Title

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Cost-Effectiveness and Estimated Health Benefits of Treating Patients with Vitamin D in Pre-Dialysis

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Abstract:
Background: The optimal timing of treatment with vitamin D therapy for patients with chronic kidney disease (CKD), vitamin D insufficiency, and secondary hyperparathyroidism (SHPT) is a pressing question in nephrology with economic and patient outcome implications.
Objective: The objective of this study was to estimate the cost-effectiveness of earlier vitamin D treatment in CKD patients not on dialysis with vitamin D insufficiency and SHPT.
Design: A cost-effectiveness analysis based on a Markov model of CKD progression was developed from the Medicare perspective. The model follows a hypothetical cohort of 1000 Stage 3 or 4 CKD patients over a 5-year time horizon. The intervention was vitamin D therapy initiated in CKD stages 3 or 4 through CKD stage 5/end-stage renal disease (ESRD) versus initiation in CKD stage 5/ESRD only. The outcomes of interest were cardiovascular (CV) events averted, fractures averted, time in CKD stage 5/ESRD, mortality, quality-adjusted life years (QALYs), and costs associated with clinical events and CKD stage.
Results: Vitamin D treatment in CKD stages 3 and 4 was a dominant strategy when compared to waiting to treat until CKD stage 5/ESRD. Total cost savings associated with treatment during CKD stages 3 and 4, compared to waiting until CKD stage 5/ESRD, was estimated to be $19.9 million. The model estimated that early treatment results in 159 averted CV events, 5 averted fractures, 269 fewer patient-years in CKD stage 5, 41 fewer deaths, and 191 additional QALYs.
Conclusions: Initiating vitamin D therapy in CKD stages 3 or 4 appears to be cost-effective, largely driven by the annual costs of care by CKD stage, CV event costs, and risks of hypercalcemia. Further research demonstrating causal relationships between vitamin D therapy and patient outcomes is needed to inform decision making regarding vitamin D therapy timing.

Keywords: 25-hydroxyvitamin D, cardiovascular disease, chronic kidney disease (CKD), cost-effectiveness, disease progression, economic analysis, end-stage renal disease (ESRD), fracture, health care costs, parathyroid hormone (PTH), pre-dialysis care, secondary hyperparathyroidism (SHPT)
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1 Introduction

Patients with chronic kidney disease (CKD) face heightened risk for cardiovascular events, fractures, and mortality, among other outcomes (Go et al. 2004: p. 1300; Dalrymple et al. 2011: p. 383; Elliott et al. 2013: p. 1374). The use of vitamin D therapies, including nutritional, active, and analog forms, has been shown to reduce the risk of these outcomes in CKD patients (Stavroulopoulos et al. 2008: p. 64–66; Ravani et al. 2009: p. 91; Tomida et al. 2009: p. 681) yet the influence of treatment timing on economic and clinical outcomes has not been studied. Guidelines on the benefits of treating secondary hyperparathyroidism (SHPT) in pre-dialysis patients are equivocal and have varied in recent years (Kidney Disease Improving Global Outcomes (KDIGO) (2017)). The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) states:

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> *In patients with CKD G3a–G5D, we suggest that 25(OH)D (calcidiol) levels might be measured, and repeated testing determined by baseline values and therapeutic interventions…We suggest that vitamin D deficiency and insufficiency be corrected using treatment strategies recommended for the general population (§ 3.1.3…In adult patients with CKD G3a–G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD G4–G5 with severe and progressive hyperparathyroidism (§4.2.2)* (Kidney Disease Improving Global Outcomes (KDIGO) (2017)).

These two sections within the same updated guideline offer different recommendations for treating vitamin D insufficiency and hyperparathyroidism, conditions that are often concurrent. Providers treating patients with both conditions may be unsure of the comparative effectiveness and cost effectiveness of vitamin D therapy.

The KDIGO guideline cites the lack of clinical trials studying the association of patient outcomes (e.g. fractures) with biochemical indicators, bone mineral density (BMD), patient demographics, and treatment patterns (Kidney Disease Improving Global Outcomes (KDIGO) (2017)). Although clinical trial data on the effects of treatment timing and patient outcomes are lacking, observational data suggest that treating in early stages of CKD may reduce costs and the risks of harmful clinical events. For instance, risk of all-cause mortality is higher in CKD stage 1–4 patients with serum 25(OH)D less than 15 ng/mL (Mehrotra et al. 2009: p. 979). Low serum 25(OH)D in patients with CKD has also been associated with reduced BMD in the wrist and spine, which are risk factors for fracture (Elder and Mackun 2006: p. 1780–1781). Patient-specific factors such as duration of SHPT should be considered when making vitamin D treatment decisions (Kidney Disease Improving Global Outcomes (KDIGO) (2017)). From a system perspective, costs of treatment timing policies are also of importance so that health care budgets can be managed effectively.

Current vitamin D treatment guidelines for patients with CKD not yet receiving dialysis (non-dialysis-dependent CKD) have not been evaluated formally in a cost-effectiveness analysis. We developed a data-driven simulation model of the treatment timing decision process. The model is essential to evaluating the complexities and uncertain nature of effects of receiving vitamin D therapy, CKD progression, and the costs and benefits arising from different timing policies. The objective of the present study was to determine whether administering vitamin D therapy early during the progression of CKD is cost-effective compared to initiating therapy after progression to CKD stage 5/end-stage renal disease (ESRD), and whether early treatment could attenuate the incidence of cardiovascular events, fractures, CKD stage progression, and mortality.

2 Methods

2.1 Study Design

A cost-effectiveness model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, Washington, USA) to estimate the differences in costs and clinical outcomes due to changes in serum 25(OH)D and intact parathyroid hormone (iPTH) associated with the timing of vitamin D therapy (treatment in stages 3 and 4 versus no treatment or delayed treatment in stage 5/ESRD) among CKD patients not on dialysis. The analysis was based on a Markov model of disease progression for CKD that assumed patients progress between health states and outcomes.

