INTRAVENOUS VITAMIN D TREATMENT IN HEMODIALYSIS PATIENTS: PATTERNS OF USE AND ASSOCIATION WITH FRACTURE RISK

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ABSTRACT

ANNE CHRISTINE BEAUBRUN: Intravenous Vitamin D Treatment in Hemodialysis Patients: Patterns of Use and Association with Fracture Risk
(Under the direction of Dr. M. Alan Brookhart and Dr. Betsy L. Sleath)

The administration of intravenous vitamin D therapy is central to the treatment of secondary hyperparathyroidism. Yet, there is little data documenting the variations in the use of these agents in large, representative samples and vitamin D's clinical benefits are not clear. The objectives of this dissertation were to describe patterns in the use of vitamin D and to examine the association between vitamin D exposure and fracture risk among hemodialysis patients.

We described vitamin D-related trends among patients within the United States Renal Data System between 01/01/2000-12/31/2008. Annual percentages of patients treated with each formulation were tabulated by relevant subgroups. A retrospective cohort study was conducted to examine the association between vitamin D exposure and fracture risk. Incident hemodialysis patients between 01/01/2000-05/31/2004 entered a 180-day baseline period where vitamin D exposure was assessed. Time to the first fracture hospitalization was assessed over one year using multivariable Cox proportional hazard regression. The key measures of vitamin exposure were measured at the facility-level: 1) the proportion of vitamin D users/facility (derived using mixed-effects logistic regression); and 2) the average vitamin D dose per patient (derived using mixed-effects linear regression). Fractures were grouped into four categories

Vitamin D use has increased sharply from 58.6% of patients treated in 1999 to 83.9% of patients treated in 2008. Paricalcitol was the preferred formulation during the study years. In 2008, the average dose among black patients was 84% greater than among white patients. No significant relation was observed between the proportion of vitamin D users or the average vitamin D dose per patient at the facility-level and fracture rates for all fracture types. Specifically, for any fracture, the hazard ratio (HR) in adjusted models for a facility's proportion of vitamin D users was 1.10 (95% CI 0.86-1.42) while the HR for a facility's average vitamin D dose per patient was 0.99 (95% CI 0.90-1.09).

In summary, vitamin D use has increased and parallels the rise in use of paricalcitol and doxercalciferol. Increasing vitamin D use and average vitamin D dose administered per patient within dialysis facilities did not have an observed beneficial association with fractures.

DEDICATION

To my mother, Marie Quetly Beaubrun. You are my light and inspiration.

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LIST OF ABBREVIATIONS

AOR	Adjusted odds ratio
BMI	Body mass index
CI	Confidence Interval
CKD	Chronic kidney disease
CPT	Current Procedural Terminology
ESRD	End-stage renal disease
FDA	US Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard ratio
ICD-9	International Classification of Diseases, Ninth Revision
iPTH	Intact PTH
IV	Intravenous
PTH	Parathyroid hormone
SHPT	Secondary hyperparathyroidism
USRDS	United States Renal Data System

CHAPTER I

INTRODUCTION

1.1 Overview

Disordered bone mineral metabolism is rampant in end-stage renal disease (ESRD) patients and a considerable amount of time and resources are dedicated to its evaluation and treatment.[1] Intravenous (IV) vitamin D has become a mainstay in bone-mineral disorder management and is used to treat secondary hyperparathyroidism (SHPT), a common complication among patients with ESRD.[2] SHPT, characterized by increased parathyroid hormone (PTH) levels, has been associated with abnormalities in bone metabolism, soft tissue and vascular calcification and a range of other disorders.[2, 3] Despite IV vitamin D's widespread use and its proven effectiveness in decreasing PTH levels, there is a lack of evidence demonstrating that pharmacologically reducing PTH levels can actually result in improved fracture outcomes. There are a myriad of examples from various therapeutic areas documenting instances where medications were approved for their efficacy in manipulating a surrogate biomarker but were eventually found to confer no clinical benefit or even harm.[1]

It is important to evaluate whether vitamin D's benefit extends beyond treating SHPT. Patients with renal failure commonly experience fractures, associated with significant morbidity and mortality in this patient population.[4] The age- and sex-adjusted risk of fracture is reported to be several times greater among ESRD patients when compared to the general population.[4] SHPT and changes in PTH levels are associated with a range of bone

morphologies that may be linked to an increased risk of fracture.[5] Although it would be tempting for nephrologists to use vitamin D to ameliorate the high clinical burden of fractures observed among dialysis patients, it would be ill-advised given the general lack of valid, population-based studies or clinical trials documenting any benefits or harms of IV vitamin D use for this indication.

Also, studies exploring racial, gender, geographic secular variations, and patterns of vitamin D use are needed to document any secular trends in overuse of the drug, provide evidence in support of dialysis quality improvement initiatives, and alleviate any health disparities among patients with ESRD. There have been no large-scale population-based observational studies, thus far, examining the association between vitamin D exposure and fracture risk among dialysis patients. Vitamin D exposure refers to vitamin D-related treatment decisions regarding dialysis patients. To address these salient deficits in the nephrology literature, the aims and hypotheses that comprise this dissertation are described below.

1.2 Aims and Hypotheses

Data were derived from the United States Renal Data System (USRDS), a national registry of all renal disease patients. The aims of this study were:

Aim 1: To describe patient-level, facility-level, and state-level trends in the use and dosage of three vitamin D analogs among prevalent hemodialysis patients.

Mean vitamin D dose per patient per year for each formulation was estimated at the patient, facility, and state level. The monthly percentages of patients treated with each type

of vitamin D formulation were presented in longitudinal graphs comparing secular trends in vitamin D use in each calendar year between 1999 and 2008.

Aim 2: To investigate the association between vitamin D exposure and fracture risk by fracture type and among relevant subgroups among incident hemodialysis patients.

Null Hypotheses

$H1_0$: There is no association between the non-case-mix proportion of vitamin D users within a dialysis facility and fracture risk.

$H2_0$: There is no association between the case-mix adjusted proportion of vitamin D users within a dialysis facility and fracture risk.

$H3_0$: There is no association between the non-case-mix average vitamin D dose per patient within a dialysis facility and fracture risk.

$H4_0$: There is no association between the case-mix adjusted average vitamin D dose per patient within a dialysis facility and fracture risk.

$H5_0$: There is no association between high case-mix adjusted average vitamin D doses per patient at the facility-level (the 75th percentile) and fracture risk.

Alternative Hypotheses

$H1_a$: The non-case-mix adjusted proportion of vitamin D users within a dialysis facility is negatively associated with fracture risk.

$H2_a$: The case-mix adjusted proportion of vitamin D users within a dialysis facility is negatively associated with fracture risk.

$H3_a$: The non-case-mix adjusted average vitamin D dose within a dialysis facility is negatively associated with fracture risk.

$H4_a$: The case-mix adjusted average vitamin D dose within a dialysis facility is negatively associated with fracture risk.

$H5_a$: High case-mix adjusted average vitamin D doses per patient at the facility-level (the 75^{th} percentile) are negatively associated with fracture risk.

We conducted a retrospective cohort, intention-to-treat analysis using data from 2000-2004 where vitamin D exposure variables were measured as ecological variables at the facility-level while covariates and fracture outcomes were measured at the individual-level. The measures of vitamin D exposure for Aim 2 were ecological variables measured at the facility-level during the 180-day baseline period: 1) the non-case-mix adjusted proportion of vitamin D users in each facility; 2) the case-mix adjusted proportion of vitamin D users in each facility; 3) the non-case-mix adjusted average vitamin D dose per patient in each facility; 4) the case-mix adjusted average vitamin D dose per patient in each facility; and 5) whether a facility was in the highest quartile of case-mix adjusted average vitamin D dose per patient in each facility. We focused the presentation of results on the case-mix adjusted measures of vitamin D exposure because they account for variations in patient characteristics at a dialysis facility that may have influenced how vitamin D was delivered.

The outcome measure for Aim 2 was fracture risk. The dependent variable in Cox proportional hazard models was the time to first fracture and the parameter estimates (hazard ratios) reflected the fracture risk. Hereafter, fracture risk will be described using hazard ratios, defined in this study as the hazard for patients in the exposure group relative to those who were not exposed to vitamin D. The dependent variable was the time to first fracture, the time in days from the end of the baseline period to the first fracture hospitalization. Fracture risk was assessed during the one-year follow-up period immediately following the

end of the baseline period. In sum, fracture risk was used to describe our outcome and time to first fracture was used to describe the dependent variable in Cox proportional hazards models.

A number of statistical techniques were employed to address the high likelihood of confounding by indication in this analysis given that we did not have access to clinical variables that likely mediate the association between vitamin D use and fracture risk. We adopted a facility-practice-based, grouped-treatment approach whereby vitamin D exposure was measured ecologically while covariates and outcomes were measured at the individual-level. The main measures of vitamin D exposure (the case-mix adjusted proportion of vitamin D users and case-mix adjusted average vitamin D dose per patient) reflected the facility's likelihood to prescribe vitamin D at certain doses based on the distribution of demographic and clinical characteristics of patients within the facility. There is empirical evidence in the nephrology literature suggesting that facility-level characteristics have a great influence on patient-level health outcomes. For instance, in a study of chronic hemodialysis patients within a non-profit dialysis provider, Chan and colleagues found evidence suggesting that the most important determinant of achieving optimal anemia management may be at the dialysis facility-level.[6] Even after adjusting for the use of facility treatment protocols, a patient's dialysis center was strongly associated with a patient's achievement of target hemoglobin values.[6]

Fractures in any diagnoses field in any one of four broad fracture categories were identified: 1) vertebral; 2) pelvis/hip; 3) other [femur, lower leg (tibia, fibula, patella & ankle), ribs/sternum, humerus, scapula & clavicle (shoulder/upper arm), or forearm/wrist]; and 4) any of the above fracture types. Each fracture type was an end-point in multivariable

analyses. Crude and covariate adjusted fracture rates were estimated. Cox proportional hazard models examined fracture risk in models with time to fracture as the dependent variable. Analyses adjusted for baseline patient demographic and clinical characteristics. All analyses were conducted in the overall patient population within age, sex, and racial subgroups, respectively.

