characterized as infrequent (0-1 visit) or frequent (≥ 2 visits) based on the number of office/clinic visits in the 12-month period concluding each stage.

Patients were assigned by pre-index age to 2 categories for modeling insurance coverage: Medicare (aged ≥ 65 years) and commercial (aged < 65 years, or unspecified).

Classification of Services and Medications

In the EMR data, healthcare services were grouped by calendar day and classified as IP or emergency department (ED) visits or by type of OP services. OP prescriptions were identified by generic name of the primary ingredient, regardless of dose, brand, or formulation.

Cost of Services and Medications in Claims Data

Average health plan allowed cost was obtained from 2013 commercial insurance and Medicare claims data (OptumInsight, Minneapolis, MN)

representing payments made by health insurers exclusive of patient liability, as follows: per IP day for surgical and nonsurgical admissions with various comorbidities; per visit for multiple types of hospital/facility OP visits; per calendar day for physician services in office and hospital; and per filled prescription (along with percent refills) for 120 medications accounting for approximately 75% of all postindex OP prescriptions. Costs were normalized to 2016 US dollars at 3% per annum.

All-Cause Costs: Application Cost in Claims Data for Services and Prescriptions Identified in EMR

Average allowed cost per service in commercial and Medicare insurance claims was applied to each service event occurring during each CKD stage among patients in the commercial and Medicare groups, respectively. Average cost per day of hospital care plus IP physician care was applied to each IP day, distinguishing medical and surgical admissions and patient comorbidities. The cost applied to hospital OP and ED visits included both hospital and physician services. Cost per visit was applied to each office, home health, or laboratory visit. OP dialysis services in patients without evidence of kidney transplant were excluded from ESRD costs due to significant underrepresentation in the source data. Average cost per written prescription, including initial fill of prescription and refills, was applied to each evaluated medication; the average cost per prescription of these drugs, weighted at actual usage in the data set, was applied to prescriptions of drugs for which specific cost data were not acquired. IP pharmacy costs were captured in the cost per IP day.

Descriptive Analyses

Each CKD stage (including no-CKD and ESRD) was analyzed separately within the commercial and Medicare groups. The primary analysis assessed mean annualized all-cause cost per patient in total for IP, ED, and OP services, and for OP medications, comparing each CKD stage with the preceding stage. In consideration of clinical interest in hyperkalemia as a potential driver of avoidable cost, particularly in IP admissions and readmissions, additional analyses were conducted on this variable. A secondary analysis examined the frequency and cost contribution of IP readmissions within 30 days, segmented by whether or not hyperkalemia was identified during the original hospital stay. The cost contribution of readmissions was evaluated as the percentage of total IP costs derived from IP days in 30-day readmissions.

Statistical Analyses

Analysis of variance was performed in a mixed model with repeated measures to evaluate the statistical significance of observed differences in mean annualized total costs between each CKD stage and the preceding stage by payer group. Multivariate regression assessed predictors of cost within each CKD stage and payer group, with minor exclusions (unknown/other region; RAASi above maximum recommended dose; missing age/sex; kidney transplant patients in

ESRD). The dependent variable of total annualized cost + \$1 during each CKD stage and for the postindex period in the no-CKD cohort was log-transformed due to skew. Independent variables, evaluated with a stepwise selection procedure ($\alpha = .05$), included age (continuous), sex, region, all defined comorbidities (heart failure [HF], DM, hypertension, cardiovascular disease [CVD], and hyperkalemia), RAASi therapy (maximum or submaximum dose vs discontinued), visit frequency (frequent/infrequent), and diuretics (loop/other/none). Interaction terms (selected *a priori* for clinical significance) included HF with hyperkalemia and RAASi therapy with specified comorbidities (DM, CVD, hypertension, and hyperkalemia).

A post hoc analysis of the multiple regression findings compared predicted annual cost of patients with and without hyperkalemia by modeling costs associated with variables not involving hyperkalemia at their mean values in each payer group and CKD stage, and variables involving hyperkalemia at their mean value among comparator group patients who had hyperkalemia.

P values $< .05$ were considered significant. All statistical analyses were performed using SAS/STAT software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Demographics and Clinical Characteristics

The study population included 162,811 individuals, including 106,050 patients analyzed in at least one stage of CKD or ESRD and 56,761 no-CKD controls. Of these, 90,302 were included in the commercial group (mean age 53.7 years, 50% female, 61% from South region) and 72,509 were in the Medicare group (mean age 76.0 years, 58% female, 54% from South region) (Table). Patients in the no-CKD subgroup were younger than those with CKD in both insurance groups. The prevalence of all comorbidities except hypertension increased with advancing CKD stage. There was an even more pronounced increase in hyperkalemia, with 56% of commercial patients and 58% of Medicare patients with CKD stages 4-5 experiencing hyperkalemia, and even higher rates among ESRD patients. Across nearly all CKD stages, at least 85% of patients had ≥ 2 office/clinic visits in the measured year.