The model was used to estimate costs from a payer perspective and clinical outcomes for a hypothetical cohort of 1000 patients over a 5-year time horizon with 1-year cycles. A Medicare payer perspective is taken given the baseline cohort of adult patients with CKD stage 3–4 with vitamin D insufficiency and SHPT is largely aged 65 and older. Total costs and quality-adjusted life years (QALYs) directly attributable to the patient during the model timeframe are discounted at an annual rate of 3% (Sanders et al. 2016: p. 1098). Additionally, pre-dialysis and dialysis patients are expected to reside with a single health plan for less than 5 years (Kubacki et al. 2009: p. 287; Assistant Secretary for Planning and Evaluation 2015). The model therefore takes a 5-year time horizon to make results relevant to the clinic and payer perspectives.

2.2 Intervention and Outcomes

The intervention modeled included supplementation with vitamin D compounds, which included newer vitamin D analogs, established vitamin D metabolites, and nutritional vitamin D. The effects of the intervention were based on achieving biochemical endpoints (i.e. elevated serum 25(OH)D and reduced iPTH). We note that long-term data on health outcomes and changes to biochemical parameters are limited. The primary outcome of this analysis was an incremental cost-effectiveness ratio. In addition, the model estimated important

secondary patient outcomes, including the number of cardiovascular events, number of fractures, years spent in CKD stage 5, rates of hypercalcemia, total mortality, and quality-adjusted life years in a simulated cohort of 1,000 patients.

2.3 Model Structure

A Markov model was built to evaluate cohort progression considering the selected treatment timing (treatment in CKD stages 3 or 4 versus treatment in stage 5/ESRD). The structure of the model is shown in Figure 1. Patients could transition between disease states (CKD stages) through the time horizon, and each disease state was associated with costs and QALYs. The analysis timeframe was initiated with a distribution of patients at the onset of CKD stages 3 and 4 to compare vitamin D supplementation in CKD stages 3–4 versus no treatment or delayed treatment (treatment in CKD stage 5/ESRD). The cohort starting age was 68 and 67 years for stages 3 and 4, respectively (Table 1.) (Martínez-Castelao et al. 2011: p. 4).

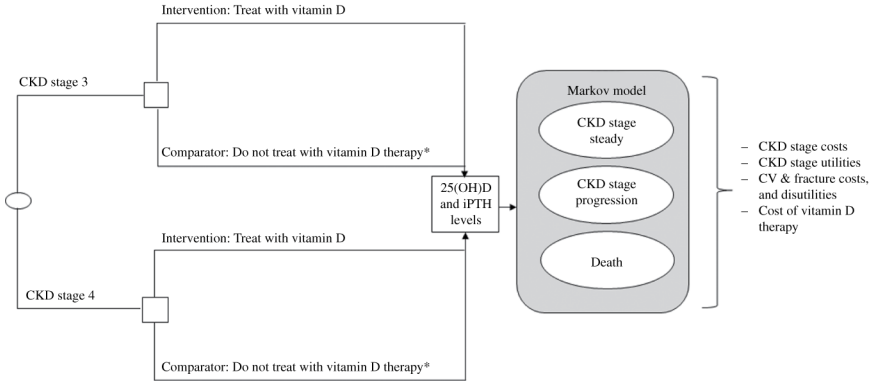

Figure 1: Markov Model Structure.
*Patients who enter CKD stage 5/ESRD are initiated on vitamin D therapy if they were not initiated in stages 3–4.
CKD, Chronic kidney disease; CV, cardiovascular; 25(OH)D, calcifediol (calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D); iPTH, intact parathyroid hormone; ○, chance node; □, decision node.

Table 1: Baseline Cohort Distribution by CKD Stage.

CKD stage	Input	Mean	95% CI	Source
Stage 3	% of cohort	81.5		United States Renal Data System 2015
	Median age, years	68	(55, 81)	Martínez-Castelao et al. 2011: p. 4
	Female, %	24.7		Martínez-Castelao et al. 2011: p. 4
Stage 4	% of cohort	18.5		United States Renal Data System 2017
	Median age, years	67	(54, 80)	Martínez-Castelao et al. 2011: p. 4
	Female, %	43.0		Martínez-Castelao et al. 2011: p. 4

CI, Confidence interval; CKD, chronic kidney disease.

After selecting treatment strategies, the cohort entered the Markov model with three health states to replicate the progression of disease. The three health states were: CKD stage steady, CKD stage progression, and death. Patients could only remain stable or progress forward in CKD stage in the model, with death being an absorbing state. A 12-month cycle length was employed and based on available literature on CKD stage transition, CV event and fracture rates, and adverse event information (Eriksen and Ingebretsen 2006: p. 377–378). Patients who are not treated initially in the decision tree were treated when they progressed to CKD stage 5/ESRD. Treatment initiation was not dependent on serum 25(OH)D or iPTH.

The time to CKD progression and number of CV events and fractures was dependent on serum 25(OH)D and iPTH, which in turn were dependent on whether the patient received vitamin D therapy. Baseline serum 25(OH)D and iPTH were adjusted by mean differences cited in the peer-reviewed literature (Tables Table 2 and Table 3). The effect of vitamin D therapy on patient outcomes (CV events, fractures, disease progression, and mortality) was simulated by adjusting the incidence rates for complications in the baseline CKD population. A

treatment discontinuation rate of 33.0% was incorporated based on medication adherence among CKD patients in the literature (Schmitt et al. 2010: p. 543).

Table 2: Natural History Inputs, Baseline SERUM 25(OH)D and iPTH by CKD Stage.

CKD stage	Input	Mean	95% CI
Stage 3	25(OH)D (ng/mL)	23.3	(8.8, 37.8)
	iPTH (ng/mL)	114.0	(39.0, 189.0)
Stage 4	25(OH)D (ng/mL)	18.6	(5.3, 31.9)
	iPTH (ng/mL)	235.0	(0.0, 470.0)
Stage 5/ESRD	25(OH)D (ng/mL)	12.0	(2.9, 21.1)
	iPTH (ng/mL)	310.0	(104.0, 516.0)

Source: LaClair et al. 2005.
25(OH)D, Calcifediol (calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D); CI, confidence interval; CKD, chronic kidney disease; iPTH, intact parathyroid hormone; mL, milliliter; ng, nanogram.

