The Economics of Renoprotective Therapy in Advanced Diabetic Kidney Disease

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ABSTRACT

Objectives: To assess the long-term impact of renoprotective therapy in patients with advanced diabetic kidney disease.

Study Design: A budget-impact model (BIM) was developed to simulate the 10-year cost savings and outcome improvements of renoprotective therapy for a cohort of privately insured patients with advanced diabetic kidney disease.

Methods: The BIM included information on chronic kidney disease (CKD) progression, end-stage renal disease (ESRD) progression, and mortality for 10 years, annually, in a cohort similar to the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) treatment and untreated arms. Direct costs associated with clinical outcomes were calculated at private insurance rates in 2012 dollars. The BIM included a base case and a conservative case reflecting variable risks of CKD progression.

Results: Estimated year 1 average total medical cost per patient under base case: $62,386 without losartan versus $58,979 with losartan; first-year savings, $3408 net of treatment costs and hyperkalemia events. Annual savings reach $10,990 in year 10 (total cost/patient $94,255 without losartan vs $83,265 with losartan), 101 fewer patients progress to ESRD (434 cumulative ERSD without losartan vs 333 with losartan), and deaths over 10 years are expected to equal 58.5% without losartan and 51.8% with losartan. The conservative scenario sees year 1 savings of $1154 per patient, annual savings of $5659 in 10 years, and 66 fewer patients (cumulative) initiating ESRD.

Conclusions: In patients with diabetes and advanced CKD, the potential cost savings to private insurers and improved patient outcomes from appropriate use of angiotensin II receptor blockers are significant.

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Approximately one-third of patients in the United States with chronic kidney disease (CKD) have type 2 diabetes mellitus.[1] Data indicate that up to 58% of these patients fail to receive recommended renin-angiotensin-aldosterone system (RAAS) inhibition therapy despite proven benefits in slowing CKD progression and delaying progression to end-stage renal disease (ESRD).[1,2] The cost to private insurance plans of the failure or inability to place these patients on appropriately dosed renoprotective therapy has not been established.

Our study sought to estimate the potential benefits of one form of RAAS inhibition therapy using angiotensin II receptor blockers (ARBs) by modeling a well-studied clinical trial cohort. We created a hypothetical patient cohort similar to the treatment and placebo arms of one of the landmark clinical trials establishing the benefit of ARB therapy in diabetics, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial.[3] Patients with macroalbuminuria similar to those studied in the RENAAL trial comprise approximately 6% of patients with stage 3 CKD and 42% of patients with stage 4 CKD.[4] We modeled CKD progression, ESRD progression, mortality, and total healthcare costs over a 10-year period under 2 disease progression risk scenarios with private insurance payment.

METHODS

A budget-impact model (BIM) was developed to assess the economic burden of diabetic kidney disease on US health insurance plans and the potential direct savings (medical and drug) to these plans from the use of ARB therapy. Data sources included the following:

Two double-blind, placebo-controlled clinical trials initially established the value of ARB therapy on hard renal outcomes in persons with diabetes and advanced kidney disease: RENAAL and Irbesartan Diabetic Nephropathy Trial (IDNT), both published in 2001.[5,6] Both trials examined a composite

PRACTICAL IMPLICATIONS

The economic impact of advanced diabetic kidney disease has not been well studied in privately insured patients, and despite clinical guidance, a significant percent of patients with chronic kidney disease (CKD) have not been prescribed renin-angiotensin-aldosterone system (RAAS) blockade therapy, including angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers. This budget-impact model illustrates the savings to private insurance plans, as well as improvements in clinical outcomes, associated with the use of renoprotective pharmacotherapies in this high-risk, high-cost patient population. Of note:

- The impact of CKD has not been well studied in private insurance.
- Costs associated with CKD progression and end-stage renal disease (ESRD) are high.
- RAAS blockade therapy is underprescribed in this population, despite clinical guidance.
- Appropriate prescribing and dosage of RAAS blockade therapy is anticipated to save private insurers, avoid ESRD initiation, and reduce mortality, all starting in year 1.

primary end point, including progression to ESRD, in similar populations. RENAAL's definition of ESRD progression (initiation of long-term dialysis or renal transplantation) corresponded to a discrete medical resource end point, while IDNT's definition also included a serum creatinine end point. Accordingly, we selected RENAAL as the representative for efficacy of ARB therapy in this study and the basis of the BIM.

To model the risk and timing of disease progression, mortality, healthcare costs, and hyperkalemia-related inputs, we conducted a search of the peer reviewed literature and clinical guidelines in Medline, Cochrane, ISPOR, and National Guideline Clearinghouse databases, with preference to sources presenting results for patients with diabetes and/or macroalbuminuria, not yet of Medicare age. Primary data sources and uses are summarized in **Table 1**; search and selection details are provided in the **eAppendix** (available at **www.ajmc.com**).