Prescribing patterns of RAASi as well as type of diuretic therapy differed by CKD stage but were comparable between the commercial and Medicare groups (Table). Overall, 15% to 19% of patients with CKD had been discontinued from RAASi therapy, with rates reaching 28% and 27% among ESRD patients in the commercial and Medicare groups, respectively. Prescriptions for loop diuretics were more common as CKD progressed.

Annualized Total Cost per Patient, by CKD Stage

Total all-cause costs increased exponentially as CKD progressed in both commercial and Medicare groups, with the slope of the cost increase steeper in the commercial versus the Medicare cohort (Figure 1). For

patients aged < 65 years, modeled at commercial insurance payment rates, average annualized cost per patient rose 57% or more with each CKD stage. Among patients aged ≥ 65 years, modeled at Medicare rates, average annualized cost per patient climbed 68% or more as patients progressed into CKD stages 4-5 or ESRD (excluding dialysis cost), while increasing 45% or less with progression into stages 3a and 3b. Commercial insurance costs exceeded Medicare costs in each CKD stage.

Cost by Medical Service Category in Each CKD Stage

The drivers of increasing costs with advancing CKD were consistent between commercial and Medicare patients (Figure 1). Rising IP costs accounted for at least 80% of the cost increase observed with disease progression into CKD stages 3b, 4-5, and ESRD, while medications contributed $\leq 5\%$ of the change at each of those stages. The pattern differed in early-stage disease: between no-CKD and CKD stage 2, medications accounted for 18% to 19% of the cost increase, while OP costs accounted for 21% and 27% of the cost increase in the commercial and Medicare groups, respectively.

Multivariate Analysis of Cost Predictors

Multivariate regression within each payer by CKD stage evaluated predictors of medical costs, which were largely consistent in pattern between the commercial and Medicare cohorts (Table S1). Important predictors of cost included office/clinic visit frequency ≥ 2 and comorbidity status, especially CVD and HF, which were consistent predictors of higher costs in each CKD stage as well as in ESRD. Diabetes was a less powerful predictor of costs than most other comorbidities, and it was omitted due to nonsignificance when evaluated in ESRD. Interestingly, diagnosed hypertension was consistently associated with lower costs in both populations. Continued RAASi therapy at maximum or submaximum doses contributed modestly to lower costs among patients with early-stage CKD, and to higher costs in Medicare patients without CKD. The impact of gender on costs was inconsistent across payers and disease stages.

A post hoc analysis using results of the multiple regressions compared predicted annual cost of patients with and without a history of hyperkalemia. Modeled costs were higher with a history of hyperkalemia in all disease groups ($P < .001$ in all CKD stages; $P < .01$ in ESRD) (Table S1). Annual costs for patients with a history of hyperkalemia were 38% higher in CKD stages 4-5 and 57% higher in ESRD compared with patients without hyperkalemia in the commercial group; they were 22% and 26% higher, respectively, in the Medicare group (Figure 2). In CKD stages 2, 3a, and 3b, a history of hyperkalemia contributed 16% to 18% higher annual costs in commercial patients and 7% to 11% higher annual costs in Medicare patients.

Costs of 30-Day Readmission Rates

As noted earlier, IP services were a major contributor to total costs in each CKD stage. Notably, 30-day hospital readmission rates

TABLE. Demographic and Baseline Characteristics by Commercial Group (A) and Medicare Group (B).