Table 3: Clinical Intervention Effects.

Clinical parameter	Base-case value	95% CI	Source
Mean difference, serum 25(OH)D (ng/mL)	19.33	(13.93, 24.74)	Kandula et al. 2011: p. 56
Mean difference, serum iPTH (ng/mL)	−49.34	(−85.74, −12.97)	Palmer et al. 2009: p. 8
RR any CV event, any vitamin D therapy	0.27	(0.13, 0.59)	Li et al. 2015: p. 709
iPTH OR, Any CV* event per 50 pg/mL reduction in iPTH	0.81	(0.70, 0.98)	Lishmanov et al. 2012: p. 544
1 ng/mL change in 25(OH)D on BMD z-score	0.88	(0.43, 1.49)	Tomida et al. 2009: p. 681
OR for 2-year risk of fracture† for every 1 standard deviation increase in BMD	0.57	(0.45, 0.77)	West et al. 2015: p. 916
Log iPTH on log of total femur BMD	−0.08	(−0.13, −0.04)	Stavroulopoulos et al. 2008: p. 66
1 standard deviation change in BMD (% from baseline)	0.91	(0.89, 0.95)	West et al. 2015: p. 916
HR per 10 ng/mL of 25(OH)D on CKD stage progression	0.57	(0.36, 0.89)	Ravani et al. 2009: p. 91
HR given serum iPTH on CKD stage progression per 51–110 change in PTH on CKD stage progression	2.15	(0.97 4.76)	Asche et al. 2012: p. 1534
HR per 10 ng/mL of 25(OH)D on all-cause mortality, in CKD stages 3–4	0.76	(0.56, 1.05)	Ravani et al. 2009: p. 91
HR per 10 ng/mL of 25(OH)D on all-cause mortality, in CKD stage 5/ESRD	0.80	(0.68, 0.94)	Zheng et al. 2013: p. 7
HR given serum iPTH on CKD stage progression per 111–199 change in PTH on CKD stage progression	5.24	(2.48, 11.10)	Asche et al. 2012: p. 1534
RR hypercalcemia given vitamin D therapy, in CKD stages 3–4	4.78	(2.20, 10.37)	Xu et al. 2013: p. 6
RR hypercalcemia given vitamin D therapy, in CKD stage 5/ESRD	3.80	(0.90, 16.12)	Palmer et al. 2009: p. 130

*Includes acute myocardial infarction, heart failure, and stroke.
†Includes hip and vertebral fractures.
BMD, Bone mineral density; CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; HR, hazard ratio; iPTH, intact parathyroid hormone; ng, nanogram; mL, milliliter; OR, odds ratio; RR, risk ratio; 25(OH)D, calcifediol (calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D).

2.4 Inputs

2.4.1 Data

Model inputs included baseline rates and associated costs of 25(OH)D, iPTH, CV events, fracture events, CKD progression, and mortality. CV events included ischaemic stroke, haemorrhagic stroke, acute myocardial in-

farction, atrial fibrillation, and congestive heart failure. Fracture types include hip and lumbar spine fractures. Clinical efficacy and adverse events rates of vitamin D therapy were based on peer-reviewed meta-analyses and surrogate clinical endpoints. The baseline cohort distribution and characteristics were used to calculate weighted averages of treatment effects and rates of CV events or fractures to create the "average" patient for the model cohort based on the inputs for the cohort's age and gender. The mean baseline serum 25(OH)D and iPTH were stratified by CKD stage and a weighted average was created using the baseline cohort demographics. The natural history rates of cardiovascular events and fractures are provided in Table 4. Patients were assumed to progress through CKD stages at the baseline rates provided in the transition matrix in Table 5.

Table 4: Natural History Rates of Clinical Events by CKD Stage.

CKD stage	Clinical event	Baseline value	Source
Stage 3	Any CV event	0.075	Go et al. 2004: p. 1300
	Any fracture	0.006	Elliott et al. 2013: p. 1374
	Mortality	0.042	O'Hare et al. 2006: p. 849
	Hypercalcemia	0.008	Xu et al. 2013: p. 8
Stage 4	Any CV event	0.218	Go et al. 2004: p. 1300
	Any fracture	0.008	Elliott et al. 2013: p. 1374
	Mortality	0.095	O'Hare et al. 2006: p. 849
	Hypercalcemia	0.008	Xu et al. 2013: p. 8
Stage 5/ESRD	Any CV event	0.366	Go et al. 2004: p. 1300
	Any fracture	0.010	Elliott et al. 2013: p. 1374
	Mortality	0.133	O'Hare et al. 2006: p. 849
	Hypercalcemia	0.043	Palmer et al. 2009: p. 130

CKD, Chronic kidney disease; CV, cardiovascular.

Table 5: Natural History Inputs, Stage Transition.

	To CKD stage, year i + 1				
	CKD stage	3	4	5	Death
From CKD stage, year i	3	69.0%	19.0%	6.0%	6.0%
	4	0.0%	25.0%	27.0%	48.0%
	5	0.0%	0.0%	16.0%	84.0%
	Death	0.0%	0.0%	0.0%	100%

Source: Anwar and Mahmoud 2014.
CKD, Chronic kidney disease.

Changes in serum 25(OH)D and iPTH were based on meta-analyses of the effects of vitamin D therapy in the pre-dialysis and dialysis populations (Table 3). The effect of vitamin D therapy on patient-level outcomes was modeled using data from observational studies on the risk of clinical events and CKD stage progression in relation to biochemical parameters of 25(OH)D and iPTH because randomized trials have not been conducted to evaluate the impact of vitamin D therapy patient-level outcomes such as cardiovascular events or mortality.

Effects of vitamin D therapy are shown in Table 3, delimited by whether the association between outcomes and therapy was due to changes in serum 25(OH)D or iPTH. When available, these effects were drawn from meta-analyses of the effects of new and established vitamin D therapies. Additionally, the effects were stratified by evidence found in the pre-dialysis and dialysis populations. The mean differences in serum 25(OH)D and iPTH due to vitamin D supplementation were obtained from a meta-analysis (Kandula et al. 2011: p. 56) and Cochrane Review (Palmer et al. 2009: p. 8), respectively. When meta-analyses were not available for model inputs, observational studies with rigorous methodologies were used to obtain effects.