Progression of CKD, Including Mortality

The most widely accepted analysis of progressive renal disease is the set of meta-analyses covering more than 1.5 million patients presented by Levey and colleagues at the KDIGO Controversies Conference in 2009.[7] This work confirmed that the critical factors determining renal risk are disease stage, as measured by estimated glomerular filtration rate, and albuminuria; it furnished the relative and absolute risk probabilities we used to predict the progression between stages 3a, 3b, and 4, and into ESRD, as well as pre-ESRD mortality risk. Annual mortality risk during ESRD treatment was computed from United States Renal Data System (USRDS) cohort survival statistics.[1] We defined the base case for the BIM as a hypothetical cohort of patients of similar size and disease characteristics as the RENAAL clinical study population, making adjustments to our foundational data sources to account for the high levels of proteinuria in the RENAAL population (median urinary albumin:creatinine ratio [UACR] >1200)[3] (see eAppendix for details). The conservative case scenario represents a similarly sized cohort but makes no adjustment for the elevated proteinuria in this patient population, instead using the absolute and relative risk of disease progression from all persons with UACR equal to or greater than 300 in the KDIGO model.[7] Thus, the conservative case represents a less acutely ill CKD population than the base case.

Efficacy of Therapy

To model outcomes in treated patients, we reduced the absolute risk of ESRD progression by 29% and the absolute risk of CKD progression by 25%, as observed in RENAAL patients on losartan.[8] We modeled no direct impact on mortality from losartan therapy.[5] However, differences in mortality emerge in the BIM due to slower progression of losartan-treated patients into higher-mortality CKD stages and ESRD.

Cost

A private insurance plan's annual cost for a member with CKD roughly doubles with each progressive stage of CKD,[9,10] is higher for patients with diabetes[11]; among patients with diabetes, is higher for those with macroalbuminuria[12]; and spikes in the months just before and after progression to ESRD.[10,11] Annual estimated baseline costs by CKD stage, used for both the base and conservative cases, are shown in **Figure 1** (stage 3: $15,000 in 2001 dollars[10] *1.27 [diabetic:total][11] *1.19 [macroalbuminuria:total among diabetics],[12] inflated[13] = $34,420; allocated $31,597 stage 3a [79%], and $44,867 stage 3b [21%],[7] to equalize the percentage cost increase. Stage 4: $28,000,[10] similarly adjusted = $64,251. ESRD: cost of stage 4 + annualized cost of progression to ESRD in a patient with diabetes and macroalbuminuria [$56,745 in 2009 dollars,[12] inflated to $63,009] = $127,350) (details in the eAppendix). To the baseline, we added an additional $52,915 in the year preceding ESRD, derived from Joyce's findings of cost acceleration at this point.[11]

Hyperkalemia (HK), defined as a serum potassium level exceeding the upper limit of normal for a given laboratory (generally >5.0 mmol/L) is a known side effect of RAAS

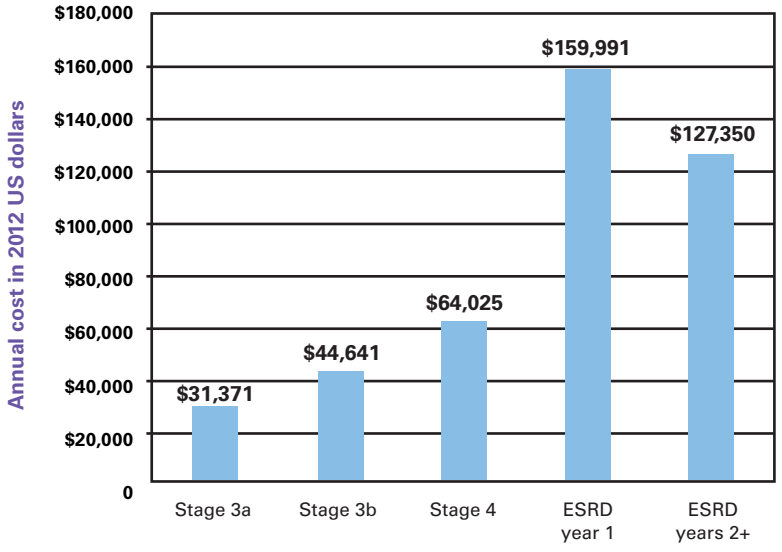
Table 1. Primary Data Sources for the Budget-Impact Model