The choice of covariates and the hypothesized relationship between important determinants of fracture risk was guided by Andersen's Behavioral Model of Health Services Use.[7] According to the model, predisposing, enabling and need factors comprise of population characteristics that determine health behavior, health service use, and health outcomes. In all the Cox proportional hazard regression models performed, adjustments were made for predisposing characteristics such as age, sex, and race, attributes inherent to the individual prior to the onset of disease. We also controlled for enabling characteristics such as eligibility for Medicaid and organizational level factors like a dialysis facility's profit-status to reflect the healthcare resources available to the patient. Comorbidities and functional status markers were included in our analysis to reflect need characteristics that compel individuals to seek health care services. These population characteristics (predisposing, enabling, and need) lead to a patient's exposure to vitamin D as they get treated for renal failure and SHPT within a hemodialysis facility. Exposure to vitamin D within a hemodialysis facility is hypothesized to be associated with the outcome of interest, fracture risk.

1.3 Significance of the Study

Surrogate endpoints are defined as symptoms, laboratory values (e.g., serum calcium levels), symptoms (e.g., inflammation), clinical markers (e.g., body mass index) , and other measures of treatment efficacy that are used as a proxy for clinical outcomes like morbidity and mortality.[8] There are grave potential safety consequences, cost-inefficiencies, and potential for mismanagement of patient care when a surrogate endpoint is assumed to be an appropriate substitute for clinical endpoints. For instance, sodium fluoride was shown to effectively increase bone mineral density but it was proven to have no effect on fracture rates among postmenopausal women in clinical trials.[9] In the nephrology community, there is a massive dearth in the literature regarding whether the metabolic changes in PTH levels induced by vitamin D administration actually correct the bone abnormalities and increased fracture risk observed among patients with ESRD. The prognostic value of altered PTH levels as a surrogate endpoint for changes in fracture risk must be validated with biochemical and epidemiological evidence from both randomized clinical trials and observational studies like that conducted herein. [9]

Additionally, data generated from this analysis will most likely be relevant for Medicare given the case-mix–adjusted ESRD prospective payment system phased-in in 2011 that changed the way in which dialysis facilities get paid for vitamin D administration.[10] During our study period, IV vitamin D and other injectable drugs were billed separately from dialysis services with reimbursement based on the total units of the drug administered.[11] This payment structure prompted large increases in vitamin D dose and expenditure.[11] Starting in 2011, IV vitamin D is billed alongside dialysis services under a single, bundled rated. With the new system, providers may be incentivized to increase cost-efficiencies by

reducing the administration of vitamin D and injectable medications.[1] Once contemporary data of the effect of the new bundled system becomes available, understanding the potential clinical benefit of vitamin D under the dosage practices of the old system can be used as evidence for task forces charged with evaluating the effect of reimbursement changes on dialysis patient care.[12]

Moreover, clinicians do have good reason to suspect an association between vitamin D and fracture even though the relation has yet to be proven. Due to its high prevalence and observable effects on bone structure, SHPT is believed to contribute meaningfully to the elevation in fracture risk observed in the dialysis population as a whole. SHPT, common among dialysis patients, has direct pathological effects on bone. Among dialysis patients, bone mineral disorders known as renal osteodystrophy has been associated with bone pain, muscle tendon ruptures and increased fracture risk.[13] The action of PTH on bone is directly mediated through promoting osteoclast activity and bone resorption that can result in high-turnover bone disease as documented by bone histology.[14, 15] These consequences are believed to increase the risk of fracture, which has been estimated to be 4.4 to 14 times higher among dialysis patients than in the general population.[16]

There is a tremendous lack of studies examining the predictors of fracture risk within the ESRD population and the few published studies have investigated factors associated with hip fractures, neglecting other fracture types**.** The current body of literature describes the association between clinical parameters and fracture risk among dialysis patients, with PTH levels as the defining surrogate marker.[17] There are, however, a number of other risk factors for fracture that likely contribute to the elevated fracture rate in dialysis patients relative to their age, race, and gender-matched peers. Despite the expectation of severe clinical

consequences for dialysis patients who fracture, the literature currently describes the effect of surrogate serum markers on fractures and no studies to date have examined the association between vitamin D dose and the risk of fracture among dialysis patients.

This was the first large, population-based study to examine the association between vitamin D exposure and bone outcomes by four fracture types and by age, sex and race. The burden of SHPT, bone diseases and fractures among a costly, and morbid ESRD population warrants the research conducted herein.

1.4 Summary

Vitamin D therapy helps to maintain appropriate mineral metabolism, prevents bone disease, and minimizes loss of bone strength by decreasing PTH levels.[18] However, the increasing and perhaps excessive doses of vitamin D administered to dialysis patients may confer minimal clinical benefit with respect to fractures. The association between IV vitamin D exposure and fracture outcomes, to date, has not been investigated. In order to fill this gap, we first provide descriptive data of secular trends in IV vitamin D use among hemodialysis patients in the United States to validate studies suggesting that the use of the drug has been increasing. Then, we examined the association between vitamin D exposure and various fracture outcomes by different subgroups and fracture type.

The paucity of research regarding the clinical efficacy of IV vitamin D and the economic pressures likely influencing medical decision-making among nephrologists buttresses the significance of this study. Results from this research can also be used to generate quality improvement initiatives aimed at addressing the high fracture risk observed in dialysis

patients. Identifying disparities in vitamin D use may assist in providing evidence for adjusting payment for vitamin D among dialysis facilities with distinct patient characteristics.

The results generated from the two study aims are presented in two distinct, stand-alone manuscripts. The following chapters describe the important published literature guiding this dissertation, the methods employed to examine the research questions, the two manuscripts produced from our investigations, and concludes with a discussion of important findings.

CHAPTER II

LITERATURE REVIEW

This section presents the epidemiology of secondary hyperparathyroidism (SHPT) and the adverse skeletal and extraskeletal health outcomes associated with the disease. Mechanisms of treating SHPT are explored with an emphasis on the three most commonly administered commercially available vitamin D formulations. The gaps in the evidence regarding the association between vitamin D, intermediate clinical markers, bone disease and fracture risk are presented to support the need for studies investigating the independent association between vitamin D and fracture risk among hemodialysis patients.

PubMed and Google Scholar were used to extract relevant articles published in English anytime before the 2013 calendar year. Google and Google Scholar were used to identify conference proceedings, academic presentations, websites and other sources with pertinent information. A free-text search strategy using a combination of Boolean operators was employed using search strings such as “vitamin D”, “fractures”, “paricalcitol”, “doxercalciferol”, “calcitriol”, “bone”, “skeletal”, “risk”, “secondary hyperparythyroidism”, “parathyroid hormone”, “race”, and “African American”. To confirm the sensitivity of the search strategy, the bibliographies of all retrieved articles were reviewed for relevant articles.

2.1 Secondary hyperparathyroidism in end-stage renal disease

2.1.1 Pathogenesis, epidemiology, and consequences

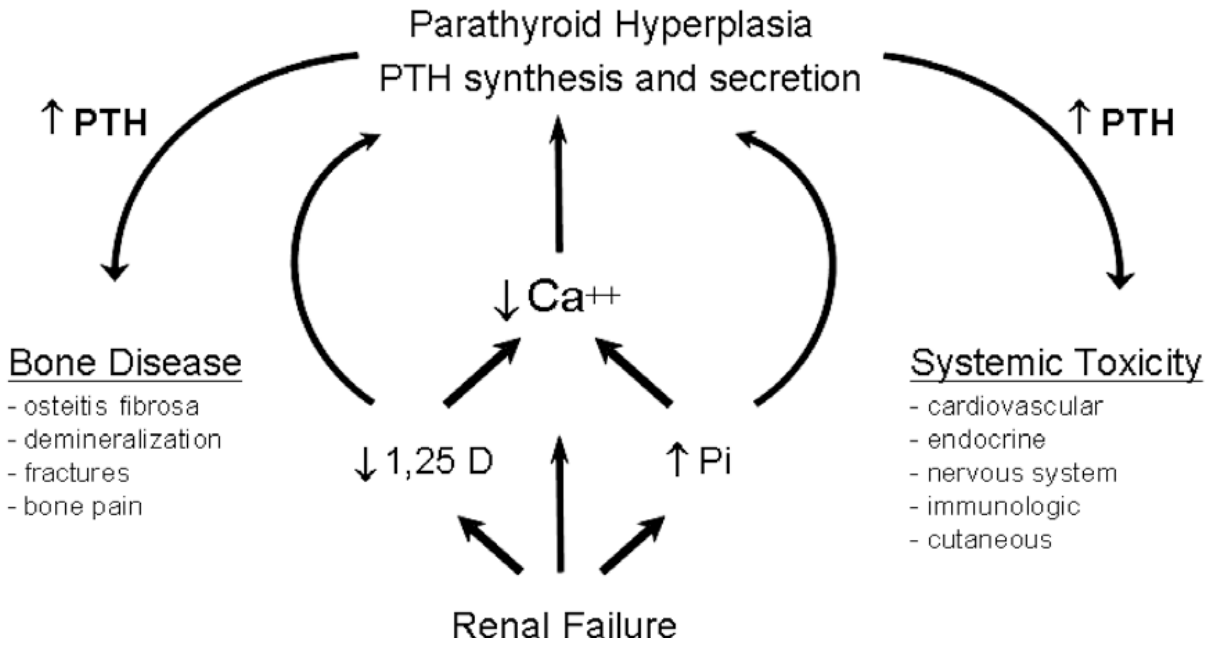
SHPT is an extremely common complication associated with chronic kidney disease (CKD) and ESRD. Approximately 78% of hemodialysis patients suffer from SHPT,[19] a disease characterized by increased parathyroid hormone (PTH) levels.[20] PTH is a polypeptide of 84 amino acids that plays a direct role in maintaining bone metabolism homeostasis and regulating calcium levels including the release of calcium into the blood and intestinal absorption of calcium.[21, 22] The primary role of PTH is to reduce the excretion of calcium from the kidneys, control the release of calcium and phosphorus from bone, increase urinary excretion of phosphorous, and direct the synthesis of active vitamin D in the kidneys.[23]

To assess bone metabolism and disease, clinicians traditionally use the intact parathyroid hormone assay system which measures the full length PTH (1-84) but also has been found to react with large truncated fragments of non-1–84 PTH.[24] Although there are newer generation assays that measure the full length 1-84 PTH[24], current dialysis care guidelines are based on iPTH levels, advising nephrologist to maintain the dialyzed patient at a range of 150 and 300 pg/mL.[25] A full discussion of the differences between PTH assays and the implications of using one versus another is beyond the scope of this work. The central point is that different assays, even those from the same generation can produce highly different PTH levels thus affecting a patient's SHPT and bone disorder classification.[25] Hereafter, "PTH" levels will reference concentrations in articles where the exact assay used was not referenced; differentiating from instances where the exact assay used was identified.