A. Commercial (aged <65 years)							
CKD Stage:	No-CKD	Stage 2	Stage 3a	Stage 3b	Stages 4–5	ESRD	Total ^a
N	52,175	28,540	6315	3963	3734	1197	90,302
Age, mean (SD) ^b	51.0 (9.17)	57.5 (7.05)	58.6 (7.00)	57.9 (7.42)	57.0 (8.01)	55.9 (9.04)	53.7 (8.98)
Gender, n (%)							
Male	25,280 (48)	14,343 (50)	3511 (56)	2170 (55)	1954 (52)	624 (52)	45,086 (50)
Female	26,819 (51)	14,069 (49)	2766 (44)	1762 (44)	1732 (46)	562 (47)	44,930 (50)
Race, n (%)							
African American	4865 (9)	5052 (18)	1365 (22)	876 (22)	894 (24)	316 (26)	12,138 (13)
Caucasian	28,486 (55)	14,003 (49)	2789 (44)	1713 (43)	1461 (39)	421 (35)	46,535 (52)
Other/Unknown	18,824 (36)	9485 (33)	2161 (34)	1374 (35)	1379 (37)	460 (38)	31,629 (35)
Comorbidities, n (%)							
Diabetes	16,692 (32)	11,962 (42)	3465 (55)	2459 (62)	2458 (66)	815 (68)	34,135 (38)
Heart Failure	1489 (3)	2011 (7)	825 (13)	800 (20)	1049 (28)	398 (33)	5320 (6)
Cardiovascular Disease	11,958 (23)	10,718 (38)	3033 (48)	2190 (55)	2357 (63)	813 (68)	27,728 (31)
Hypertension	45,001 (86)	26,377 (92)	5850 (93)	3682 (93)	3440 (92)	1107 (92)	80,118 (89)
Hyperkalemia	4551 (9)	5411 (19)	1906 (30)	1660 (42)	2099 (56)	795 (66)	13,762 (15)
RAASi Dose Level, n (%) ^c							
Maximum	8256 (16)	6159 (22)	1545 (24)	994 (25)	876 (23)	248 (21)	16,715 (19)
Submaximum	36,187 (69)	17,878 (63)	3801 (60)	2318 (58)	2148 (58)	607 (51)	59,609 (66)
Discontinued	7556 (14)	4371 (15)	943 (15)	629 (16)	689 (18)	339 (28)	13,632 (15)
B. Medicare (aged ≥65 years)							
CKD Stage:	No-CKD	Stage 2	Stage 3a	Stage 3b	Stages 4–5	ESRD	Total ^a
N	4586	43,024	15,001	12,651	10,014	1440	72,509
Age, mean (SD) ^b	71.4 (4.85)	75.1 (5.93)	77.9 (5.99)	78.7 (6.20)	78.9 (6.15)	77.5 (6.27)	76.0 (6.24)
Gender, n (%)							
Male	4353 (95)	14,436 (34)	6669 (44)	5764 (46)	4594 (46)	681 (47)	30,382 (42)
Female	233 (5)	28,588 (66)	8332 (56)	6887 (54)	5420 (54)	759 (53)	42,127 (58)
Race, n (%)							
African American	138 (3)	3504 (8)	1713 (11)	1542 (12)	1425 (14)	285 (20)	7031 (10)
Caucasian	2743 (60)	26,138 (61)	8824 (59)	7198 (57)	5298 (53)	636 (44)	42,797 (59)
Other/Unknown	1705 (37)	13,382 (31)	4464 (30)	3911 (31)	3291 (33)	519 (36)	22,681 (31)
Comorbidities, n (%)							
Diabetes	1632 (36)	16,674 (39)	6951 (46)	6449 (51)	5750 (57)	949 (66)	30,809 (42)
Heart Failure	268 (6)	4082 (9)	2894 (19)	3445 (27)	3932 (39)	643 (45)	11,078 (15)
Cardiovascular Disease	2114 (46)	22,462 (52)	9965 (66)	9077 (72)	7785 (78)	1173 (81)	41,852 (58)
Hypertension	3844 (84)	39,558 (92)	13,951 (93)	11,795 (93)	9254 (92)	1348 (94)	66,140 (91)
Hyperkalemia	562 (12)	8336 (19)	4773 (32)	5303 (42)	5819 (58)	1044 (73)	19,374 (27)
RAASi Dose Level, n (%) ^c							
Maximum	809 (18)	8995 (21)	3548 (24)	2990 (24)	2144 (21)	275 (19)	15,544 (21)
Submaximum	3098 (68)	26,640 (62)	8907 (59)	7508 (59)	5911 (59)	773 (54)	44,296 (61)
Discontinued	662 (14)	7182 (17)	2476 (17)	2087 (16)	1910 (19)	386 (27)	12,416 (17)

CKD indicates chronic kidney disease; ESRD, end-stage renal disease; RAASi, renin-angiotensin-aldosterone system inhibitor.

^aTotal population represents unique patients and does not foot to sum of Ns by stage because patients could contribute data in more than one stage of CKD. For total population characteristics, each patient was evaluated as of the first included CKD stage or the index date (No-CKD). Totals by sex exclude patients who lack data on gender and age for privacy reasons (n=286; included in the larger commercial group).

^bAge at each stage was computed from birth year; patients born before 1924 were designated 1924 for privacy reasons.

^cPatients on higher-than-recommended dose of RAASi (n=346 commercial, n=353 Medicare) were excluded from the Table.

increased steadily as disease progressed in the commercial and Medicare cohorts (Figure 3). Readmissions contributed substantially to total IP costs, representing 35% to 36% of total IP costs among ESRD patients and 18% to 33% of such costs among patients with CKD stages 3a, 3b, and 4-5 (Figure 4). In comparison, costs associated with 30-day readmissions represented 10% to 12% of total IP costs for patients in the no-CKD cohort. Post hoc univariate analysis found a trend towards higher rates of 30-day readmission following hospital admissions in which hyperkalemia occurred; this trend reached statistical significance in several CKD subgroups, including stage 2 ($P < .001$) and ESRD ($P = .048$) in the commercial cohort and no-CKD ($P = .003$), stage 2 ($P < .001$), and stage 3b ($P < .001$) in the Medicare cohort.