Author (year)	N	Nature of Study and Population	Source(s)	Primary Use in Model
Levey (2010)[7]				
CKD cohort: Astor (2010)[14]	1.5 million (total) 1,345,319 (general population) 266,975 (high risk for CKD) 21,688 (CKD)	Pooled relative risks of varying levels of eGFR and albuminuria from a trio of meta-analyses using solicited data from established worldwide cohorts. Within CKD cohort: mean age 65 years; 57% male; 7.5% African American; mean UACR 260.	45 cohorts, including Framingham, HUNT, NHANES III, AusDiab, AKDN, ONTARGET, ZODIAC, KP Hawaii, RENAAL, STENO, KP Northwest, AASK, British Columbia, et al (full names in appendix of source)	Foundational study for disease progression. Relative risk of CKD progression between stages, ESRD initiation, and all-cause mortality in persons with stage 3 to stage 4 CKD and macroalbuminuria.
US Renal Data System (USRDS) 2011 Annual Report, volume 2 (ESRD)[1]	652,885	US residents undergoing hemodialysis, peritoneal dialysis, or kidney transplant, or on transplant wait list	CMS and mandatory reports from dialysis and transplant providers	Annual mortality risk for each year of ESRD treatment
Brenner (2001)[5]	1513 (losartan, 751; placebo, 762)	Patients with diabetes and CKD, minimum UACR 300; median UACR 1237 (treatment) to 1261 (placebo); 15% African American; 63% male	RENAAL clinical trial	Benefit of therapy (treatment arm); absolute risk of ESRD initiation in target population (control arm)
Amedia (2003)[10]	1.2 million members (CKD cohort size and demographics not specified)	"Typical managed care organization" population enrolled in traditional indemnity, HMO, and Medicare+Choice products	Renal disease management	Source of base cost assumptions: commercial health plan annual cost per member with CKD in stage 3 or stage 4
Joyce (2004)[11]	4190 (total) 2020 (with diabetes) 2170 (without diabetes)	Insured persons with ESRD initiation having continuous enrollment for 12 months before, and at least 1 month after ESRD initiation, excluding short-term dialysis; under age 65 years, 74%; 55% male	Pharmetrics (data from 61 health plans across the United States)	Ratio of cost in patients with diabetes with CKD vs all CKD patients; % increase in cost above prior level in the year prior to ESRD; private health plan cost of patient on ESRD in the first year and subsequent years
Nichols (2011)[12]	7758 (total) 399 macroalbuminuria 2136 microalbuminuria 5223 normoalbuminuria	HMO members with diabetes and 2 UACR readings, followed for mean 4.9 ± 2.2 years. Macroalbuminuria group: initial mean eGFR 86; mean age 62 years; 3.5% African American; 50% male	Kaiser Permanente Northwest	Ratio of annual cost in patients with diabetes with macroalbuminuria vs all patients with diabetes; incremental cost of progression to ESRD
Einhorn (2009)[15]	245,808 (total) 35,744 (patients with diabetes with stage 3 to stage 5 CKD)	Veterans with ≥1 hospitalization, an outpatient serum creatinine reading and ≥1 serum potassium reading. Male, 98%; diabetes, 54%; mean age, 68 years	Veterans Health Administration (national cohort)	For diabetic patients with stage 3 to stage 5 CKD: incidence of lab values consistent with hyperkalemia; % of patients receiving ACE inhibitor/ARB therapy
Smith (2011)[16]	60,464 (total) CKD cohort 6523	Patients who were new users of ACE inhibitors or ARBs. Mean age 73 years; 37% male	Kaiser Permanente Northwest (HMO with 450,000 members)	Frequency of medical services in which hyperkalemia was the primary diagnosis
Agency for Healthcare Research and Quality[17]	215,742 projected discharges 47,859 projected ED visits	Projections based on 20% stratified sample of inpatient discharges and ED visits at US hospitals	HCUP Nationwide Inpatient Sample (NIS) and HCUP Nationwide Emergency Department Sample (NEDS), 2009	Relative frequency of hyperkalemia as a secondary diagnosis vs primary diagnosis in hospital-based services

CKD indicates chronic kidney disease; ED, emergency department. eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HCUP, Hospital Cost and Utilization Project; HMO, health maintenance organization; RENAAL, reduction of end points in non-insulin dependent diabetes mellitus with the angiotensin II Antagonist Losartan; UACR, urinary albumin:creatinine ratio.

inhibition therapy, including ARB therapy. RENAAL investigators reported that 22.8% of losartan-treated patients experienced potassium (K) greater than 5.5 mmol/L versus 5.1% of placebo patients.[5] Einhorn reported 30.8% annual incidence of lab values of K greater than 5.5 mmol/L among 35,744 community-setting diabetics with stage 3 to stage 5 CKD,[15] which we adjusted for the frequency with which HK has been noted among similar patients as a primary[16] or secondary[17] reason for medical care, estimating that 28% of patients with excessive potassium lab readings received explicitly related healthcare services (3.18% treatment event incidence with HK primary diagnosis[16]/30.8%

Figure 1. Baseline Annual Cost Per Patient, by CKD Stage



CKD indicates chronic kidney disease; ESRD, end-stage renal disease (dialysis or transplantation).

lab value incidence[15] * 39% of HK-related events in which HK diagnosis was primary[17] + 12.12% HK secondary event rate[16,17]/30.8% * 61% of HK-related events in which HK diagnosis was secondary[17] = 28%).

For patients in the treatment arm, we calculated an annual cost for generic losartan therapy of $168, based on an Internet-accessed retail price of $14 per month for losartan 100 mg. We ceased applying cost for losartan therapy when patients progressed to ESRD, as any continuation after that point is for purposes other than preventing kidney failure. We added the cost of generic losartan therapy and the costs of treating hyperkalemia to the baseline costs in the BIM.

Using the inputs described above, we modeled distribution by CKD stage of the RENAAL losartan and untreated study arms at trial baseline, and projected disease progression and mortality annually for 10 years, assuming ongoing effectiveness of therapy at levels demonstrated in RENAAL. We applied cost in 2012 dollars to the cohort of patients at each stage in each study arm, with adjustments for short-term costs surrounding progression to ESRD, the differential cost of HK, and the cost of therapy. Average annual cost per patient in each year was calculated as the sum of costs for treating patients at each stage (baseline plus relevant additions) divided by the number of surviving patients; all costs were normalized to 2012 dollars.[13] All modeling and nonstatistical analyses were conducted in Microsoft Excel (2007). Differences between cumulative proportions in the 2 study arms of the modeled population were evaluated using a χ^2 test, and carried out using SAS/STAT software (version 9.2).