The effects of therapy on CV events were based on whether the patient was receiving vitamin D supplementation rather than on changes to serum 25(OH)D or iPTH. The impact of supplementation was drawn from a large observational study within an integrated health care system (1). The effects of vitamin D levels on CKD progression and mortality were limited to patients reaching a serum level 40 ng/mL from the vitamin D therapy. This threshold is in line with recommendations for the optimal levels of 25(OH)D to achieve iPTH reductions and other clinical outcomes in pre-dialysis CKD patients (Holick et al. 2011: p. 1916; Durup et al. 2015: p. 2432; Ennis et al. 2016: p. 66). With this benefit threshold approach, we recognized that the clinical benefits of vitamin D therapy do not persist indefinitely.

The effects of therapy on rates of fractures were calculated using the association between 25(OH)D and iPTH on BMD and the association between BMD and fracture risk from The Rotterdam Study (Rivadeneira et al. 2007: p. 1784). To account for an increased risk of CV events and fractures associated with patients who have had a previous CV events or fractures, the risks of these events were multiplied by additional relative risks (Goicoechea et al. 2005: p. S-37; Naylor et al. 2014: p. 813–814).

The effects of changes in 25(OH)D and iPTH were modeled separately and were additive for CV event and fracture outcomes. However, the effects of serum 25(OH)D and iPTH could not be modeled additively for CKD stage progression and mortality because the outcomes were not studied separately in the existing literature. The hazard ratios (HRs) for these outcomes were based on studies that did not control for the other biochemical parameters. For these outcomes, the effects of changes in serum 25(OH)D were used.

2.4.2 Economic Data

Costs were estimated from a Medicare payer perspective and included the costs of vitamin D supplements, costs of treating CV events and fractures (including any inpatient hospital costs), and standard costs associated with treating patients in each CKD stage (Table 6). Total costs and quality-adjusted lifetime directly attributable to the patient over the time horizon are discounted at an annual rate of 3% per cost-effectiveness recommendations (Sanders et al. 2016: p. 1098). Costs were adjusted to USD $2017 using the Medical Care component of the Consumer Price Index.

Table 6: CKD Management and Clinical Event Medicare Costs, USD 2017.

Cost parameter	Base case value	Source
CKD stage 3, PPPY	$21,441	United States Renal Data System 2017
CKD stage 4–5, PPPY	$32,117	United States Renal Data System 2017
All dialysis, cost PPPY	$93,113	United States Renal Data System 2017
CV event*	$26,454	Lee, Belozerff, and Song 2013: p. 28
Fracture event†	$28,227	Lee, Belozerff, and Song 2013: p. 28
Hypercalcemia	$6278	Hillner et al. 2000: p. 77

*Includes acute myocardial infarction, heart failure, and stroke.
†Includes hip and vertebral fractures.
CKD, Chronic kidney disease; CV, cardiovascular.

Health-related quality of life information used to estimate health states and benefits was taken from the literature. Utility values by CKD stage and disutility values for CV events and fractures were estimated using the time-trade off method among CKD patients (Gorodetskaya et al. 2005: p. 2804; Davies et al. 2015: p. 6). Utility values were multiplied by the number of alive patients in each stage at the end of the 12-month cycle to calculate QALYs.

2.4.3 Medication Costs

Annual vitamin D therapy costs were calculated by multiplying the number of doses per prescription by the cost per dose (Medicare Part D reimbursed amounts) by the number of patients on treatment at the end of the treatment cycle. Drug therapy costs were based on a market basket comprised of vitamin D therapies, including RAYALDEE®, DRISDOL® (ergocalciferol), HECTOROL® (doxercalciferol), ROCALTROL® (calcitriol), SENSIPAR® (cinacalcet), ZEMPLAR® (paricalcitol), doxercalciferol, calcitriol, and paricalcitol. Table 7 lists wholesale acquisition costs (WAC) and Part D reimbursed amounts by therapy. For certain therapies without Part D reimbursement data, the average WAC to Part D reimbursement ratio, derived from the other therapies, was applied to estimate the Part D reimbursement amount. We assumed that costs of vitamin D therapies did not change during the time horizon, based on historical pricing and price change data from REDBOOK– (IBM Corporation, Armonk, NY, USA) (Red Book 2017).

Table 7: WAC and Part D Vitamin D Therapy Costs, USD 2017.

Product	WAC daily price per dose	Part D daily price per dose	Daily dosage (μg)	WAC monthly cost	Part D monthly cost
RAYALDEE® (Calcifediol)	$30.93	$24.65	30	$928.00	$739.50
DRISDOL® (Ergocalciferol)	$2.91	$2.32	1250	$87.33	$69.59
HECTOROL® (Doxercalciferol)	$29.07	$21.53	1	$872.06	$645.83
ROCALTROL® (Calcitriol)	$1.56	$0.57	0.25	$46.70	$17.14
SENSIPAR® (Cinacalcet)	$26.87	$30.30	30,000	$806.00	$908.86
ZEMPLAR® (Paricalcitol)	$13.01	$11.03	1	$390.92	$330.80
Doxercalciferol	$26.13	$17.71	1	$783.98	$531.18
Calcitriol	$0.97	$0.58	0.25	$29.03	$17.53
Paricalcitol	$4.17	$5.06	1	$125.00	$151.75
Weighted average cost*				$1043	$943

Sources: Red Book 2017, CMS Part D Prescriber Data 2016.
*Weighted by estimated market share as of December 2017, data on file.
WAC, Wholesale acquisition cost, lowest WAC used.

2.5 Model Outcomes and Analyses

2.5.1 Overview

Model outcomes included clinical outcomes and associated costs of early versus late vitamin D therapy. The outcomes and analyses were evaluated by outcome and by incremental cost-effectiveness ratios (ICERs), reported as the incremental cost per QALY gained. The model also estimates total costs and savings, patient-years in CKD stage 5/ESRD, number of CV events, number of fractures, and QALYs related to the treatment strategy.