Average Length of Hospital Stay

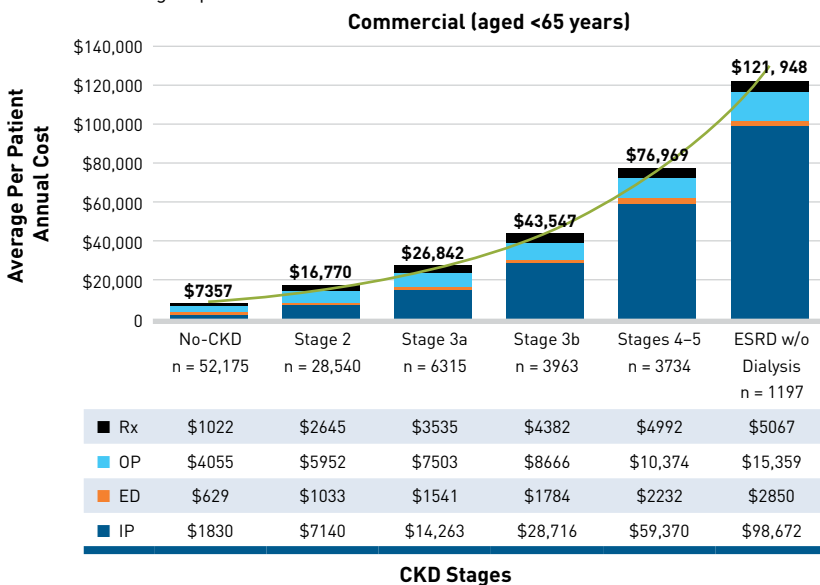
In both the commercial and Medicare groups, average length of hospital stay (ALOS) increased with each stage of CKD (Figure 4). ALOS in 30-day readmissions exceeded the ALOS of nonreadmissions by 0.8-1.1 days in the commercial group, 0.5-0.9 days in the Medicare group in stages other than ESRD, and 0.2 (commercial) to 0.4 (Medicare) days in ESRD.

DISCUSSION

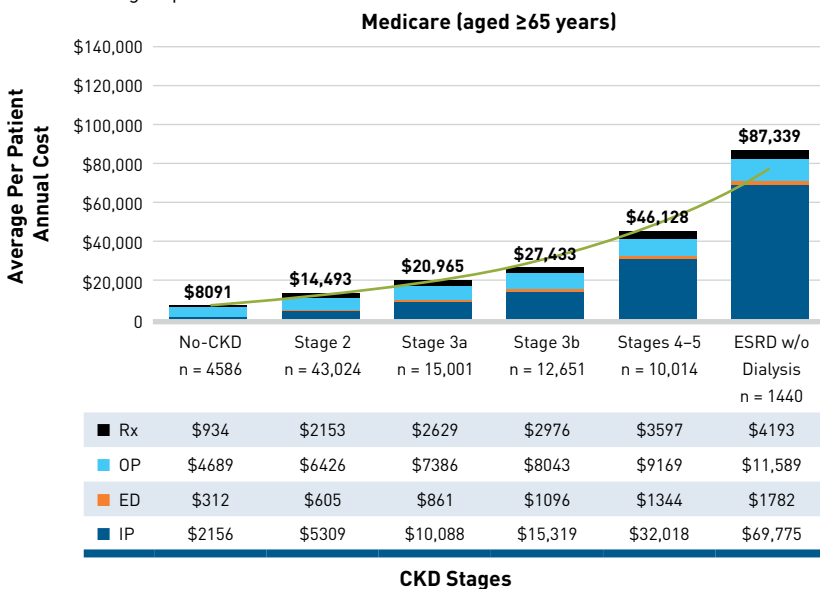
These results demonstrate that costs increase exponentially with advancing CKD stage in patients prescribed RAASi in the commercial and Medicare groups. Importantly, costs increased significantly with each disease stage, even at early stages. The cost increase with advancing CKD in the commercial group was greater than the cost increase in the Medicare group, particularly from stage 3a through ESRD. The reasons for the disproportionate increase between insurance groups warrant further investigation but likely reflect, at least in part, lower levels of federal government reimbursement, along with slightly higher IP readmission rates in the commercial group. IP costs were the key driver of the cost increase, becoming a larger proportion of total costs for each successive CKD stage. Moreover, 30-day readmissions were a key driver of IP costs, as the percentage of IP stays resulting in readmission increased steadily with each CKD stage. Costs for OP

FIGURE 1. Mean Annualized Costs by Medical Service Category and CKD Stage by Commercial Group (A) and Medicare Group (B).

A. Commercial group.



B. Medicare group.



CKD indicates chronic kidney disease; ED, emergency department; ESRD, end-stage renal disease; IP, inpatient; OP, outpatient; Rx, prescription. All Comparisons $P < .0001$. Total Costs and costs by service category have been rounded to the nearest dollar.

services, ED use, and medications also increased incrementally with CKD disease stage, albeit to a much smaller extent than IP costs. The cost increases with increasing CKD stage are consistent with observations showing that age-standardized mortality, cardiovascular events, and hospitalization rates increase dramatically as eGFR declines.⁶

TABLE S1. Predictors of Total Annualized Cost (log-transformed) by CKD Stage in the Commercial Group (A) and Medicare Group (B).