RESULTS

For the base-case scenario, the average annual total healthcare cost to a private insurance plan for a cohort of patients matching the RENAAL population was estimated to be $58,979 per patient treated with losartan and $62,386 per patient without ARB therapy (ie, untreated) in year 1. Average savings in healthcare costs during the first year (net of the cost of losartan therapy and the cost of treating increased hyperkalemia) was estimated at $3408. By year 3, average annual savings reach $6323 per patient with treatment. After 10 years, annual costs equal $83,265 per person on losartan versus $94,255 per untreated patient, for annual savings with treatment of $10,990 per patient.

Under the conservative case (ie, less acutely ill patients), the average savings in healthcare costs (or the net of cost of therapy) during the first year are estimated at $1154 per patient. By year 3, average annual cost is $57,180 for patients taking losartan versus $59,864 for untreated patients, a savings of $2685. By year 10, the losartan cohort costs, on average, $64,776 per patient compared with $70,435 per untreated patient, for an annual savings of $5659 per patient (**Table 2**).

Under the base case, assuming a patient cohort of diabetic CKD patients similar in number to the RENAAL trial

Table 2. Results of Base Case and Conservative Scenarios

	BASE CASE	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Base Case	**Cost per patient ($)**										
	Losartan	58,979	63,438	67,219	70,476	73,301	75,776	77,966	79,920	81,677	83,265
	Placebo	62,386	68,462	73,542	77,863	81,567	84,778	87,589	90,072	92,279	94,255
	Annual savings per patient	3408	5024	6323	7387	8266	9002	9623	10,151	10,602	10,990
	No. of patients initiating ESRD										
	Losartan	46	43	40	37	35	32	29	26	24	21
	Placebo	65	61	56	50	45	40	35	31	27	23
	Reduction in ESRD onset	20	18	15	13	11	8	6	5	3	2
	Deaths										
	Losartan	27	35	39	42	43	43	42	41	39	37
	Placebo	27	40	46	49	51	51	49	47	44	41
	Reduction in deaths	0	4	6	7	8	8	7	6	5	4
Conservative Case		**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
	Cost per patient ($)										
	Losartan	53,241	55,369	57,180	58,739	60,087	61,263	62,297	63,215	64,036	64,776
	Placebo	54,395	57,353	59,864	62,025	63,894	65,527	66,967	68,248	69,397	70,435
	Annual savings per patient	1154	1985	2685	3286	3807	4264	4670	5033	5361	5659
	No. patients initiating ESRD										
	Losartan	22	21	20	19	18	17	16	15	14	13
	Placebo	31	30	28	26	25	23	21	20	19	17
	Reduction in ESRD onset	9	9	8	7	7	6	6	5	4	4
	Deaths										
	Losartan	27	30	32	33	33	33	32	31	30	29
	Placebo	27	33	35	36	37	37	37	36	34	33
	Reduction in deaths	0	2	3	4	4	4	4	4	4	4

ESRD indicates end-stage renal disease.
Yearly costs, ESRD initiation, and mortality based on RENAAL Study, from initiation of therapy, for 10 years of projected follow-up.

(about 750 treated patients), cumulative cost savings with losartan treatment reach $11.1 million by year 3 and $18.4 million by year 5, compared to $5.3 million in year 3 and $9.5 million in year 5 for the conservative case. Expected cumulative savings by year 10 reach $24.4 million in the base case and $16.4 million under the conservative case.