2.5.2 Sensitivity Analyses

We performed 1-way sensitivity analyses to examine how robust the base case results were to alternative assumptions about model parameters. In the 1-way sensitivity analyses, each of the cost parameters in Table 8 as varied by ±25% of the baseline value, and each of the intervention effects was varied by the standard errors or 95% confidence interval values reported in the source literature. The variables in the 1-way sensitivity analysis were selected for inclusion given their impact on the clinical and economic outcomes. In scenario analyses, certain inputs were varied separately to more extreme values.

Table 8: One-Way Sensitivity Analysis Parameter Values.

Parameter	Base-case value	Lower-bound	Upper-bound
Annual cost of vitamin D therapy	$942.59	$706.94	$1178.24
Cost of CV event	$26,453.55	$19,840.16	$33,066.94
Cost of CKD stage 5/ESRD	$93,113.21	$69,834.90	$116,391.51
25(OH)D ng/mL treatment threshold	40	30	50
Mean difference, 25(OH)D | vitamin D therapy	19.33	13.93	24.74
HR, CKD stage progression per 10 ng/mL of 25(OH)D	0.57	0.36	0.89
RR, CV event | vitamin D therapy	0.27	0.13	0.59
RR, hypercalcemia	4.78	2.20	10.37

25(OH)D, Calcifediol (calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D); CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; HR, hazard ratio; ng, nanogram; mL, milliliter; RR, relative risk.

A threshold analysis was also performed to determine the parameter values at which the net total cost difference between treating with vitamin D therapy in CKD stages 3–4 and waiting until CKD stage 5/ESRD reaches $0 (breakeven). The threshold analysis was conducted on parameters shown to be influential to the total cost difference in the 1-way sensitivity analysis. In a probabilistic sensitivity analysis (PSA), we compared treating

in CKD stages 3–4 to treating in CKD stage 5/ESRD. The PSA sampled each parameter from selected distributions (Table S1, available as supplementary material) given the point estimates and 95% confidence intervals or standard deviations from the literature. Parameters with unavailable dispersion or confidence interval estimates were varied by ±25% of baseline values. The net monetary benefit (NMB) approach was used to facilitate PSA comparison across treatment timing policies. NMB is calculated as the total QALYs, multiplied by the willingness to pay (WTP) for a QALY, less the total cost. We sampled 1,000 replications, and for each, we calculated the NMB of each policy and recorded the proportion of times the treat early policy yielded a positive NMB.

As the maximum WTP per QALY is not a universally accepted amount in the United States, sensitivity analysis using estimates ranging from $0 to $150,000 (in increments of $1,000) was undertaken to estimate the cost-effective strategy at each value. Due to uncertainty in the value of model parameters, further analysis was undertaken to estimate the likelihood that the treat early strategy would be the cost-effective strategy.

2.5.3 Scenario Analysis

In the base-case analysis, we modeled the effects of vitamin D treatment timing by simulating the effects of treating in CKD stages 3 and 4 versus waiting until stage 5/ESRD. Alternatively, we performed a scenario analysis in which we restricted the analysis to CKD stages 3 and 4. In this scenario, patients are either treated or not (in CKD stages 3–4), and patients exit the model when they reach either the dead state or CKD stage 5/ESRD.

For certain parameters of interest, we performed extra sensitivity analyses beyond the bounds of the ±25% or standard deviation range (annual cost of vitamin D therapy, cost of CKD stage 5/ESRD, and the hazard ratio for CKD progression given vitamin D therapy). These parameters were varied to their extremes in scenario analyses.

3 Results

3.1 Base-Case Analysis

3.1.1 Cost-effectiveness

Compared with waiting to treat with vitamin D until CKD stage 5/ESRD, treating in CKD stages 3 and 4 ("treat early") was associated with an additional 191 QALYs (95% CI estimated in probabilistic sensitivity analysis: 79–277) at a cost savings of $19.9 million (95% CI: $0.7 million to $44.3 million) in a cohort of 1000 patients (Table 9). The estimated savings and gain in health benefits indicated that the treat early strategy was the dominant alternative.

Table 9: Cost-Effectiveness Outcomes.*

Outcome	Treatment timing		Difference
	Intervention (treat with vitamin D therapy in CKD stages 3–4)	Comparator (do not treat with vitamin D therapy in CKD stages 3–4)	
Total costs	$208,953,654	$228,895,627	($19,941,974)
Life years	3,663	3,532	131
QALYs	3,135	2,944	191
Cost per life year gained	Dominant	–	–
Cost per QALY	Dominant	–	–

*All outcomes and costs were discounted at 3% annually.
CKD, Chronic kidney disease; ESRD, end-stage renal disease; QALY, quality-adjusted life year; WTP, willingness to pay.

3.1.2 Clinical Outcomes

Patient-level outcomes in the base-case model for 1,000 patients over a 5-year time horizon are presented in Table 10. For patients in CKD stages 3–4, increasing serum 25(OH)D and decreasing serum iPTH due to vitamin D

therapy in CKD stages 3–4 versus stage 5/ESRD was shown to result in a marked decrease in the incidence of CV events and fractures, the number of patient-years in CKD stage 5/ESRD, and mortality. Most notably, the model estimated that in a cohort of 1,000 patients, 159 CV (95% CI: 75–287) events and 269 patient-years in CKD stage5/ESRD (95% CI: 73–398) were averted, and 131 life years (95% CI: 9–208) were gained.

Table 10: Discounted* Clinical Model Outcomes for 1000 Patient Cohort, 5 Years.