Calcium is the most important parameter dictating SHPT progression. PTH secretion is primarily regulated by calcium-sensing receptors located on the surface of parathyroid cells.[23] In order to maintain homeostasis, calcium concentrations must be rigorously controlled and typically must not fluctuate above or below 2% of the normal level.[23]

Figure 1 describes the pathogenesis and consequences associated with SHPT.

Figure 1. Pathogenesis and consequences of secondary hyperparathyroidism



Source: Brown Alex J., Slatopolsky Eduardo: Vitamin d analogs: Therapeutic applications and mechanisms for selectivity. *Molecular Aspects of Medicine* 29: 433-452, 2008

In an individual with CKD, declines in kidney function engender phosphorous retention.[26, 27] Decreased renal phosphorous excretion causes the retention of phosphorous in the body.[27] Traditionally, control of phosphorous levels between 4.0 to 6.0 mg/dL ideally manages metabolic changes.[27] Hyperphosphatemia, elevated phosphorous levels, has a direct impact on parathyroid cells and plays a role in increased PTH synthesis and secretion. PTH synthesis is additionally increased due to vitamin D deficiency.[26]

Progressive kidney decline is also associated with declines in vitamin D synthesis by the kidney.[28] Reduced activation of parathyroid vitamin D receptors (VDRs) are a consequence of vitamin D deficiency, fostering PTH mRNA transcription and inducing PTH synthesis.[26] The mRNA transcription of PTH by the parathyroid gland is further increased because of the decreased ionized calcium available for binding to calcium sensing-receptors on the surface of the parathyroid glands.[27]

Increased PTH levels, a uremic toxin, are linked to a myriad of serious, adverse clinical skeletal and non-skeletal effects.[29] Skeletal-related clinical consequences of elevated PTH levels include a series of bone abnormalities termed renal osteodystrophy while non-skeletal effects include hypertension, left ventricular hypertrophy, atherosclerosis, immune dysfunction and renal anemia.[29] Renal function and PTH levels are inversely correlated as PTH levels continually increase with decreased renal function.[30] SHPT-induced variations in bone histology and increased serum phosphorous and calcium, have all been implicated as factors in part responsible for the increased morbidity and mortality observed in hemodialysis patients.[30]

The hypocalcemia induced by the decrease in serum vitamin D levels and increased phosphorous retention leads to pathyroid gland hyperplasia, the effects of which are clinically manifested with bone disease and system toxicity.[28] The skeletal consequences of SHPT such as demineralization, bone pain and fractures are described in detail in later sections of this chapter.

2.1.2 Disparities

Racial disparities in the incidence of ESRD are well documented and persist.[3] The incidence of ESRD is greater among minority populations than in white populations.

Compared to whites, the incidence of new black and Native American ESRD patients in 2009 was 3.5 and 1.9 times greater, respectively. The ESRD incidence rate among Hispanics was 1.5 times that found in non-Hispanic populations.[3] Given the current racial disparities in ESRD incidence, it was important to consider possible racial variations in the manifestation of SHPT and other disorders clinically present in the dialysis population.

Race is a major determinant of SHPT.[31] Black dialysis patients generally have higher iPTH levels in comparison to other races.[19] Gupta and colleagues reported an average PTH level of 641.7 pg/mL in black dialysis patients and 346.0 pg/mL in white dialysis patients.[31] In comparison with white patients, black patients were reported to have a higher mean PTH level in a cohort of 218 patients within an ambulatory nephrology. [32] Wolf and colleagues also reported that black patients are given the most vitamin D therapy when compared to other ethnicities[33], presumably because black patients have these reportedly higher PTH levels.

In the general population, parathyroid gland mass is greater among blacks and there may be an increased risk of SHPT among black individuals when diagnosed with chronic kidney disease.[29] Nearly all non-Hispanic blacks (97%) currently suffer from vitamin D deficiency in the general population.[34] Additionally, some scholars have posited that because of their darker skin tones, black individuals synthesize less active vitamin D, $25(OH)D_3$, causing SHPT and greater parathyroid gland mass.[29]

Thus, compared to white patients, black dialysis patients are more likely to be vitamin D deficient and have more severe SHPT.[35] However, black patients in the general population, also observed to have lower levels of circulating vitamin D compared to whites, do not have an increased risk of musculoskeletal disease.[36] In fact, blacks have a lower rate

of fractures compared to other ethnicities. There is some evidence that the clinical consequences of SHPT and renal osteodystrophy may vary by race, but the studies are scant and traditionally have focused on white subjects. Elevated PTH levels and SHPT of greater severity may actually be protective in blacks, serving as a physiologically adaptive mechanism to maintain bone turnover.[31] For instance, studies of predominantly white patients have concluded that a PTH level of 120 to 240 pg/mL is optimal for dialysis.[31] However, treating black ESRD patients using these guidelines may led to over-suppression of parathyroid gland and a greater risk of adynamic bone disease.[31]

There is considerable debate regarding whether current therapeutic guidelines are applicable to black hemodialysis patients given documented differences in calcium balance and bone histomorphometry between blacks and non-blacks in the general population.[13] Differences in iPTH level between blacks and non-blacks have been discussed in the literature but there is currently no consensus on the optimal level of iPTH and subsequent ideal vitamin D dosing for hemodialysis patients by patient ethnicity.[13] Moore and colleagues concluded that the published K/DOQI guideline iPTH threshold of less than 150 pg/mL may not accurately identify black hemodialysis patients with adynamic bonde disease because the authors identified many black patients with adynamic bone disease above this cutoff after performing transiliac bone biopsies.[13]

Adynamic bone disease, low born-turnover, affects approximately 30% of hemodialysis and 50% of peritoneal dialysis patients.[31, 37] Patients with relative hypoparathyrodism (1-84 PTH, 150 pg/mL) are susceptible to adynamic bone disease while patients with severe hyperparathyroidism (1-84 PTH, 150 pg/mL) are susceptible to osteitis fibrosa cystica.[31] The applicability of current research in this area for black patients is

unknown given that the relationship between PTH levels and bone turnover has been investigated predominantly among whites.[31]

Higher serum iPTH thresholds may be necessary among black hemodialysis patients to prevent adynamic bone disease, a disorder associated with fractures and increased mortality.[13] Black dialysis patients are therefore at risk for over-therapy with the PTH overestimation resulting in adynamic bone disease and subsequent fracture and death.[38] This analysis was warranted because trends over time in vitamin D dosing among different subgroups, including race, has not been documented to date. More importantly, the relation between vitamin D therapy and bone outcomes by race may contribute to our understanding of the association between facility-level vitamin D dosing practices and fractures among black dialysis patients.

2.2 Vitamin D therapy

SHPT therapy attempts to maintain mineral metabolism, prevent bone disease and minimize the skeletal complications that eventually induce loss of bone strength and fractures.[18] Additionally, treatments for SHPT aim to prevent the numerous extraskeletal complications such as vascular calcification that are associated with the high cardiovascular morbidity observed in ESRD patients. SHPT is currently managed with the concurrent use of phosphate binders, phosphate diet restrictions, and vitamin D therapy.[39] These therapeutic modalities aim to address the range of mineral metabolism disturbances found in SHPT.

These therapies are also instrumental in the prevention of hyperphosphatemia, phosphate retention, and the control of serum calcium levels. The consequences of hyperphosphatemia and elevated calcium phosphorous product levels include hemodynamic

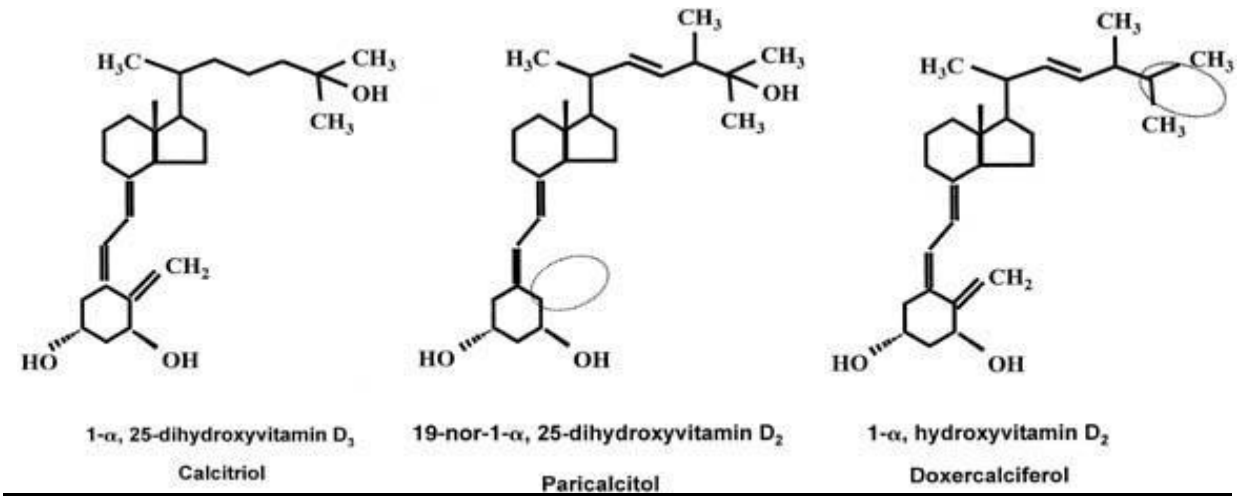
effects such as increased cardiac stroke index, vessel calcification and cardiac calcification.[40] A 1mg/dL increase in phosphorous levels is associated with a 6% incremental increase in the relative mortality risk among hemodialysis patients.[40, 41] The mortality rate among hemodialysis patients has been shown to increase by 11% for every $10mg^2/dL^2$ increase in calcium phosphorous product. [40, 41]

The pathogenesis of SHPT and the confluence of factors that foster it illustrate the tremendous complexities associated with treating the disease. Vitamin D, phosphorous, calcium, and PTH levels must be simultaneously controlled, especially since the manipulation of one parameter directly or indirectly elicits a profound influence on another. Treatment regimens must be evaluated often and tailored to the disparate needs of a growing ESRD population.