Covariate	A. Commercial Cohort											
	Commercial Payer: Multivariate Regression of Specified Covariates											
	R2 = .1459 No-CKD		R2 = .1459 CKD2		R2 = .1370 CKD3a		R2 = .1348 CKD3b		R2 = .1397 CKD 4-5		R2 = .1144 ESRD	
	Estimate	P value	Estimate	P value	Estimate	P value	Estimate	P value	Estimate	P value	Estimate	P value
Age	.00428	<.0001	-.0041	<.0001	-.00772	.0003	-.00571	.0303	-.00765	.0072	x	x
Sex - Female (Male) ^a	.25103	<.0001	.23334	<.0001	.20836	<.0001	.13371	.0006	.1024	.0232	x	x
Region-Midwest (South) ^a	-.33592	<.0001	-.28937	<.0001	-.296	<.0001	-.39537	<.0001	-.50987	<.0001	-.34617	.0001
Region-Northeast (South) ^a	-.39753	<.0001	-.31998	<.0001	-.22814	<.0001	-.33597	<.0001	-.53168	<.0001	-.25362	.0919
HF	.14624	<.0001	.20874	<.0001	.40189	<.0001	.50001	<.0001	.35764	<.0001	.245	.1448
DM	.22151	<.0001	.21293	<.0001	.29742	<.0001	.0048	.9612	.36623	<.0001	x	x
HTN	-.21201	<.0001	-.22345	<.0001	-.13819	.0168	-.20381	.0088	-.19088	.0261	x	x
CVD	.21713	<.0001	.28919	<.0001	.46294	<.0001	.46092	<.0001	.59425	<.0001	.41014	<.0001
HK	.11428	<.0001	.12765	<.0001	.14568	<.0001	.16317	<.0001	.3223	<.0001	.29022	.0039
RAASi - Max/Submax (Discontinued) ^a	-.03241	.321	-.2222	<.0001	-.09606	.0287	-.27924	.0008	x	x	x	x
Diuretic - Loop (Diuretic - None) ^a	.23589	<.0001	.26491	<.0001	.12607	.0075	x	x	x	x	x	x
Diuretic - Other (Diuretic - None) ^a	.00111	.9172	-.02256	.1142	-.07277	.0338	x	x	x	x	x	x
Visit (Infrequent) ^a	.84206	<.0001	.62599	<.0001	.52682	<.0001	.51386	<.0001	.37336	<.0001	.26286	.0324
HF by HK interaction	x	x	.29285	<.0001	x	x	x	x	x	x	.38424	.0462
RAASi by DM interaction	.12451	<.0001	.16257	<.0001	x	x	.30615	.0045	x	x	x	x
RAASi by CVD interaction	.07776	.0166	.14526	<.0001	x	x	x	x	x	x	x	x
RAASi by HF interaction	x	x	x	x	x	x	x	x	x	x	x	x
RAASi by HK interaction	x	x	x	x	x	x	x	x	x	x	x	x
RAASi by HTN interaction	.08484	.0128	x	x	x	x	x	x	x	x	x	x

(continued)

The high costs associated with CKD underscore the need to identify interventions and strategies for reducing costs. Identifying reliable drivers of costs associated with CKD stage progression is important for informing health policy, as it provides more accurate attributes of the determinants of healthcare utilization within a diverse population. Based on our results, identifying drivers of hospital admissions and readmissions may be key because some may be preventable. Hospitalization risk with CKD is disproportionate with advancing CKD, reflecting the burden of complications due to kidney disease,¹⁴ although some studies do show a plateau effect on cost in advanced stages due to a survivor effect, in which the sickest and most costly die sooner than other patients.¹¹ In one study, patients with higher CKD stage, despite their increased complexity, had higher risk of potentially preventable hospitalizations than those without CKD, with the most frequent admission diagnoses being hyperkalemia, HF, and volume overload.¹⁸ Hospitalization risk, as well as adverse outcomes, were attenuated in CKD patients who had regular follow-up with measurements of serum creatinine; this difference was evident in stage 3a but not in the more advanced stages.⁶ More aggressive CKD management may also reduce hospitalizations; for example, use of angiotensin-converting enzyme inhibitors (ACEis) was associated with reduced hospitalization risk in CKD,¹² but these and other RAASi were underutilized in large cohort studies due to concerns about hyperkalemia.²¹⁻²⁴

Readmissions were identified as a key driver of costs in our study. CKD is an independent risk factor for higher 30-day readmission rates in a variety of settings, including after percutaneous

TABLE S1. Predictors of Total Annualized Cost (log-transformed) by CKD Stage in the Commercial Group (A) and Medicare Group (B). (Continued)