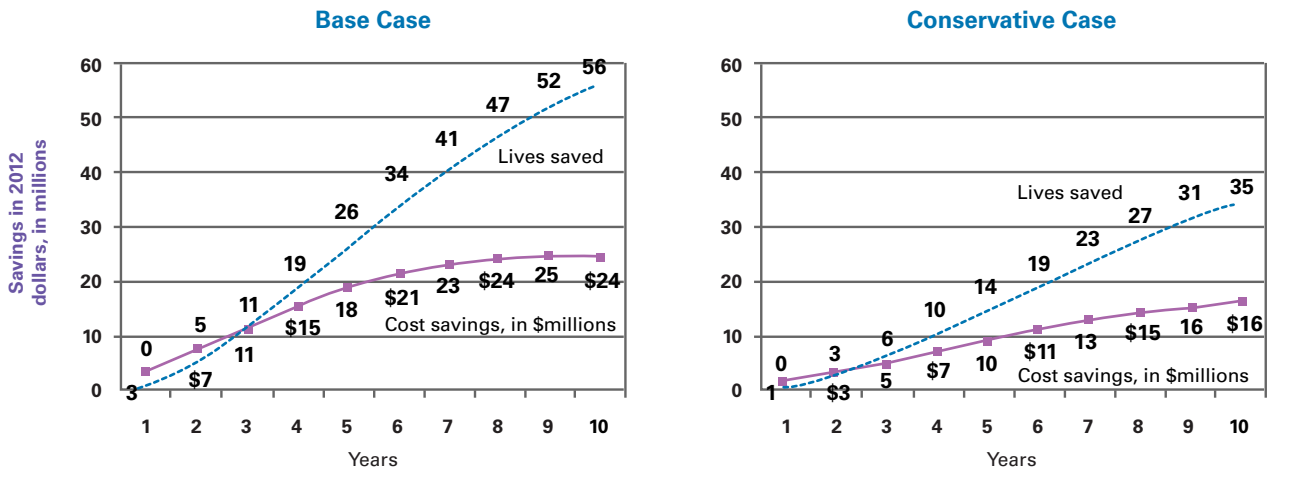
ESRD Progression

In the first year, 46 losartan patients and 65 untreated patients were expected to progress to ESRD under the base case. The cumulative number of patients presenting with ESRD within 3 years rose to 129 patients (17.2%) with losartan versus 182 patients (23.9%) without losartan therapy (odds ratio [OR], 0.66; 95% CI, 0.51-0.85, as shown in **Figure 3**). Outcomes were expected to continue to diverge in subsequent years, with 76 fewer losartan-treated patients in the base case progressing to ESRD after 5 years: 201 losartan patients (26.8%) versus 277 untreated patients (36.4%) (OR, 0.64; 95% CI, 0.51-0.80). Over 10 years, ESRD progression is expected in 333 patients on losartan (44.4%) versus 434 untreated patients (56.9%) (OR, 0.60; 95% CI, 0.49-0.74). In the conservative case, ESRD progression after 3 years is expected in 62 patients on losartan (8.3%) and 89 (11.6%) untreated patients (OR, 0.68; 95% CI, 0.48-0.96). By year 10, disease progression is expected in 174 patients on losartan (23.1%) and 239 (31.4%) untreated patients (OR, 0.66; 95% CI, 0.53-0.83).

Mortality

In the base case, expected deaths in this cohort exceed 50% over 10 years, with or without treatment. Within 3 years, 101 losartan patients (13.5%) and 113 untreated patients (14.8%) are expected to expire (OR, 0.89; 95% CI, 0.67-1.19). Cumulative mortality at 5 years is 186 losartan patients (24.8%) versus 213 untreated patients (27.9%) (OR, 0.85; 95% CI, 0.67-1.07). After 10 years, deaths reach

Figure 2. Cumulative Savings in Lives and Private Insurance Costs With and Without Losartan Treatment, Base Case and Conservative Case



In the model, noninteger values are used for persons in order to avoid accruing distortion over time due to rounding; thus, values displayed may not foot.

51.8% (389 patients) with losartan versus 58.4% without ARB therapy (445), and the difference achieves significance (OR, 0.77, CI, 0.62-0.94). In the conservative case, mortality differences within 10 years for 310 losartan patients (41.2%) versus 345 untreated patients (45.2%) are not significant (OR, 0.85; 95% CI, 0.69-1.04).

DISCUSSION

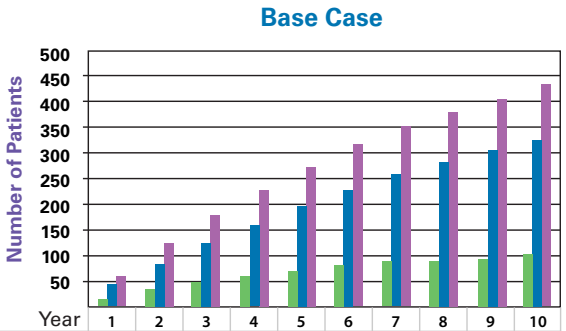
CKD progression is mitigated for many patients by the appropriate use of RAAS inhibitors, yet the proportion of CKD patients receiving this renoprotective therapy remains relatively low despite clinical guidance.[1] Our study sought to estimate the potential benefits of one form of RAAS inhibition therapy—angiotensin II receptor blockers (exemplified by losartan)—illuminating the economic impact of CKD both before and after the progression to ESRD.

Economic analyses of CKD often focus on the financial benefit of avoiding ESRD, for which the increase in costs is large and easily substantiated. Our study suggests that this common approach may understate the full cost burden of CKD progression at the earlier stages likely to be reached before patients age to Medicare coverage. Indeed, systematic searching for data distinguishing costs for CKD patients in stages 3 and 4 with private insurance, without excluding end-of-life costs, yielded cost estimates that are higher than more commonly cited sources requiring continuous insurance coverage,[1] or evaluating only ESRD avoidance as an economic benefit.[18]

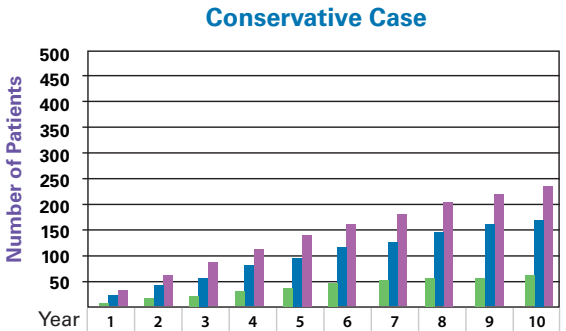
Our analysis shows that even under conservative assumptions of disease progression, the impact of CKD among the privately insured is significant, both clinically and economically, particularly among patients who do not receive appropriately dosed RAAS therapy. In our base case cohort model, net savings of treatment costs averaged more than $3400 for every patient on losartan therapy in the first year, and increased each year, reaching annual savings of $10,990 per surviving patient in year 10. Importantly, expected cumulative savings peak at $24.7 million in year 9 for this cohort of patients similar in size and severity to the RENAAL patient population (about 750 treated patients). By year 10 in the base case, the cost of treating the larger number of survivors in the losartan study arm finally outweighs the per patient savings with treatment, and cumulative savings decline to $24.4 million, as shown in Figure 2. In our more conservative scenario, savings average $1154 for every patient on losartan therapy in the first year, reaching savings of $5,659 per surviving patient in year 10 and cumulative savings exceeding $16 million over 10 years. In either case, the potential cost savings with therapy are substantial and associated with reduced mortality and increased quality of life, as patients avoid or delay dialysis. With the increasingly obese US population developing type 2 diabetes mellitus at younger ages, these findings raise important considerations for private insurers in the United States.