2.2.1 Role of vitamin D therapy

Vitamin D therapy suppresses PTH levels in both direct and indirect ways. Treatment with vitamin D directly reduces PTH levels by either inhibiting the enlargement of parathyroid glands or decreasing PTH synthesis.[42] When active vitamin D is administered, messenger RNA synthesis to induce PTH production by parathyroid glands is decreased.[30] In addition to reducing PTH synthesis and secretion by the parathyroid glands, active vitamin D plays a role in the absorption of dietary calcium by the intestines and in skeletal bone formation/resorption. [30] Indirectly, activation of the VDR increases calcium levels that subsequently activate the calcium sensing receptor.[42] The advent of newer vitamin D agents is driven by the need to weigh the target effectiveness endpoint of reaching the goal serum iPTH of 150-300 pg/mL while simultaneously maintaining appropriate calcium and phosphorous levels.[30]

Figure 2. Structure of IV vitamin D formulations



Source: Martin KJ, González EA: Vitamin D analogues for the management of secondary hyperparathyroidism. *Am J Kidney Dis* 38**:** S34-S40, 2001

Figure 2 depicts the structures of IV calcitriol (1α,25-dihydroxyvitamin D3; Calcijex, Abbott Laboratories, North Chicago, IL, USA), paricalcitol (19-nor-1α,25-dihydroxyvitamin D2; Zemplar, Abbott Laboratories) and doxercalciferol (1α-hydroxyvitamin D2; Hectorol, Genzyme). Calcitriol, paricalcitol and doxercalciferol are the three most commonly prescribed IV vitamin D therapies used to manage SHPT among dialysis patients. Calcitriol is the native, endogenous form of vitamin D while paricalcitol and doxercalciferol are considered vitamin D analogs, compounds of similar structure and properties.[43] All vitamin D formulations can be categorized as D_2 (e.g, paricalcitol) or D_3 (e.g, calcitriol) contingent on the presence of a single or double bond between carbons 22 or 23 of the vitamin D side chain.[44] Paricalcitol has the vitamin D_2 side chain but the double-bond structure at the 19-carbon position is lacking.[45] Like paricalcitol, doxercalciferol also contains the vitamin D_2 side chain but the structure further incorporates an α-hydroxyl group at the 1-carbon position.[45]

Moreover, it is important to differentiate nutritional (inactive or native) from active (vitamin D_3 or calcitriol) vitamin D medications. The generic term "vitamin D" refers to numerous substances and variants of vitamin D with very different effects and physical consequences. Nutritional vitamin D refers to compounds such as cholecalciferol and ergocalciferol found in foods high in vitamin D content.[44] Active vitamin D compounds refer to agents with the ability to activate VDRs.[44] In contrast to active vitamin D compounds, nutritional vitamin D is less efficacious in the suppression of PTH levels and in improving or maintaining the status of bone histology in dialysis patients.[46] Precursors to active vitamin D are found in food and ultraviolet light exposure.[21] In healthy individuals, a series of enzymatic reactions convert these precursors to the calcitriol/active vitamin D_3 molecule.[21] The conversion of nutritional vitamin D (25-$(OH)D_3$) to active vitamin D ($1,25(OH)_2D_3$) occurs due to the 1-α-hydrolase enzyme located in the mitochrondria of proximal tubular cells of the kidney.[27] With declining renal function, the kidney becomes less able to perform 1α-hydroxylation, the final reaction response for the synthesis of active vitamin D, and PTH levels rise.[21]

IV rather than oral vitamin D formulations were the predictors of interest for the work presented herein. IV vitamin D is preferred for hemodialysis patients because these medications can be easily administered during dialysis sessions while oral forms are generally most appropriate for patients with CKD.[27] Although the route of administration will vary with patient-provider preference, IV administration is advantageous for several reasons. Foremost, higher peak blood concentrations result given the lack of hepatic first-pass metabolism with IV administration.[27] By bypassing the gastrointestinal tract, IV dosing may decrease the risk of hypercalcemia.[27] Lastly, similar to the issues encountered with

patient intake of most oral medications, prescribers must consider the decrease in medication efficacy associated with patient non-adherence of oral vitamin D therapy.[27]

Evidence regarding optimal treatment of bone mineral disorders in dialysis patients is scant with guidance predominantly provided by the opinion-based National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (K/DOQI).[47] Decisions to administer vitamin D sterols are guided by PTH levels, with physicians urged to concurrently consider serum calcium and phosphorous levels.[48] IV vitamin D should be given to dialysis patients with a PTH level greater than 300pg/mL in order to suppress PTH levels to the target range of 150pg/mL to 300pg/mL.[47] The K/DOQI disseminates guidelines three opinion-based algorithms for the management of vitamin D sterols based on either serum calcium, phosphorous or intact PTH levels. Appendix 1 depicts the guideline based on dialysis patient intact PTH levels.[47]

2.2.2 Calcitriol

Calcitriol administration in dialysis patients has been associated with elevated serum calcium and phosphorous concentrations and also low bone turnover (hypodynamic bone disease).[44] Nine chronic hemodialysis patients were administered 2µg of IV calcitriol three times a week for ten weeks.[49] Following therapy, baseline PTH levels were reduced from 902 +/- 126 pg/mL to 466 +/- 152 pg/mL ($p < 0.01$).[49]

2.2.3 Paricalcitol

Paricalcitol, a biologically active, manufactured vitamin D analog, is used to prevent and treat SHPT associated with ESRD.[39] IV paricalcitol gained FDA approval in 1998 while the oral form was approved in 2005.[50] Paricalcitol decreases PTH levels by suppressing PTH

release and preventing PTH synthesis.[39] Additionally, the drug promotes bone mineralization and intestinal calcium and phosphorous absorption.[39] In multicenter, prospective trials of greater than 12 months, paricalcitol reduced PTH levels by approximately 59% to 82%.[51] In hemodialysis patients, a 0.24mcg/kg bolus IV administration of paricalcitol has a mean elimination half-life of 19.9 hours. [39]

The efficacy of paricalcitol has been evaluated in numerous clinical trials with the majority of trials comparing paricalcitol users to patients receiving placebo. Three double-blind, placebo-controlled, dose-escalating, randomized, multicenter trials of 78 hemodialysis patients treated for 12 weeks found a significant decrease in iPTH levels from 795 ± 86 to 406 ± 106 pg/mL ($p< 0.001$).[52] Long-term studies of paricalcitol have confirmed these findings. In an open-label, multicenter, 13-month study of 164 hemodialysis patients, IV paricalcitol administered at a dose of 0.04-0.394µg/kg 2-3 times per week rapidly and effectively suppressed iPTH levels.[53] Mean iPTH levels reached designated target levels of 100-300 pg/mL, going from a baseline mean of 628.3 +/- 27.65 pg/mL to 295.3 +/- 25.69 pg/mL.[53] Paricalcitol has been shown to suppress PTH levels even in in patients with protracted SHPT resistant to calcitriol therapy.[54]

2.2.4 Doxercalciferol

Doxercalciferol is a synthetic vitamin D agent that is converted to the biologically active form of vitamin D_2, 1-α-hydroxy-vitamin D_2 through the hepatic metabolic, post administration.[30] Doxercalciferol, brand name Hectorol, is available as an 4µg/2mL solution or a 2µg/1mL solution for IV injection.[55] Although the ideal dose of doxercalciferol must be tailored to the individual needs of each dialysis patient, the recommended starting dose is 4µg, bolus injections three times per week.[55]

Both intermittent oral and IV doxercalciferol therapy effectively suppress iPTH levels but IV doxercalciferol does so with less instances of hypercalcemia and hypophosphatemia.[56]

2.2.5 Clinical and economic differences of vitamin D formulations

The first available vitamin D analog, calcitriol, can effectively lower serum PTH levels.[57] However, calcitriol has also been shown to increase serum calcium levels by inducing intestinal calcium absorption and bone resorption. The risk of both hypercalcemia and coronary artery calcification may increase when calcitriol is used simultaneously with calcium-based phosphorous binders or dialysate with high calcium concentrations.[57] The vitamin D_2 analogs, paricalcitol and doxercalciferol, are vitamin D analogs also considered mainstream therapy among dialysis patients.[57] Both vitamin D_2 analogs, like calcitriol, can effectively lower PTH levels but do so with a smaller effect on serum calcium and phosphorous concentrations compared to calcitriol.[57] Unlike calcitriol, paricalcitol is considered a selective VDR activator, indicating that the administration of paricalcitol results in less activation of vitamin D receptors in the gastrointestinal tract, invariably leading to reduced calcium and phosphorous absorption.[44]

Several studies have demonstrated equivalent or even superior PTH level suppression with the use of these paricalcitol or doxercalciferol compared to calcitriol.[58] A 2007 meta-analysis of randomized controlled trials of chronic kidney disease patients actually demonstrated both potentially positive and detrimental effects of paricalciltol and doxercalciferol. Paricalcitol and doxercalciferol were shown to significantly reduce PTH levels by about 11pmol/L (100 pg/mL) but they also simultaneously increase phosphorous levels.[58] Reduced PTH levels may correspond to a decrease in patient mortality risk by

approximately 5% to 10% over a 3 year span but the increase in phosphorous concentrations may increase mortality by an equivalent amount.[58]