Covariate	B. Medicare cohort												
	Medicare Payer: Multivariate Regression of Specified Covariates												
	R2 = .1082 No-CKD		R2 = .0866 CKD2		R2 = .0911 CKD3a		R2 = .0904 CKD3b		R2 = .0827 CKD 4-5		R2 = .0573 ESRD		
Estimate	P value	Estimate	P value	Estimate	P value	Estimate	P value	Estimate	P value	Estimate	P value	Estimate	P value
Age	.00792	.0218	.00505	<.0001	-.00344	.0228	.0005	-.0059	.0004	-.00712	.0004	x	x
Sex - Female (Male) ^a	-.29028	.0001	.04706	<.0001	.0729	<.0001	x	x	x	x	x	x	x
Region-Midwest (South) ^a	-.08729	.0559	-.22706	<.0001	-.16448	<.0001	-.27445	<.0001	-.36431	<.0001	-.28745	-.28745	.0012
Region-Northeast (South) ^a	-.27343	<.0001	-.19568	<.0001	-.101	<.0001	-.18342	<.0001	-.2243	<.0001	-.26529	-.26529	.0206
HF	x	x	.22414	<.0001	.31891	<.0001	.3084	<.0001	.28122	<.0001	.50555	.50555	<.0001
DM	.14401	<.0001	.08799	.0003	.1582	<.0001	.17204	<.0001	.15356	<.0001	x	x	x
HTN	-.15591	.0006	-.31547	<.0001	-.25358	<.0001	-.23598	<.0001	-.28531	<.0001	x	x	x
CVD	.2131	<.0001	.22777	<.0001	.36803	<.0001	.38064	<.0001	.33345	<.0001	.21364	.21364	.041
HK	x	x	.08064	<.0001	.06976	.0002	.10339	<.0001	.13073	<.0001	.22962	.22962	.0085
RAASi - Max/Submax (Discontinued) ^a	.24253	<.0001	-.23900	<.0001	x	x	x	x	x	x	x	x	x
Diuretic - Loop (Diuretic - None) ^a	.17107	.0133	.13263	<.0001	.06517	.0108	.08772	.0015	-.00742	.8068	x	x	x
Diuretic - Other (Diuretic - None) ^a	.04581	.2104	-.04909	<.0001	-.15277	<.0001	-.10659	<.0001	-.07591	.0221	x	x	x
Visit (Infrequent) ^a	.81071	<.0001	.57055	<.0001	.47036	<.0001	.42729	<.0001	.3638	<.0001	.4152	.4152	.0006
HF by HK interaction	x	x	x	x	x	x	x	x	.15165	.003	x	x	x
RAASi by DM interaction	x	x	.10489	<.0001	x	x	x	x	x	x	x	x	x
RAASi by CVD interaction	x	x	.09585	.0002	x	x	x	x	x	x	x	x	x
RAASi by HF interaction	x	x	x	x	x	x	x	x	x	x	x	x	x
RAASi by HK interaction	x	x	x	x	x	x	x	x	x	x	x	x	x
RAASi by HTN interaction	.08484	.0128	x	x	x	x	x	x	x	x	x	x	x

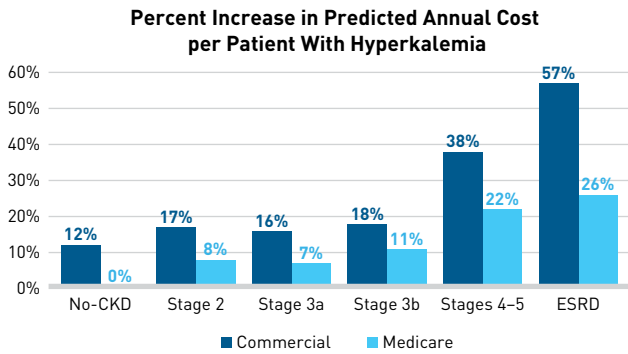
CKD indicates chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; HF, heart failure; HK, hyperkalemia; HTN, hypertension; RAASi, renin-angiotensin-aldosterone system inhibitor.

^aBaseline values for multipart variables: Sex = Male; Region = South; Visit = Infrequent; Loop diuretic = None; Other diuretic = none.

coronary intervention,²⁵ acute myocardial infarction,²⁶ total hip arthroplasty,²⁷ or treatment for HF.²⁸ Notably, a significant proportion of readmissions among CKD patients may be avoidable. For example, in a tertiary medical center in Boston, 2398 of 10,731 consecutive adult discharges (22.3%) were followed by readmission within 30 days, including 410 of 1776 patients (23.1%) with CKD.²⁹ In the CKD cohort, nearly half of the readmissions were classified as potentially avoidable, most frequently with primary readmission diagnoses of HF, infection, renal failure, and ischemic heart disease. Taken together, these findings support guideline recommendations that efforts to reduce hospitalizations and readmissions in CKD patients should focus on the management of associated comorbid conditions, particularly CVD.^{16,17} By extension to the present results, these efforts should translate into substantial cost reductions. One approach for reducing 30-day readmissions may be to assess CKD stage from available laboratory data to identify high-risk patients. Such patients may benefit from a postdischarge kidney disease clinic, which has not been endorsed thus far by guidelines but could hold great potential for reducing some of the iatrogenic drivers of CKD, as well as help to tailor care around the dynamic needs of patients during such a crucial time.