Outcome	Treatment timing		Difference†	95% CI‡
	CKD stages 3–4	CKD stage 5/ESRD		
CV events				
Difference attributable to change in serum 25(OH)D	872	993	−120	
Difference attributable to change in serum iPTH	1,146	1,184	−38	
Total difference in CV events			−159	(−75, −287)
Fractures				
Difference attributable to change in serum 25(OH)D	23	28	−5	
Difference attributable to change in serum iPTH	29	29	0	
Total difference in fractures			−5	(−2, −9)
Patient-Years in CKD Stage 5/ESRD§	786	1,055	−269	(−73, −398)

*Discounted at 3% annually for costs and benefits.† Differences may not sum to individual columns due to rounding.
‡95% confidence intervals were estimated in the probabilistic sensitivity analysis using 1,000 runs with distributions specified in the supplementary material.
§Only differences attributable to changes in serum 25(OH)D are used to estimate economic effects of vitamin D therapy for mortality, which is used to estimate differences in life years and quality-adjusted life years.
25(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; iPTH, intact parathyroid hormone; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

3.1.3 Economic Outcomes

Among the cohort of patients who initiated vitamin D therapy in CKD stages 3 and 4, the cost of therapy was estimated to be $1,416,006 versus $345,053 for the cohort who did not initiate treatment until CKD stage 5/ESRD, for a difference of $1,070,953 over 5 years. Net of these costs for vitamin D therapy, the early treatment cohort resulted in savings of $19.94 million during the 5 years, comprised of reduced CV events, fractures, and progression to CKD stage 5/ESRD (Figure 2). The net savings of early treatment are largely driven by fewer patient-years spent in CKD stage 5/ESRD ($25.1 million in reduced costs) (Figure 2).

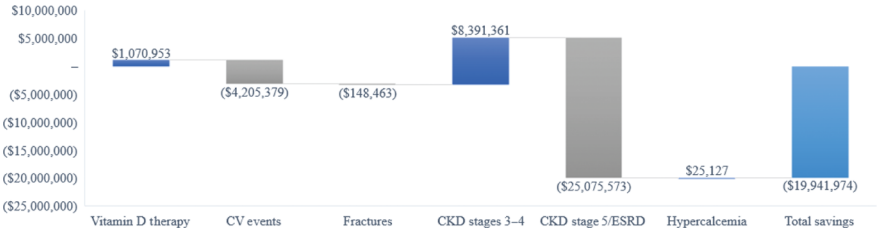

Figure 2: Discounted* (Savings) and Costs† of Early (CKD Stages 3–4) versus Late (CKD Stage 5/ESRD) Vitamin D Therapy by Category across 1,000 Patient Cohort, 5 years, 2017 USD.
*Discounted at 3% annually. †Negative values represent cost savings estimated due to treating with vitamin D in CKD stages 3–4 versus waiting until CKD stage 5/ESRD. Positive values indicate incremental additional costs associated with treatment in CKD stages 3–4 versus CKD stage 5/ESRD. CKD, Chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease, ■, increase; ■, decrease; ■, total.

3.2 One-Way and Probabilistic Sensitivity Analyses

The base-case results were robust to several 1-way sensitivity analyses. The HR associated with CKD stage progression per 10 ng/mL increase in 25(OH)D was the most sensitive parameter (Figure 3). Nonetheless, when

varying the HR by the standard errors reported in the source literature (0.36, 0.89) (Ravani et al. 2009: p. 91), treating early persisted as a cost-saving strategy with net savings ranging from $3.2 million to $28.7 million over 5 years over a cohort of 1000 patients.

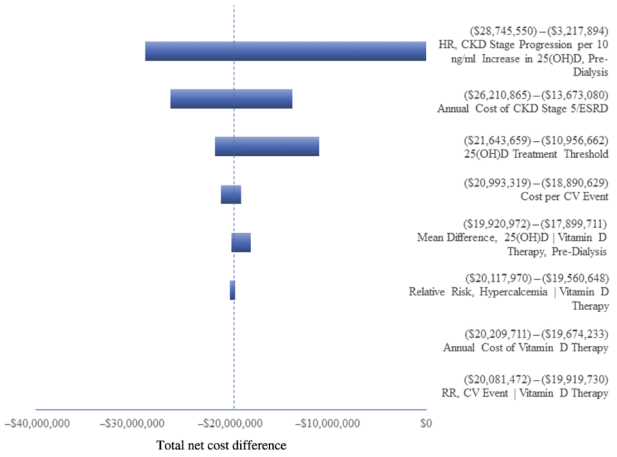

Figure 3: One-Way Sensitivity Analysis on Variables That Most Influenced the Net Difference in Total Costs Associated with Treating with Vitamin D Therapy in CKD Stages 3–4 Versus CKD Stage 5/ESRD, Lower and Upper Bounds of Net Total Cost Difference Across Cohort (n = 1000), 2017 USD, by Tested Parameter.
25(OH)D, 25-hydroxyvitamin D; CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; HR, hazard ratio; iPTH, intact parathyroid hormone; RR, relative risk; | base case; ▬, range of outcomes.

Results indicating cost-savings associated with early vitamin D therapy were also robust in threshold analyses. Based on the results of the one-way sensitivity analysis, the cost per CV event, annual cost of CKD stage 5/ESRD, mean difference in 25(OH)D given vitamin D therapy, and the HR for CKD stage progression were varied to determine levels at which treating early did not produce cost savings (Figure 4). Feasible changes to the cost per CV event and mean difference in 25(OH)D (i.e. costs cannot be less than $0 and mean difference is not expected to be lower than 0) would not result in incremental additional costs associated with treating during CKD stages 3–4 versus waiting until CKD stage 5/ESRD. The 25(OH)D threshold for treatment effect would have to decrease to 21.8 for treatment to not produce any cost savings (i.e. breakeven) (Figure 4A). The annual cost of treating CKD stage 5/ESRD patients would need to decrease to $19,071 (from $93,113 in the base-case analysis) for treating with vitamin D early to breakeven with treating late (Figure 4B). The HR for CKD stage progression given increases in serum 25(OH)D would be required to increase to 0.95 in order for the early treatment strategy to breakeven (Figure 4D).