Sprague and colleagues performed the first double-blind, randomized, multicenter study of 263 hemodialysis patients at 27 facilities in the United States, The Netherlands, Spain, and Switzerland to assess the comparative effectiveness and safety of paricalcitol versus calcitriol,.[59] Dosed at a 4:1 paricalcitol to calcitriol ratio, paricalcitol decreased PTH concentrations more rapidly compared to calcitriol.[59] From baseline, paricalcitol treated patients achieved at least a 50% mean reduction in baseline PTH levels at week 15 compared to week 23 for patients receiving calcitriol.[59] The authors found no statistically significant differences in the incidence of hyperphosphatemia in paricalcitol versus calcitriol treated subjects, a finding contrary to previously published studies comparing the two drugs.[59] However, compared to calcitriol subjects, patients receiving paricalcitol experienced lower hypercalcemic episodes (18% versus 33%, p=0.008) and fewer elevated calcium-phosphorous product incidences.[59]

Also, in a study by Dobrez and colleagues, approximately 94% of paricalcitol-treated patients remained on the therapy whereas only 58.7% of patients who initiated with calcitriol stayed on the drug, suggesting that paricalcitol may be better tolerated.[39, 60]

In addition to the clinical differences between the three IV vitamin D formulations, there remain economic and cost variations in administering the drugs. There are over 570,000 prevalent ESRD patients as of December 31, 2009, a 2.1% increase than in the previous year. Although patterns of IV vitamin D formulation use and dose effects have never been explored within this growing population, cost data from the 2011 USRDS annual report provides a strong indication of potential racial and geographic disparities in use.[3]

Approximately $509 million was spent on IV vitamin D therapy in 2009, accounting for 18.3% of the $2.78 billion spent on all injectable medications for dialysis patients that year.[3] In 2009, per person per year costs were greatest for paricalcitol ($1,926), followed by doxercalciferol ($1,326) with calcitriol annual per person costs lowest at $456.[3]

2.2.6 Factors currently associated with vitamin D use

Compared to patients receiving calcitriol, patients administered paricalcitol were more likely to be black, have an arteriovenous fistula, and have higher baseline serum levels of calcium, phosphorus, and PTH. Paricalcitol treated patients were also less likely to be diabetic.[61] Paricalcitol use has been found to be greatest in the southern region of the country.[60]

Cost data suggests racial and geographic differences in vitamin D use. In 2009, IV vitamin D per person per year Medicare expenditures for black patients was $1,846 compared to $1,059 for white patients, constituting a 74% difference. This difference in Medicare medication costs by race, however, seems only to be specific to IV vitamin D with relatively similar costs observed for other injectable medications across races.[3] For instance, in 2009, per person IV iron Medicare expenditures for whites and blacks were $789 and $814, respectively, representing only a 3% difference.[3] Similar to geographic patterns observed with ESA and IV iron costs, the USRDS annual reported showed that the lowest per person per year costs of IV vitamin D were in the western portion of the country while the highest costs were found in the East and along the Gulf Coast region.[3]

2.3 Adjunct therapies

In addition to vitamin D, therapy for the regulation of PTH levels and to maintain mineral homeostasis also includes oral phosphate binding agents, calcimimetics and parathyroidectomies.[62] Serum concentrations of phosphorous are reduced with oral phosphate binding agents like calcium, sevelamer, lanthanum, magnesium and aluminum.[62] Phosphate binders are frequently prescribed to dialysis patients to control the deleterious effects of elevated phosphorus levels, hyperphospatemia.[40] Calcimimetic agents actively reduce PTH secretions without simultaneously increasing calcium and phosphorous levels.[62] Sensipar, Cinacalcet HCL, the only U.S. Food and Drug Administration (FDA) approved calcimimetic agent, is available in oral form as a daily treatment of hypercalcemia in ESRD patients with SHPT or parathyroid carcinoma.[62] Sensipar increases the sensitivity of the calcium-sensing receptor on parathyroid glands to extracellular calcium.[63] Sensipar was able to suppress iPTH levels in a phase 3, multicenter, randomized, placebo-controlled, double-blind study of dialysis patients independent of treatment with traditional SHPT therapies.[64] The subsequent decrease in calcium levels directly decrease PTH levels.[63]

Parathyroidectomies, the oldest SHPT treatment, are perhaps the least preferred option. Surgery to remove the parathyroid glands, usually performed in patients with recalcitrant SHPT, is accompanied by numerous potential risks and complications.[62] In addition to the traditional risks associated with anesthesia, following surgery, patients may experience severe hypocalcemia, permanent hypoparathyroidism, or require additional surgery.[62]

It is important to note that in the general population, anti-osteoporosis agents such as bisphosphonates are used to prevent bone disorders.[65] Bisphosphonates are not generally

prescribed to dialysis patients because of safety concerns over toxicity related to impaired renal excretion[66-68], and bone disease in dialysis patients is often due to SHPT and other forms of renal osteodystrophy, including osteomalacia and adynamic bone disease[4], which effect fracture risk independent of bone density.

2.4 Renal osteodystrophy and fractures in End Stage Renal Disease

2.4.1 Epidemiology of renal osteodystrophy

Renal osteodystrophy is an overarching label for both high-turnover bone disorders termed osteitis fibrosa cystica and low-turnover disorders such as osteomalcia and adynamic bone disease.[30] Specifically, renal osteodystrophy can present itself in any of five histopathological forms including osteitis fibrosa, osteomalcia mixed lesions, mild lesions, and adynamic bone disease.[69] Often a consequence of SHPT, osteitis fribrosa, the most common form of renal osteodystrophy, is characterized by increases in bone formation, resorption and marrow fibrosis.[27] On the contrary, in addition to low bone-specific alkaline phosphatase levels, adynamic bone disease is characterized by low iPTH levels below 200pg/mL and decreased bone formation.[70]

At this juncture, it is important to differentiate renal osteodystrophy from osteoporosis. The bone histology in renal osteodystrophy is characterized by bone remodeling and is best diagnosed with a bone biopsy.[70] Osteoporosis, contrarily, is a systematic skeletal disease defined by low bone mass and deterioration of bone tissue.[71]

In sum, disturbances in the vitamin D-PTH axis and disturbances in PTH, calcium, phosphorous, and vitamin D regulation lead to renal osteodystrophy.[72] Both high and low

bone turnover characterize renal osteodystrophy as the disease can be classified broadly into osteitis fibrosa, osteomalcia, adynamic bone disease, and mixed osteodystrophy.[72]

2.4.2 Clinical and economic burden of fractures

ESRD patients have been observed to be at increased risk of fractures relative to those without renal impairment.[73] Patients with ESRD are 4.4 to 14 times more likely to experience a hip fracture compared to individuals in the general population.[16] These estimates, however, were derived using data solely from Caucasian incident dialysis patients within the USRDS between 1989 and 1996.[74] The incidence of any fracture is approximately 20 per 1000 patient years on dialysis with a three-to-four fold increased risk of hip fracture reported for ESRD patients.[75, 76] Dialysis patients who have never had a kidney transplant and those who have undergone transplantation have an observed hip fracture incidence rate of 2.9 fractures and 3.3 fractures per 1,000 person-years, respectively.[73]

The average or median time to fracture following dialysis initiation is informative for this analysis to serve as a benchmark to assess whether time to first fracture, the dependent variable in Cox regression models, is reduced with the administration of vitamin D. Published studies, however, currently do not explicitly provide this data. Although we do not have information regarding the mean or median time to fracture since dialysis initiation, we can infer from a few studies that time since dialysis initiation (dialysis vintage) is associated with an increased risk of fracture.[74, 77] Alem and colleagues stratified patients into four vintage categories (3 months-1 year, 1-2 years, 2-4 years, and greater than 4 years.[74] The authors found that fracture incidence rates increased by 2.7-fold when comparing patients in the shortest versus longest vintage category among males and increased by about two-fold among females. Fractures dramatically increase one's likelihood of death and the one-year

mortality rate following a hip fracture has ranged from about 15 to 40% in the general population.[78] In the US, there are over a quarter of a million hip fractures every year resulting in 14% to 36% mortality in the first year following fracture.[79] Coco and colleagues reported a hip fracture incidence rate of 13.9 per 1,000 patient-years among a cohort of 1,272 patients within outpatient dialysis facilities in New York between 1988 and 1998.[80] Mortality one year subsequent to the hip fracture event was by far greater among dialysis patients when compared those in the general population. A 64% one-year mortality rate was found among the dialysis cohort compared to a 20% one-year mortality rate in the general population.[80]

A population based cohort study by Mittalhenkle and colleagues found that, among U.S. incident dialysis patients between 1995 and 2000, hip fractures were associated with a 2.15 time increase in the incidence rate ratio for all-cause mortality.[81] After experiencing a hip fracture, dialysis patients had a one-year survival rate of approximately 50%.[81] Among patients with no history of cardiovascular disease, the risk of cardiovascular events was 40% greater and the risk of cardiovascular mortality was 84% greater among dialysis patients who sustained a fracture compared to those who did not, respectively.[81]

The subsequent morbidity following hip fractures is also remarkably high with surviving patients experiencing decreased functional ability even several months post fracture.[79] Following a fracture, patients may need care at a skilled nursing facility and assistance with mobility, and personal care including needing help with self dressing and bathing.[79 73, 74, 77, 82-84] In the general population, a hip fracture is associated with permanent disability and admission to long-term nursing facilities.[78, 85]

There is a substantial economic burden associated with the occurrence and treatment of fractures in the US. Using a Markov state-transition model, Burge and colleagues predicted the incidence and costs associated with osteoporosis-related fractures in the general population of the US from 2005 to 2025.[86] The investigators predicted an incidence of two million fractures in 2005 at a cost of $17 billion with hip fractures accounting for 72% of total costs but only 14% of the overall distribution of fractures.[86] By 2025, the incidence of fractures is expected to increase by 48%, contributing to $25.3 billion in costs.[86]

Furthermore, there is strong evidence that there is interstate variability in both the incidence and economic burden of fractures in the United States. Also using a Markov state-transition model of osteoporosis-related fractures, King and colleagues highlighted the geographic and hospital fracture care pattern differences in five states.[87] In 2000, mean hospital charges for hip fractures ranged from $16,700 in Massachusetts to $29,500 in California.[87] The disparity in mean charges was not explained by the length of stay associated with hip fracture hospital admissions.[87] The fracture incidence estimated in 2005 ranged from 199 per 10,000 in California to 266 per 10,000 in Massachusetts.[87] In 2005, total costs attributable to fractures varied from $270 million in Arizona to $1,434 million in California.[87]

In the dialysis population, an episode of hip, vertebral, and pelvic fracture was associated with a total cost of $20,810 (SD=$16,743), $17,063 (SD=$26,201), $14,475 (SD=$19,209), respectively.[88] Total costs were primarily attributable to hospitalizations and skill nursing facility care with 65%-74% of costs due to hospitalizations and 11%-21% caused by costs accrued during skilled nursing facility stays.[88]

Although this analysis did not explore variations in the cost of fractures among dialysis patients, it does contribute to the literature by documenting the burden of fracture related hospitalizations in the hemodialysis population.