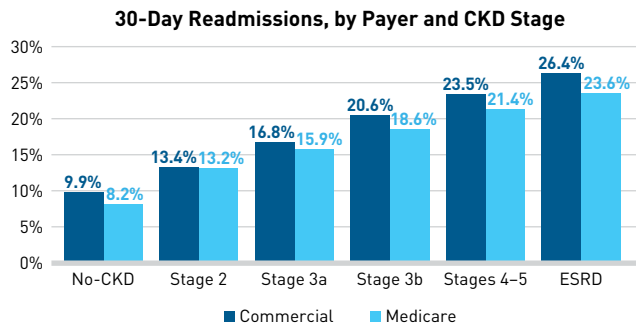
The cost increases with advancing CKD stage also underscore the need to identify interventions that will slow progression at earlier disease stages. Several lifestyle interventions

FIGURE 2. Percentage Difference in Predicted Annual Cost With Versus Without Hyperkalemia.^a



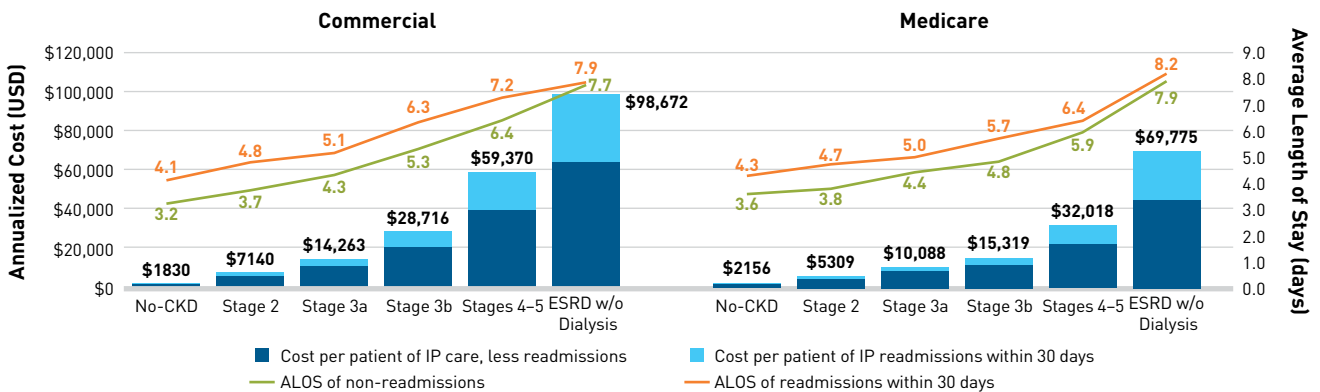
CKD indicates chronic kidney disease; ESRD, end-stage renal disease; RAASi, renin-angiotensin-aldosterone system inhibitor.
^aAdjusted for age, sex, region, comorbidities, RAASi and diuretic therapies, and clinically significant interactions in multivariate regression analyses.

FIGURE 3. Percentage of IP Hospital Stays Resulting in Readmissions Occurring Within 30 Days of Discharge.



CKD indicates chronic kidney disease; ESRD, end-stage renal disease; IP, inpatient.

FIGURE 4. Annualized Cost per Patient of IP Care, Showing the Contribution of Readmissions Within ≥30 Days, and ALOS for Readmissions Occurring Within 30 Days of Discharge Versus Other IP Admissions.



ALOS indicates average length of stay; CKD, chronic kidney disease; ESRD, end-stage renal disease; IP, inpatient.

are recommended, including weight management, smoking cessation, exercise, dietary sodium restriction, and drug interventions targeting key risk factors such as elevated blood pressure and lipid and blood glucose levels.⁵ Blood-pressure control with antihypertensive medications is the foundation for managing CKD and for reducing cardiovascular risk. ACEi or angiotensin receptor blockers (ARBs) are recommended for CKD patients, particularly those with proteinuria.^{16,17} In a recent meta-analysis, use of ACEi or ARBs in CKD patients was associated with reduced risk of renal failure and adverse CVD outcomes compared with antihypertensive controls or placebo.³⁰ However, use of RAASi in recommended doses is often limited by risk of hyperkalemia, resulting in either subtherapeutic dosing or avoidance of these agents even when clinically indicated.³¹⁻³³ In previous communications, we showed that RAASi therapy at guideline-recommended doses was generally associated with lower adverse-outcome rates and costs, compared

with subtherapeutic doses or discontinuation in CKD patients with commercial insurance or Medicare.^{21,22}

In the multivariate regression analyses, the strongest predictor of costs was having ≥ 2 healthcare visits per year, which was reported for a large majority of patients in both cohorts. The assessment of 0-1 visit compared with ≥ 2 visits appears reasonable because it may distinguish between patients who do not versus do know they have CKD. Furthermore, it is possible that patients who are noncompliant may cost less, as they do not utilize the healthcare system as much as compliant patients might. The presence of comorbid CVD and HF were strong predictors of higher costs, especially in patients with CKD stage 3a or higher. These findings are consistent with other studies showing the cost impact of comorbid conditions on CKD,^{34,35} as well as the impact of these comorbidities on hospitalization rates.^{6,18} Hyperkalemia contributed modestly, but significantly, to higher costs at every stage of CKD. The cost contribution of hyperkalemia was

generally consistent across early stages of CKD, but then increased dramatically by CKD stages 4-5, and even more so in ESRD.