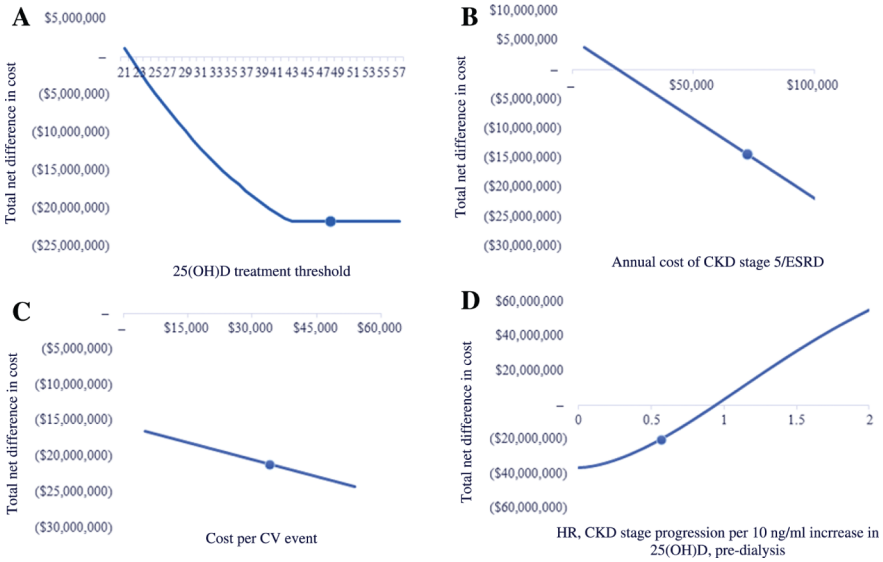

Figure 4: Threshold Analysis on Variables That Most Influenced the Net Difference in Total Costs* Associated with Treating with Vitamin D Therapy in CKD Stages 3–4 Versus CKD Stage 5/ESRD Across Cohort (n = 1000), 2017 USD, by Tested Parameter.
*Negative values represent cost savings estimated due to treating with vitamin D in CKD stages 3–4 versus waiting until CKD stage 5/ESRD. Positive values indicate incremental additional costs associated with treatment in CKD stages 3–4 versus CKD stage 5/ESRD. ● Indicate base case values of parameters and associated total net difference in cost.

In the PSA, early vitamin D therapy (treating in CKD stages 3–4 versus waiting until CKD stage 5/ESRD) was the dominant strategy (more effective and less costly) in 98.6% of the trials (Figure 5). We found that treating in CKD stages 3–4 has a 100% probability of being the most cost-effective treatment strategy at all WTP thresholds of $11,000 per QALY or greater.

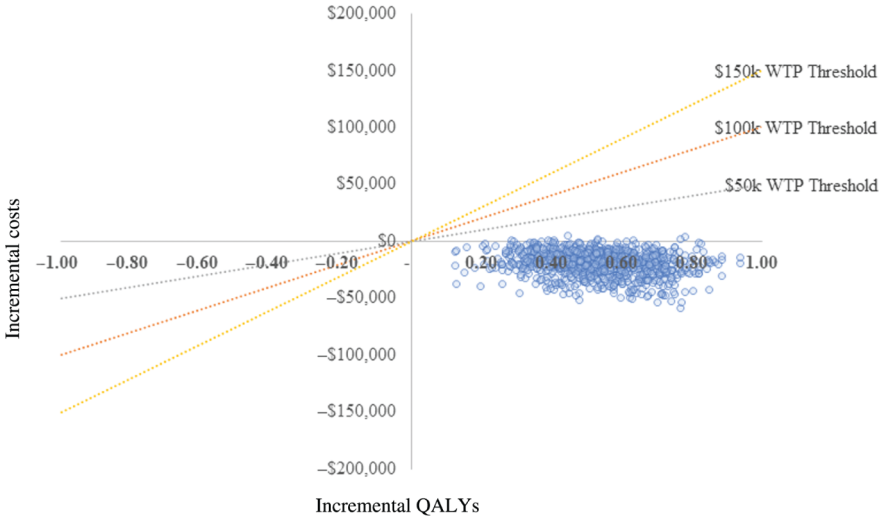

Figure 5: Cost-Effectiveness Plane* Compared to Willingness to Pay Thresholds of $50,000, $100,000, and $150,000, Probabilistic Sensitivity Analysis with 1,000 Runs.
*Cost-effectiveness plane: treating with vitamin D therapy in CKD stages 3–4 versus CKD stage 5/ESRD compared to a willingness to pay thresholds. Five-year time horizon and discounted costs and QALYs. 1,000 iterations. QALYs, Quality-adjusted life years; WTP, willingness to pay.

3.3 Scenario Analysis

In the base-case analysis, we modeled the effects of vitamin D therapy in CKD stages 3–4 versus waiting until CKD stage 5 for the risk of clinical events at different serum concentrations of 25(OH)D and iPTH. However, some vitamin D therapies are only indicated for pre-dialysis patients. We therefore performed a scenario analysis in which patients exited the model when they reached CKD stage 5. In this scenario, we compared the effects of treating versus never treating with vitamin D supplements. Across the 1,000-patient cohort over 5 years, the model in this scenario showed that treating during CKD stages 3–4 resulted in total net costs of $7.50 million, due mainly to extended time in stages 3–4 resulting from decreased mortality and delayed stage progression. An estimated 119 CV events, 3 fractures, and 114 deaths were averted in this scenario.

We also varied influential parameters to extreme levels to test the robustness of the results. In this scenario, we compared treating early (CKD stages 3–4) versus late (CKD stage 5/ESRD). Using a cost of annual cost of vitamin D therapy of $10,900, the net total savings of early vitamin D treatment was $10.28 million. The model results are largely dependent on savings from CKD stage 5/ESRD; hence, we also reduced the annual costs associated with treating patients in this stage to be equal to the costs of CKD stage 4. In this scenario, estimated total net savings associated with treating early were $3.68 million. Finally, we varied the HR for CKD progression given vitamin D therapy to 1.0 (no effect). In this scenario, the estimated total net cost of treating early was $3.03 million.

In order to make the results relevant to policy stakeholders, a separate analysis was conducted to extrapolate the results across the entire United States Medicare population. An estimate of 1,015,376 was generated for the relevant Medicare insured population with CKD Stage 3 or 4 and SHPT and vitamin D insufficiency (Karlsson et al. 2005: p. 161; Levin et al. 2007: p. 34; Kaiser Family Foundation 2018; United States Census Bureau, Population Division 2019). Across 1,015,376 patients, early treatment resulted in 161.4K CV events offset, 5.3K fewer fractures, 273.4K fewer years in CKD stage 5, 42.1K deaths averted, and 132.7K life years gained. Among the cohort of patients who initiated vitamin D therapy in CKD stages 3 and 4, the cost of therapy was estimated to be $1.44 billion versus $350.3 million for the cohort who did not initiate treatment until CKD stage 5/ESRD, for a difference of $1.09 billion over 5 years. Net of these costs for vitamin D therapy, the early treatment cohort resulted in savings of $20.2 billion during the 5 years, comprised of reduced CV events, fractures, and progression to CKD stage 5/ESRD.