2.4.3 Factors associated with fractures

Hemodialysis patients are susceptible to the risk factors for fracture observed among individuals in the general population but also experience additional risk factors attributable to their disease. The following section describes the risk factors for fracture observed in the general population and then summarizes the current literature investigating the risk factors for fracture among the dialysis population.

Fracture risk is multifactorial and risk factors related to falling, bone strength, and clinical characteristics have been identified.[89] In the general population, approximately 90-97% of proximal humerus fractures and greater than 95% of hip fractures are due to falls.[89, 90] Approximately 40% of dialysis patients fall per year, likely contributing to the increased fracture risk in this population.[91] The relationship between low vitamin D levels, muscle weakness, falls and subsequent fracture risk has yet to be elucidated.[91] Frail patients and those who are not physically active are more likely to fall.[90] Certain medical conditions can also increase one's risk of falls and subsequent fracture. Diabetic patients, for instance, are more likely to fall due to gait impairment, peripheral neuropathy and poor visual acuity.[90] Epileptic seizures and side effects like dizziness and sleepiness associated with anti-epilectic drugs may also increase one's fall and fracture risk.[90]

Clinical characteristics such as age, female sex, Asian or white ethnicity and cigarette smoking are also strong predictors of fracture in the general population. For instance,

decreased bone mineral density and a 50% greater lifetime risk of hip fracture has been attributed to smoking.[89]

Several explanations have been advanced to attempt to explain the excess risk of hip fractures observed among ESRD patients when compared to the general population. Concomitant conditions associated with ESRD such as metabolic bone disease, hypogonadism, avascular necrosis, and chronic acidosis may engender bone loss among this population, increasing one's risk of fracture.[74]

Using USRDS data in a population-based cohort study, Stehman-Breen and colleagues investigated the risk factors for hip fracture among ESRD patients.[92] The authors found that Caucasian race, female sex, lower BMI, age, and peripheral vascular disease were all independently associated with an increased risk of fracture.[92] Specifically, compared to whites, black ESRD patients demonstrated a 42% lower risk of hip fracture (adjusted RR 0.58; 95% CI 0.37-0.91).[92] A two-fold or greater increase in the risk of hip fracture was independently associated with peripheral vascular disease (adjusted RR 1.94; 95% CI 1.29-2.92), female sex (adjusted RR 2.26; 95% CI 1.48-3.44) or a BMI less than 23 (adjusted RR 2.51; 95% CI 1.65-3.82).[92] Interestingly, clinical parameters such as iPTH, aluminum, calcium and phosphate were not associated with the risk of hip fracture in the study.[92]

Disparities in incidence and mortality rates have been observed across race and sex with white dialysis patients experiencing the greatest incidence of hip fracture.[80] Women incurred the greatest burden of hip fractures with an incidence rate of 24.1 per 1,000 patient-years compared to 11.7 per 1,000 patient-years in male dialysis patients.[80] The overall incidence of hip fracture has been confirmed to be less among men than women in a study by Alem and colleagues.[74] The authors observed an overall fracture incidence rate of 7.45 per

1000 person-years among men but a 13.63 per 1000 person-years rate among women.[74] White patients, those with higher alkaline phosphatase levels and PTH levels less than 195 pg/dL are all significant predictors of hip fractures.[80]

Vertebral fractures are more prevalent in female, diabetic hemodialysis patients over the age of 65 (32.3%) in comparison to hemodialysis patients without diabetes (13.2%) after adjustment for age, dialysis vintage and several laboratory parameters.[82] The impaired bone formation and low bone turnover observed in type 2 diabetics, including those with ESRD, may be due to abnormalities in vascular function. Complications induced by microvascular issues in diabetics may decrease blood supply to bone cells which in turn may interfere with osteoblast function.[82] Other possible explanations for the observed increase in fractures among diabetic hemodialysis patients include factors that may induce falls such as impaired sight, gait and balance from diabetic retinopathy and cataracts.[82] The study was conducted among a relatively homogenous population of hemodialysis patients maintained at Shirasagi Hospital in Japan and, therefore, race was not included as a risk factor in the analyses.

This analysis contributes to the current medical literature regarding the risk factors for fractures among dialysis patients by specifically examining the association between vitamin D exposure and fracture risk.

2.5 Vitamin D therapy and non-skeletal and skeletal outcomes

2.5.1 Vitamin D therapy and non-skeletal outcomes

The relationship between vitamin D therapy and non-skeletal outcomes like hospitalization and mortality has been explored with varying results depending on the robustness of methodologies used.

In a retrospective study of 11,443 adult hemodialysis patients, Dobrez and colleagues were the first and only researchers to date to examine the relationship between specific vitamin D therapies and several hospitalization outcomes.[60] Compared to calcitriol users, patients who initiated dialysis on paricalcitol were 14% less likely to be hospitalized (HR=0.863, $p<0.0001$), had 6.84 fewer hospitalization days per year ($p<0.0001$) and 0.642 fewer hospital admissions per year ($p<0.0001$).[60] The reduced hospitalization days from the use of paricalcitol at the start of dialysis therapy may result in a potential cost savings of between $7,699 to $11,000 per year.[60] It should be noted that these study estimates were rather conservative given that a greater percentage of paricalcitol treated patients in the study had abnormally high baseline iPTH and more comorbidities in comparison to calcitriol-treated patients.[60]

In a study of 14,967 chronic hemodialysis patients at a not-for-profit dialysis facility, Tentori and colleagues investigated the relationship between specific vitamin D formulations and mortality.[57] Compared to doxercalciferol-treated patients, individuals treated with paricalcitol did not demonstrate a survival advantage.[57] Paricalcitol treated patients had a mortality rate (death/100 patient-years) of 15.3 (95% CI 13.6-16.9; $p<0.0001$), virtually identical to the mortality rate of 15.4 (95% CI 13.6-17.1; $p=0.0003$) observed among patients treated with doxercalciferol.[57] Contrarily, patients administered calcitriol exhibited a significantly worse mortality rate of 19.6 (95% CI 18.2-21.1) compared to those treated with other vitamin D analogs.[57] The poorer mortality outcomes associated with calcitriol were also reflected in unadjusted hazard models but the mortality differences between doxercalciferol and paricalcitol versus calcitriol were not statistically significant in models that adjusted for various laboratory parameters.[57]

A significant 7-17% adjusted risk reduction in all-cause mortality has been observed among regular vitamin D users in comparison to non-users with the greatest reductions found in patients where dialysis sessions were shorter.[93] In 2003, Teng and colleagues published a historical cohort study comparing the three year survival of 67,399 long term hemodialysis patients who were treated with either paricalcitiol or calcitriol at for-profit dialysis centers between 1999 and 2001.[61] Paricalcitol treated patients experienced a significantly lower mortality rate (0.180 per person-year) compared to patients receiving calcitriol (0.223 per person-year).[61] In adjusted Cox propotional-hazards models, paricalcitol treatment conferred a 16% survival advantage (95% CI 10-21%) compared to calcitriol treatment.[61] Teng and colleagues also published a historical cohort study in 2005 of 51,937 incident hemodialysis patients within a large, for-profit organization.[94] Patients administered any vitamin D formulation had a 20% survival advantage compared to patients who did not receive vitamin D, a result that was consistent among patients at all levels of serum calcium, phosphorus and PTH.[94] Mean dose per administration of paricalcitol and calcitriol has been found to be approximately 4.3 µg and 1.1 µg, respectively.[61] Consistent with the majority of studies of vitamin D analogs, Teng et al. did not assess the effect of dose on mortality outcomes.

With regards to mortality, a study of dialysis patients within a not-for profit facility found that paricalcitol-treated and doxercalciferol-treated patients were identical in their risks for all-cause and artherosclerotic cardiovascular disease.[57] Mortality risk was higher among patients receiving calcitriol compared to paricalcitol or docercalciferol, but the magnitude of the differences in mortality risks varied depending on whether models had been adjusted for important covariates like race.[57]

There is recent controversy regarding whether the use of vitamin D generally confers a survival benefit to dialysis patients. No survival advantage was found among patients administered vitamin D therapy when models rigorously controlled for previously unmeasured confounding variables such as underlying health status.[95]

Furthermore, Shinaberger and colleagues presented one of the only studies suggesting a dosage-response association between increasing weekly doses of paricalcitol and survival. Shinaberger and colleagues followed 23,727 hemodialysis patients served at DaVita. Inc outpatient clinics who received only paricalcitol as vitamin D therapy.[96] As the weekly dose of paricalcitol per unit of serum PTH increased, patients experienced better survival.[96] The dosage-response association of paricalcitol with greater survival suggests that dose is an important, yet frequently neglected factor that may have a direct impact on patient outcomes. Confounding by indication may have plague previous studies that found the converse, the association of lower survival rates with higher doses of IV vitamin D. Patients with elevated PTH levels, worse SHPT, and who ultimately were more likely to die were likely given higher doses of vitamin D.[96]

The reduced hypercalcemic and hyperphosphatemic effects of paricalcitol have been hypothesized to be among one of the major reasons why the drug has been observed to have a survival benefit in dialysis patients when compared to other vitamin D formulations.[44]