RAAS inhibition therapy is not expensive. We estimated $168 per patient per year for generic losartan. Although the reasons for nontreatment and undertreatment with RAAS inhibitors are multifactorial,[1,19-22] one well-recognized limiting factor is concern about HK.[8] Potassium

Figure 3. Cumulative ESRD Initiation, by Year, Base Case, and Conservative Case



Year	1	2	3	4	5	6	7	8	9	10
ESRD avoided	20	37	53	66	76	85	91	96	99	101
Losartan	46	89	129	167	201	233	262	288	312	333
Placebo	65	126	182	232	277	318	353	384	411	434



Year	1	2	3	4	5	6	7	8	9	10
ESRD avoided	9	18	26	34	40	47	52	57	62	66
Losartan	22	43	62	81	99	116	132	146	161	174
Placebo	31	61	89	115	139	162	184	204	222	239

ESRD indicates end-stage renal disease.

levels in both the RENAAL and IDNT trials were significantly higher among patients treated with RAAS inhibitors, and elevation in potassium level has been noted in much of the literature on RAAS inhibition therapy.[15,23] Preventing or treating HK may, therefore, be one of the keys to fulfilling the potential of RAAS inhibitors. Emerging therapies designed to manage potassium levels show promise in this regard.[24] Trials evaluating these pharmacotherapies should address the potential for optimization of RAAS inhibitors, as well as potassium control itself.

Limitations

Results are specific to persons with advanced diabetic kidney disease (ACR >300) without heart failure treated with and without losartan, and cannot be generalized to broader populations. Fewer African Americans were represented in Nichols' study (3.5%) and in the CKD meta-analysis contributing key results to the Levey model (7.5%)[14] than in RENAAL (13.8%) or among ESRD patients in the United States (27.8%). Because CKD is a widely studied clinical condition, we focused on the use of methodologically sound and frequently cited studies using large, well-known data sources of relevance to private insurers rather than conducting an original systematic review or a meta-analysis of the literature. The duration and statistical power of the RENAAL study was insufficient to draw specific conclusions about the effect of therapy on mortality; thus, our model's calculated mortality benefit was based exclusively on estimated deaths tied to CKD progression and ESRD.

Our linear assumption of losartan efficacy necessarily extends beyond the time studied in the clinical trial. Available data on the relationship between hyperkalemic lab values and actual treatment cost was particularly scant, warranting further study. Also, reliance on the RENAAL study as representative of ARB therapy necessarily excludes the extensive accumulated research on the full family of RAAS inhibition therapies; the average cost per patient of ARB therapy may be higher, particularly if non-generic drugs are utilized. Estimated savings to an individual private insurer could be lower than predicted over time as patients move into Medicare coverage or switch to another commercial plan. Conversely, cost savings may be higher in patients using RAAS inhibitors if serum potassium can be managed; Miao et al's post hoc adjustment of RENAAL results for serum potassium suggested that losartan's renoprotective effect could improve from 21% to 35%.[25] Thus, our study should be considered a first step in eliciting further investigation of diabetic CKD in privately insured populations.

CONCLUSION

ACE inhibitor and ARB therapies have been shown to delay progression of advanced diabetic kidney disease. Our BIM suggests that, at private insurance payment rates, the use of ARB therapy reduces average annual healthcare costs for patients with advanced diabetic kidney disease between $1150 and $3400 in the first year. These savings rise to between $5600 and $11,000 per surviving patient in year 10, provided that HK or other factors do not prevent patients from remaining on therapy. We hope our findings will stimulate greater sharing of non-Medicare cost data on patients with diabetes and renal disease, and direct investigation into the benefits/risks associated with renoprotective therapies.

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Authorship Information: Concept and design (NLR, SEF); acquisition of data (NLR, SEF); analysis and interpretation of data (NLR, SEF, GLB); drafting of the manuscript (NLR, SEF, GLB); critical revision of the manuscript for important intellectual content (NLR, SEF, GLB); and statistical analysis (NLR).

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eAppendix

METHODS

Search terms and source study selection criteria

For cost-related inputs, we conducted a focused search in Medline [Limits: published in last 10 years, humans, English language; search string: (CKD or "chronic kidney disease" or ESRD or "end stage renal disease") AND diabetes AND (cost* or expenditure* or economic or spending or resource* or LOS or utilization or "physician visits")], and hand-searched references. From searches related to cost and disease progression, we identified 663 citations, selected 64 studies for review, and entered relevant data (where available) into a database.