Limitations

Several study limitations should be recognized. First, consistent with the retrospective design, the diagnosis of CKD stage depended upon diagnosis codes and the frequency of eGFR measurements in real-world clinical practice. Therefore, there may have been limitations in the timing (ie, onset, duration) of CKD stages and, consequently, in costs attributed to specific stages. Second, the costs attributed to ESRD excluded dialysis costs, which could not be captured in the Humedica database. Costs in ESRD are likely to be higher than those reported here. The additional annual cost of dialysis is estimated to be at least \$29,000 per Medicare patient²; for commercial patients it is approximately 4 times higher than the Medicare rate, or about \$120,000 per patient, based on revenue reported by DaVita (DaVita Inc, Denver, Colorado).³⁶ Third, these data are not a longitudinal study of CKD progression; rather, they provide a cross-sectional snapshot of the costs within a disease stage and the costs associated with transitioning to the next disease stage. Because the accuracy of cost estimates increases with longer time frames, we used a 90-day minimum duration for capturing costs. The disease stage ended only if the patient progressed to the next greater stage, or if the study end date was reached. Fourth, the study population had already received a prescription of RAASi therapy based on the selection criteria, and consequently may not represent the general CKD population, but rather a sample generally engaged with the healthcare system, possibly providing a selection bias towards better outcomes. Finally, the commercial and Medicare cohorts were overrepresented by patients from the South region, which may have impacted costs as well as the generalizability of the study results to the US population.

CONCLUSIONS

In summary, costs increased exponentially with advancing CKD in patients who were prescribed RAASi therapy. IP costs were the key driver of total costs, becoming increasingly more important with each successive CKD stage. Readmissions increased in frequency with each CKD stage, contributing substantially to the cost increases. In comparison, pharmacy costs were found to be only a small contributor to the higher costs with advancing CKD stage. Based on these findings, efforts to slow CKD progression and reduce hospitalization/readmission rates may be expected to result in cost reductions. Although RAASi are recommended in CKD and do reduce hospitalizations, their full benefit is often limited by hyperkalemia. Efforts to design care with a focus on managing the burden of increasing comorbidities with advancing CKD—including HF, diabetes, and hyperkalemia—and implementing strategies to decrease CKD progression are clinically worthwhile and should offer the potential for cost reductions. ■

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SUPPLEMENTARY ITEM S1. Renal Condition Definitions.

Chronic kidney disease (CKD):

- CKD stage 2: *International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM)*, code 585.2 or single estimated glomerular filtration rate (eGFR) [60–89]
- CKD stage 3a: single eGFR [45–59]
- CKD stage 3b: single eGFR [30–44]
- CKD stage 4: ICD-9-CM code 585.4 or single eGFR [15–29]
- CKD stage 5: ICD-9-CM code 585.5 or single eGFR [11–15]

End-stage renal disease (ESRD):

- ESRD: ICD-9 code 585.6 or single eGFR (≤ 10)

SUPPLEMENTARY ITEM S2. Identification of Comorbidities.

Comorbidities were identified by single occurrence of any indicator in prestage data using *International Classification of Diseases, Ninth Edition (ICD-9-CM)*, diagnosis codes, and other indicators as follows:

- Diabetes mellitus (includes both type I and type II): any occurrence of ICD-9 -CM diagnosis codes 250.xx, 357.2, 362.0x, or 366.41; glycated hemoglobin $\geq 6.5\%$; or any outpatient prescription for a diabetes medication
- Heart failure: any occurrence of ICD-9-CM diagnosis codes 398.91, 402.x1, 404.x3, 425.xx, 428.xx, or V42.1; or a left ventricular ejection fraction $<40\%$
- Hypertension: any occurrence of ICD-9-CM diagnosis codes 362.11, 401.x–405.x, 437.2
- Cardiovascular disease: any occurrence of ICD-9-CM diagnosis codes 404.x1, 410–414, 420–421, 423–424, 426–427, 429, 430–438, 440–444 (except 440.1, 442.1), 447 (except 447.3), 451–453, 557, 785.0–785.3, V42.2, V43.3, V45.0, V45.81, V45.82 and V53.3
- Hyperkalemia: single occurrence of serum potassium ≥ 5.1 mEq/L, in any setting of care

SUPPLEMENTARY ITEM S3. Evaluated RAASi Drugs.

Evaluated RAASi drugs and their maximum recommended doses, listed in alphabetical order:

aliskiren, 300 mg	eprosartan, 800 mg	perindopril, 8 mg
azilsartan, 80 mg	fosinopril, 40 mg	quinapril, 80 mg
benazepril, 80 mg	irbesartan, 300 mg	ramipril, 10 mg
candesartan, 32 mg	lisinopril, 40 mg	spironolactone, 200 mg
captopril, 450 mg	losartan, 100 mg	telmisartan, 80 mg
enalapril, 40 mg	moexipril, 30 mg	trandolapril, 8 mg
epplerone, 100 mg	olmesartan, 40 mg	valsartan, 320 mg

RAASi indicates renin-angiotensin-aldosterone system inhibitor. Aliskiren/valsartan formulated 150 mg–160 mg (a partial dose of each of 2 RAASi drugs) was considered a partial dose (submaximum).

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