2.5.2 Vitamin D therapy and skeletal outcomes

Studies suggest that vitamin D therapy has an effect on skeletal outcomes. A randomized controlled trial of 60 peritoneal, pediatric patients concluded that calcitriol and doxercalciferol were equivalent in their ability control serum PTH levels and suppressing bone formation rates.[97] Compared to calcitriol, paricalcitol likely does not inhibit osteoclast

activity at therapeutic doses, an observation that may explain the lower calcemic effects of paricalcitol in comparison to calcitriol.[98]

Using rat models, Jokiharaa et al. found that paricalcitol effectively treated renal-insufficiency induced bone mineral loss and bone mechanical competence.[99] Forty-five rats were either randomized to a 5/6 nephrectomy or Sham-operation initially and then rats were further randomized later to either uremic control or paricalcitol treatment.[99] Uremic control rats were observed to have an 8.1% and 6.6% decrease in bone mineral density at the femoral neck and midshaft, respectively, but the paricalcitol treated rats did not experience similar bone mineral density changes.[99]

2.5.3 Relationship between clinical parameters, secondary hyperparathyroidism treatment and skeletal outcomes

The exact relationship between SHPT, PTH, bone disease, and fracture risk remains unclear. Although the relationship is well established in the healthy population, there are large discrepancies in the association between bone mineral density and fractures in dialysis patients.[4] For instance, bone density measured at the lumbar spine has been predictive of fractures but no associations were found between fractures and bone density measured at the femoral neck.[4] Furthermore, dialysis patients are also at greater risk compared to the general population for several metabolic bone diseases, such as osteomalacia and adynamic bone disease, that effect fracture rates independent of alterations in bone density.[4]

SHPT and changes in PTH levels may be associated with bone disease and a range of bone morphologies collectively known as renal osteodystrophy among patients with kidney impairment.[100] PTH, considered a surrogate indicator of bone turnover, predicts the histologic bone disease type.[31] The main forms of osteodystrophy (osteitis fibrosa cystica,

adynamic bone disease, and osteomalacia) may be linked to an increased risk of fracture in ESRD patients due to changes in bone turnover, mineralization, and volume, but the link has yet to be established in the literature.[100] Patients with relative hyperparathyroidism, 1-84 PTH less than 150 pg/mL, are predisposed to adynamic bone disease, occurring in approximately 30% of hemodialysis and 50% of peritoneal dialysis patients.[31] Contrarily, osteitis fibrosa is associated with 1-84 PTH levels greater than 500pg/mL.[31] Evidence suggests that fracture rates among dialysis patients may vary by type of renal osteodystrophy. In a study of 31 dialysis patients, Piraino and colleagues found a higher rate of 0.2 fractures/year among patients with low bone turnover osteodystrophy when compared to osteitis fibrosis patients with a fracture rate 0.1 fractures/year.[101]

The exact relationship between PTH levels and underlying bone disease has yet to be established and the ability to diagnose bone disorders is currently inadequate.[72] Several studies have been unable to find a definite link between reduced bone density and PTH levels.[75] In one of the few studies modeling the effect of clinical parameters on fracture risk, Danese et al. examined the relationship between serum calcium, phosphorus, and PTH levels and the risk of hip, pelvic, and vertebral fractures among dialysis patients.[88] The adjusted relative hazard associated with PTH levels was U-shaped , decreasing from a maximum then progressively increasing, for both vertebral and hip fractures.[88] Other researchers have concluded that the increased PTH levels associated with vitamin D deficiency lead to high bone turnover which in turn causes cortical bone loss and low bone density, both of which cause hip fracture.[5]

It is very important to note that the relationship between PTH levels and bone diseases have been derived overwhelmingly based on studies of white dialysis patients and,

therefore, associations may not necessarily hold for black dialysis subjects.[31] However, previously published studies do provide researchers some insight into the potential association of several covariates with fracture risk among all dialysis patients.

In sum, the heterogeneous pathology of bone disease contributes greatly to the complexity and uncertainties associated with solidifying the causal relationship between vitamin D deficiency, SHPT, PTH levels, bone disease, bone density, and fracture risks in ESRD patients. In a population-based study of ESRD patients, Caucasian ethnicity, older age, female gender, peripheral vascular disease, and lower BMI were found to be independent predictors of hip fractures.[92] Although the aforementioned risk factors have been established, no studies thus far have examined the association between vitamin D dose and fracture risk among dialysis patients**.** Given that white patients are generally at a greater risk for fracture in the hemodialysis population, it was important to discern whether the magnitude of the association between IV vitamin D and fractures varied by race.

The study conducted herein attempted to address the question of whether IV vitamin D actually affected the hard-endpoint of fracture risk outside of the drug's established influence on PTH levels and surrogate indicators of bone disease.

Clinical parameters

Clinical parameters such as hemoglobin levels (g/dL), albumin levels (g/dL), PTH levels (pg/mL), transferrin saturation (TSAT, %), phosphorous levels (mg/dL), calcium levels (mg/dL), and ferritin levels (ng/mL) have been documented to have an effect on the observed morbidity, mortality, or fracture risk found in dialysis patients. These clinical parameters were not available in the USRDS. However, it is important to discuss these

surrogate markers of bone histology since they play a role in dictating the influence of vitamin D exposure on fractures.

Although there have been some studies indicating that the relative risk of death and hospitalization among ESRD patients is inversely associated with hemoglobin levels,[102] recent findings suggest that targeting higher hemoglobin levels with erythropoietin-stimulating agents may confer no benefit or actually increase the risk of harm to anemic CKD patients.[103-107] Transferrin saturation (TSAT) levels (normal: 20%-30%) and serum ferritin levels (normal >150ng/ml) are commonly used measures of iron deficiency and renal anemia- an independent risk factor for heart disease and mortality in ESRD patients.[108, 109] With regards to albumin levels, hypoalbuminemia (low serum albumin levels) has been an established marker of morbidity, mortality, nutrition, inflammation and plasma volume in dialysis patients.[110]

Calcium, phosphorous, and PTH levels are three of the most important clinical parameters involved in bone-mineral homeostasis and overall ESRD patient health. In a nationally representative incident dialysis cohort, Melamed and colleagues found that elevated phosphate levels were independently associated with all-cause mortality but elevated calcium and PTH levels were only associated with all-cause mortality in time-dependent models.[111] No consensus has been reached regarding the influence of PTH levels on fracture outcomes. Using data from the Dialysis Morbidity and Mortality Study (DMMS) Waves 1 to 4, Danese and colleagues found no association between calcium and phosphorus concentrations and the risk of fracture and a weak association was found between PTH concentrations and the risk for hip and vertebral fractures.[88] Coco and colleagues determined that, compared to patients with higher PTH levels, patients with lower serum PTH levels

were more likely to experience a hip fracture ($p < 0.006$).[80] In contrast, Stehman-Breen and colleagues did not find a statistically significant relationship between iPTH levels and the risk of hip fractures.[112]

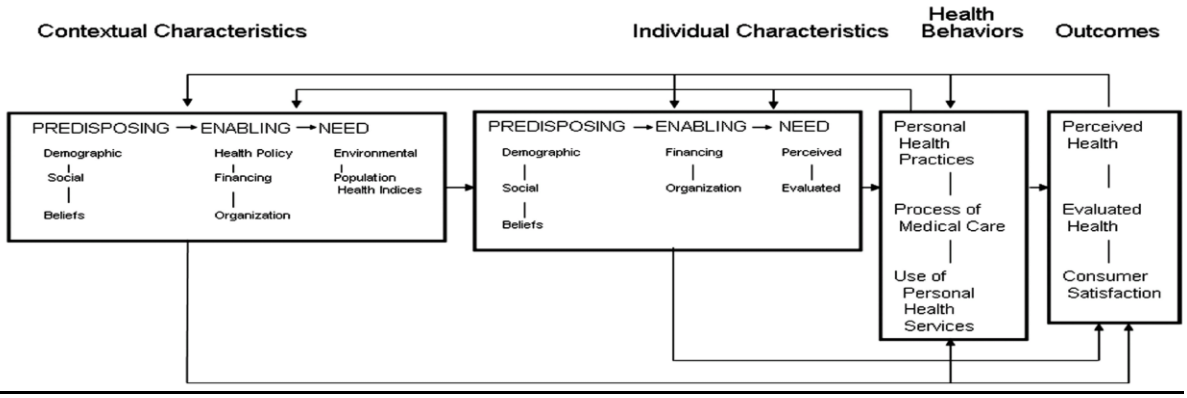
2.6 Conceptual Framework

2.6.1 Andersen's Behavioral Model of Health Services Use

The hypotheses and inclusion of variables presented in this dissertation were guided by Andersen's Behavioral Model of Health Services Utilization. Overall, the model posits that the use of health care services is contingent upon the predisposition to use health care services, variables that enable or restrict use, and the need for those services.[113] Initially published in the 1960's to aid in assessing the predictors dictating the use of health services by families, the model has undergone significant revisions over the last few decades in order to account for novel issues in health system delivery and research.[7]

The first iteration of the model in the 1960s focused on measuring the multifaceted aspects of healthcare access including "potential access," the presence of enabling factors and "realized access," referring to when health care services are actually used.[113]

Figure 3. Andersen's behavioral model of health services use



Source: Andersen RM. National health surveys and the behavioral model of health services use. *Med Care.* Jul 2008;46(7):647-653.

The most recent version of the model is depicted in Figure 3 and incorporates macro level factors influencing health behavior. Contextual characteristics represent the aggregate health system, organizational, community- and provider- level determinants of health services use.[113] With this latest iteration of the model, a different set of variables are assigned to the predisposing, enabling, and need categories, differentiating contextual and individual characteristics. At the aggregate level, contextual characteristics include predisposing factors like community structure, enabling factors like number of medical facilities and need factors like community disability rates that impact individual health services use.

At the individual-level, predisposing characteristics refer to demographic (e.g., age, gender), social structure (e.g., race, education, occupation), and health belief related factors.[7] Enabling characteristics at this level include financial and organizational factors such as whether an individual has a regular source of care, income, and whether an individual has health insurance. Need characteristics describe both perceived and evaluated indicators of an individual's health that include factors such as number of illnesses and mental health status.