No single source offered comprehensive data on a population similar to that studied in Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial.[1] For disease progression and for cost, we started with a foundational study establishing differences by disease stage, then adjusted the results using findings from more targeted studies differentiating for diabetes and albuminuria level. We gave preference to clinical findings reviewed and accepted by the U.S. Food and Drug Administration, and to meta-analyses and larger studies cited in clinical guidelines by widely recognized national and international organizations, or derived directly from the RENAAL clinical trial cohort. In selecting sources for costs, we specifically sought studies referencing privately insured patient populations, not yet of Medicare age. We gave preference to meta-analyses or studies in peer-reviewed journals that aligned as closely as possible to our target population and/or study issues, were based on large samples from well-known sources, included end-of-life costs as well as costs of survivors, offered results in sufficient detail to permit derivative calculations where needed, and delineated methods and limitations that could affect our study.

Risk adjustment for the high level of macroalbuminuria in the RENAAL population

For the base case, we assumed that risks in a population meeting RENAAL's characteristics would have the same relative relationships as Levey[2] found, but at a higher absolute level by an unknown amount due to the very high albuminuria levels seen in RENAAL. We found no study that offered a direct comparison between these risk levels. In order to estimate the magnitude of the increase in absolute risk, we modeled disease progression, end

stage renal disease (ESRD) initiation and mortality in the placebo study arm year by year for 3.5 years using absolute risk (as specified by Levey)[2] multiplied by the unknown Factor, and then solved for the value of Factor (i.e., the increase in risk) needed for our model to project ESRD onsets equal to the number of patients in the RENAAL placebo arm who had initiated ESRD (207 of 762) after 3.5 years[3] (see **Appendix Table 1**). The conservative case was developed using data on the risks of ESRD onset and CKD progression directly from Levey, shown in Appendix Table 1, without adjustment for the high level of macroalbuminuria observed in the RENAAL population.

Appendix Table 1. Establishing Absolute Risks of ESRD Initiation and CKD Progression Appropriate to the RENAAL Population Placebo Arm (Base Case) From Unadjusted Risks (Conservative Case)

		Conservative Case			Base Case	
CKD Stage	Estimated RENAAL population distribution[a]	Absolute risk of ESRD onset per 1000 patient-years, Levey[2]	Absolute risk of CKD progression per 1000 patient-years, Levey[2]	Factor[b]	Annual absolute risk of ESRD per 1000 patients estimated for RENAAL	Annual absolute risk of CKD progression per 1000 patients estimated for RENAAL
3a	21%	5.9	115.1	2.09211	5.9 x Factor = 12.3	115.1 x Factor = 240.9
3b	54%	30.5	44.4	2.09211	30.5 x Factor = 63.9	44.4 x Factor = 93.0
4	26%	91.4	15.6	2.09211	91.4 x Factor = 191.3	*
Weighted average					85.9	108.1

[a]RENAAL population by stage per Remuzzi[4] (combining 95 stage 2 patients into stage 3, and 1 stage 5 patient into stage 4); subjects allocated between stages 3a and 3b using population demographics and creatinine values.
[b]Factor is the solved-for increase in absolute risk from Levey's population (albumin-to-creatinine ratio >300 mg/g with and without diabetes) to that of the RENAAL study (diabetes, median ACR >1200) that yields at 3.5 years 207 patients initiating ESRD without losartan therapy (RENAAL actual), when all other factors are modeled.
*Progression from stage 4 to stage 5 was assumed to result in ESRD status, which was modeled directly from the risk of progression to ESRD.

The fit of the model using the derived Factor was tested by comparing the weighted average annual absolute risk of ESRD per 1000 patients estimated for RENAAL (85.9) to the 9.1 per 100 patient years (91 per 1000 patient-years) reported by Brenner,[1] which we deemed an acceptable level of difference, since the two measures use slightly different denominators.

Calculating baseline costs and adjustments, including ESRD

As baseline for stages 3 and 4, we began with pre-ESRD private insurance cost for patients with stage 3 or 4 CKD ($15,000-$28,000 in 2001 dollars), based on Amedia's observations,[5] confirmed by Sullivan[6] (compared with $5000-$12,000 per patient with CKD stages 1-2). As detailed in **Appendix Table 2**, we increased baseline costs by 27%, per Joyce's finding (from Pharmetrics private insurance claims data on 4190 persons who progressed to ESRD) that cost per patient was 69% higher in diabetics than in non-diabetics pre-ESRD, and 27% higher among the 48% of patients with diabetes than the weighted average cost of patients with and without diabetes.[7] Baseline cost data from Nichols' analysis of 7758 Kaiser-Permanente members with diabetes and hypertension with normoalbuminuria (67%), microalbuminuria (28%) and macroalbuminuria (5%) shows total annualized cost per patient 19% above the mean for those with macroalbuminuria, while mean eGFR did not significantly differ.[8] Accordingly, we increased baseline costs adjusted for diabetes by 19% to reflect RENAAL's selection criteria, which included both diabetes and macroalbuminuria. We found no published data on cost differences at the higher levels of macroalbuminuria seen in RENAAL, and therefore made no further adjustment for this factor.

Appendix Table 2. Cost Adjustments to Baseline Stage 3 and Stage 4 Values

	Baseline, in 2001 dollars[5]		Diabetic: Total[7]		Macroalbuminuria: Total, among diabetics[8]		Inflation factor[9]		Estimated annual cost per patient in 2012 dollars
Stage 3	$ 15,000	x	1.27	x	1.19	x	1.52	=	$ 34,420
Stage 4	$ 28,000	x	1.27	x	1.19	x	1.52	=	$ 64,251

Calculations subject to rounding.