4 Discussion

Results from this analysis suggest both health gains and healthcare cost savings are likely to be realized by treating patients with vitamin D insufficiency and SHPT in CKD stages 3–4 rather than waiting until CKD stage 5/ESRD. From a strictly cost perspective (disregarding quality of life and life expectancy benefits), this analysis suggests that after 5 years, the return on investment of vitamin D therapy is fully recouped through savings in healthcare care costs to treat cardiovascular events, fractures, and CKD stage progression.

Many studies have demonstrated a relationship between vitamin D therapy and clinical outcomes in the CKD population (Barreto et al. 2009: p. 1130; Palmer et al. 2009: p. 8; Ravani et al. 2009: p. 91; Pilz et al. 2011: p. 378); however, few studies have connected these clinical outcomes to the economic effects of treatment timing. Given ambiguities in vitamin D treatment guidance, CKD patients not on dialysis may not receive treatment until they progress to CKD stage 5/ESRD. In this economic analysis, we therefore examined the cost-effectiveness of treating with vitamin D supplements in CKD stages 3–4 versus waiting to treat until CKD stage 5/ESRD. Our analysis showed that early therapy may be clinically and economically favorable to later treatment. These results were robust to changes in inputs and model assumptions. To the best of our knowledge, this study is the first cost-effectiveness analysis of vitamin D therapy timing. This research supports and extends findings of other studies showing an association between serum 25(OH)D and important clinical outcomes. Our results contribute to important rationale for the use of vitamin D therapy in CKD patients not on dialysis.

While robust to sensitivity and scenario analyses, our study has limitations. The results may not be generalizable to other specific groups or subpopulations. We do not consider patient-specific factors such as age, gender, duration of CKD, previous CV events and fractures, and other heterogeneous physiological factors that may influence costs and clinical outcomes. Our analysis was performed from the Medicare payer perspective in the United States, and parameters for the simulation model were derived mostly from US-based studies. CKD patients in the US may be more prone to CV events and fractures compared to patients in other countries; however, the cost of vitamin D therapy may also be considerably higher in the US than in other countries. We did not investigate clinical outcomes other than CV events, fractures, CKD stage progression, mortality, and hypercalcemia thus, the analysis may not capture the entire impact of vitamin D therapy in CKD.

To simulate outcomes based on available literature, we made assumptions about the costs, transition probabilities, mortality rate, and effects of vitamin D therapy for patients with CKD. While our assumptions were based on the best available data, we also explored the implications of those assumptions using extensive sensitivity analyses. The model inputs were based on published literature on associations observed between serum 25(OH)D and iPTH and health outcomes. We may have overestimated or underestimated the impact of changes to biochemical parameters that are associated with outcomes but may have a different causal influence.

Slowing progression to CKD stage 5/ESRD is a major source of cost savings in this analysis. Many studies assessing the impact of biochemical parameters on CKD outcomes aggregate CKD stage 5 with ESRD; yet, the cost of treating a patient in CKD stage 5 not yet on dialysis is expected to be much lower than the cost of treating a patient on dialysis (Damien et al. 2016: p. 5). We were unable to disaggregate effects on non-dialysis patients in CKD stage 5 patients from patients on dialysis. A diagnosis of ESRD usually begins in Stage 5 CKD (GFR <15 mL/min/1.73 m^2), but many patients do not begin renal replacement therapy until the eGFR is lower than 15, and some patients never receive dialysis. In contrast, some patients may start dialysis at an eGFR greater than 15 (United States Renal Data System 2017). Thus, treatment costs in early CKD stages may be underestimated and costs in CKD stage 5 may be overestimated in our model. This assumption may bias our results towards concluding that vitamin D therapy in early stages is cost-effective.

The input for the effect of 25(OH)D on disease progression is based on a single study (6), but the HR was varied in sensitivity analyses. Given the reliance on published literature, we were unable to control for confounding factors that may bias the model results; however, when possible, inputs were taken from studies that controlled for changes to other biochemical parameters and patient demographics.

The use of vitamin D therapy in CKD stages 3–4 is likely to improve clinical outcomes for patients and to be cost-effective for payers. The persistent prevalence of CKD, comorbidities, and costs associated with treating CKD (Murphy et al. 2016: p. 5) suggest the need to evaluate possible therapies to reduce the costs and improve the outcomes in these patients. Although hypercalcemia and hyperphosphatemia are possible adverse events associated with vitamin D therapy, these concerns should be balanced with the benefits of maintaining appropriate serum 25(OH)D and iPTH concentrations in CKD patients not on dialysis.

Further studies are needed to validate the findings from our simulation model, namely to test effects of vitamin D therapy on patient outcomes using randomized control trials. Investigation into the effects of specific types of vitamin D therapy is also warranted to establish the differential effects of therapies on rates of adverse events.

Conflict of Interest Statement: Sophie Snyder is an employee of BluePath Solutions. Matthew Gitlin is the Managing Director of BluePath Solutions. Akhtar Ashfaq is an employee of OPKO Health, Inc. Christopher S. Hollenbeak and Kamyar Kalantar-Zadeh have no conflicts of interest to declare. OPKO Health, Inc. funded the model development upon which this manuscript was based, as well as manuscript development. Aside from the contributions of the OPKO-employed authors, the funder had no role in study design; the collection, analysis, and interpretation of data; or in the writing of the report. The manuscript was provided to OPKO Health, Inc. for review prior to submission.

Authors' Contributions

AA, CH, KKZ, MG, and SS designed research; AA, MG, and SS conducted research; MG and SS analyzed data; SS wrote the paper; AA and SS had primary responsibility for final content, CH and KKZ provided supervision and mentorship. All authors read and approved the final manuscript.

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