We allocated costs between stage 3a (78.7% of stage 3 patients) and stage 3b (21.3% of stage 3 patients)[2] mathematically such that the rate of increase in annual cost per patient was consistent between progression from stage 3a to stage 3b and progression from stage 3b to stage 4 (cost increases by a factor of 1.4 at each of these steps), while maintaining a weighted average cost of $34,420 for stages 3a and 3b combined. The resulting estimated annual cost per patient was $31,597 for stage 3a and $44,867 for stage 3b (minor differences due to rounding). Since the cost of hyperkalemia was modeled separately, we subtracted $226 per patient (detailed below) from the estimated annual cost per patient, yielding baseline annual costs per patient of $31,371 for stage 3a, $44,642 for stage 3b, and $64,026 for stage 4.

ESRD. For private health plan cost for patients on ESRD, we started with the estimated annual cost per patient with diabetes, macroalbuminuria and stage 4 CKD ($64,251, as detailed above) and added the annualized cost of progression to ESRD reported by Nichols in patients with diabetes and macroalbuminuria ($56,745 in 2009 dollars,[8] which inflates to $63,099 in 2012 dollars), yielding a baseline ESRD cost to the private insurer (when primary insurer) of $64,251 + 63,099 = $127,350. Consistent with reports that insurer costs spike during the first year of ESRD,[5,7] we added extra costs of $32,641 in the first year of ESRD to the baseline ($127,350 + $32,641 = 159,991) calculated as follows: We started with Joyce's finding of mean per-member costs of $96,014 in 2002 dollars for diabetics in the first year of ESRD, combining survivors and non-survivors.[7] Joyce reported that per-patient monthly costs stabilized toward the end of the first year of ESRD; we annualized average monthly claims for persons with diabetes in the 11th and 12th months of ESRD to estimate average cost of $54,258 per diabetic member during the second and third years of ESRD. Using these year-specific costs in conjunction with cohort survival rates,[10] we calculated a mortality-adjusted 3-year average annual cost for diabetics on ESRD of $73,714 in 2012 dollars. The difference ($96,014 in first year costs - $73,714 in estimated second year costs) of $22,300 inflates to $32,641 in 2012 dollars. We found no published data on differences in cost per patient on ESRD by albuminuria level, and therefore made no further adjustment in ESRD costs.

Year prior to ESRD initiation. Multiple studies[5,7,11] document an increase in private insurance cost per patient in the year prior to the onset of ESRD treatment. To quantify this effect, we annualized average monthly cost at 10, 11 and 12 months prior to ESRD initiation (the

first three months of Joyce's study) among patients with diabetes to be representative of prior cost level, and compared this to total average annual costs in the pre-ESRD year, which were 83% higher than the prior cost level.[7] Accordingly, our model includes a one-time incremental cost increase of $53,101 [83% * $64,251 (stage 4 cost)] for the year prior to ESRD onset.

Hyperkalemia treatment frequency and cost

Hyperkalemia. In order to establish the differential cost of hyperkalemia (HK), we considered the frequency with which abnormal lab values result in medical services, along with the mix and cost of those services. As baseline, we used the 30.8% annual incidence of lab values of K>5.5 mEq/L reported by Einhorn among 35,744 persons (mostly males) with diabetes and stage 3-5 CKD in a community setting.[12] We noted the frequency with which HK caused (as primary diagnosis) utilization of medical services in Smith's 2011 study (3.18% of CKD patients with eGFR<60),[13] and used federal data[14] to expand Smith's findings to allow for cases in which HK contributed to the decision to seek medical care even if it was not the primary diagnosis. Using these sources, we estimated that 28% of patients with excessive potassium laboratory readings received explicitly related services [3.18% treatment event incidence with HK primary diagnosis[13]/**Error! Bookmark not defined.**30.8% lab value incidence[12] * 39% of HK-related events in which HK diagnosis was primary[14] + 12.12% HK secondary event rate[13,14]/30.8%* 61% of HK-related events in which HK diagnosis was secondary[14] = 28%]. A majority of these treatment events (56% per Smith,[13] 53% per Einhorn[12]) would be inpatient services. We updated Smith's analysis of hospital costs by rerunning it in a more recent version of the same data set and, using contemporaneous sources, adjusted the result for the estimated difference between hospital cost and health plan reimbursement for hospital and related physician claims.[14] The resulting estimates of cost per treatment event by setting and in total are shown in **Appendix Table 3**.

Appendix Table 3. Cost Per Hyperkalemia Event Requiring Treatment

Setting of Care	% of treatment events[13]	Private health plan cost per event (2012 dollars)[14]
Inpatient	56%	$ 13,389
Emergency Department	11%	$ 9427
Outpatient	33%	$ 72
Average Private health plan cost per hyperkalemia event requiring treatment		$ 8592

We calculated annual cost per patient as the product of HK incidence, the percentage of patients with elevated potassium receiving services as a result, and the average health plan cost per treatment event. Using Einhorn's percentage of patients treated with ACE inhibitor/ARBs (66%) and the ratio of hyperkalemia in treatment versus placebo patients in RENAAL (22.8% to –5.1%),[15] we allocated the overall average annual cost per patient of $739 to a cost of $1009 for patients receiving losartan versus $226 per untreated patient.

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