Predisposing, enabling, and need population characteristics subsequently determine health behavior, comprising of personal practices, use of health services, and processes of medical care.[113] Personal practices include diet, tobacco use, exercise and other self-care activities that affect an individual's health. Use of health services include doctor and emergency room visits and processes of medical care describe prescriptions, test ordering and other activities that define the interaction between providers and patients.[113]

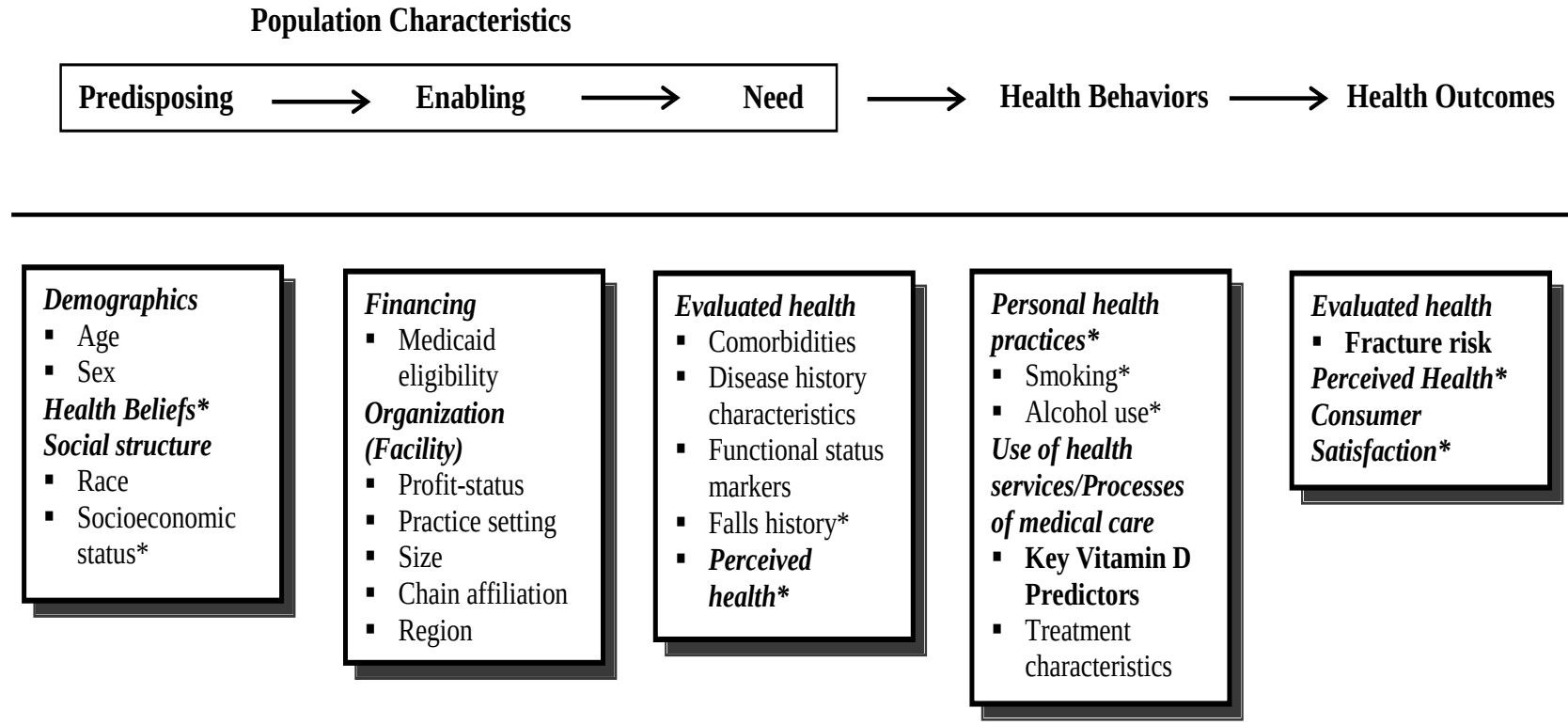
Finally, the health outcomes component, similar to the needs component, measures both perceived hand evaluated health status. Perceived health status measures patient or a

proxy's measure of patient well-being, quality of life, and functionality.[114] Evaluated health outcomes, contrarily are based on professional judgments and established health care standards.[114] Additionally, the health outcomes component contains a measure of patient satisfaction with the care they have received and is driven by, among a myriad of other factors, a patient's assessment of wait times, the quality of the patient-provider relationship, and inconveniences of travel time.[114]

2.6.2 Proposed Conceptual Framework

Figure 4 presents the conceptual model that was used to guide this research. The model, adapted from Andersen's Behavioral Model of Health Services Utilization, frames each predictor within key model components. The adapted model is revised to include relevant factors dictating medication use in dialysis facilities and to fit the research question herein. Among the differences from the latest iteration of Andersen's model include the omission of the feedback loops and reverse arrows that serve to illustrate the recursive nature and simultaneity of each model component. Instead, our simplified, revised model emphasizes the direct associations between factors that predict vitamin D use and fracture outcomes. Health beliefs, perceived health and consumer satisfaction are traditional measures in the model, frequently measured through patient reported outcome instruments, and are not available in our dataset but displayed in the conceptual model for completeness.

Figure 4. Proposed conceptual framework



NOTES

*Variable not available in data but added for completeness

Furthermore, the final phase of Andersen's model depicts contextual characteristics defined as aggregate health organization, community, and provider level variables.[113] We believe that, given the limited availability of community level factors in our data sources, these contextual characteristics were best modeled as enabling characteristics under the "organization" subheading. For example, our data are unable to capture the effects of governmental policies, environmental pollutants, and other general environmental factors that may influence health-related outcomes and patient medication use.

The predisposing characteristics included in our model capture demographic factors such as age and sex. The social structure subheading of the predisposing characteristics component encompasses the myriad of factors that dictate social status in one's community, affect an individual's coping strategies, and dictate the health and viability of one's physical environment.[7] Patient race is, thus, included in the social structure category of the model. Race has been included in the model because black patients have been reported to have a 62% lower fracture risk in comparison to white patients.[73] Black hemodialysis patients have also been observed to be more likely to be administered IV vitamin D compared to white patients.[33] Socioeconomic status is included in the model for completeness but not included in our dataset.

Enabling characteristics, as the name implies, represent the resources that must be available for use of health care services to occur. Both individual financing variables such as an individual's Medicaid eligibility and organizational factors were captured. In addition to health insurance that directly affects whether patient's have a usual source of care, dialysis facility-level structural features such as profit status, chain affiliation and size are also included.

Moreover, need characteristics include the individual's perceived need inasmuch as need can be altered by an individual's mutating health education, and financial ability to afford health care. We were able to only measure an individual's evaluated need as exemplified by objective measures like comorbid conditions and not whether a patient had a history of falls.

Population characteristics (predisposing, enabling, and need) are linked to health behaviors that ultimately influence health outcomes. Health behaviors consist of personal health practices, use of health services, and processes of medical care. Measurable personal health practices of the ESRD population such as exercise and healthy eating habits are not readily available in the USRDS dataset.

Andersen's model effectively captures the effect of predisposing, enabling, and need characteristics on IV vitamin D use and the association between vitamin D use and fractures. Measures of vitamin D exposure fall under both the use of health services and processes of medical care categories. In-center hemodialysis patients receive IV medications during in-center sessions from health care providers within their dialysis facility. The nature of ESRD care means that the use of health care services is intrinsically intertwined with processes of dialysis care. The use of health care services is reflected in the patient's choice to attend dialysis sessions while the administration of IV medications during dialysis reflects a process of care.

Lastly, the health outcomes component of the synthesized model depicts the outcome variable for Aim 2, fracture risk. The hypothesized relationship between the ecological level measures of vitamin D exposure, covariates, and fracture outcomes are depicted in Appendix 2.

CHAPTER III

RATIONALE FOR METHODS USED TO ASSESS FRACTURE RISK

The following chapter provides a broad review of the methodological approaches used to investigate phenomena in nephrology, the biases certain approaches attempt to mitigate, and presents the rationale for the statistical approach employed in this dissertation. Aim 1 of this dissertation is purely descriptive and provides evidence of the secular patterns of use of vitamin D among hemodialysis patients over a decade. Aim 2 investigates the association between vitamin D exposure and fracture risk among incident hemodialysis patients. This chapter serves as a precursor to the methodology chapter and provides the justification for our choice of a retrospective cohort study using the grouped-treatment approach for Aim 2 to assess fracture risk whereby vitamin D exposure was measured at the facility-level and the fracture outcome was measured at the individual-level. We begin with a historical comparison of randomized controlled trials (RCTs) versus non-experimental studies in explaining the importance of our use of an observational study and then justify the use of the grouped-treatment approach to address concerns regarding confounding by indication.

3.1 Justification for the use of observational studies

To begin with, although randomized controlled trials are often deemed the most robust study design when examining treatment effects, they are not without their

challenges.[115] As in our study, performing an RCT is likely inappropriate and unethical. Given the known pharmacological benefits of IV vitamin D therapy in the treatment of SHPT among dialysis patients, it would be unethical to withhold vitamin D treatment in any attempts to establish a counterfactual when investigating the association between vitamin D exposure and fracture risk in a RCT. Also, studying the unintended effects of vitamin D exposure on fractures may be inappropriate since the outcome of interest may occur over a relatively long time span, a potentially cost-prohibitive issue for RCTs.

Additionally, RCTs are generally plagued by the presence of effect modification, preventing study results from being generalizable to different subgroups or patients who do not fit the study's eligibility criteria.[116] In the analysis herein, we were are able to bypass this issue and perform subgroup analyses whereby the association between vitamin D exposure and fracture risk wasexamined within age, sex, and race strata. Calculating stratum-specific relative risks is further advantageous as a means of controlling for confounding.[117]

Results derived from observational studies have been found to be less prone to heterogeneity when compared to RCTs.[118] Observational studies are more likely to include a varied patient case mix, with a spectrum of comorbidities and treatments that are personalized to the patient.[118] In contrast, RCTs may not represent clinical practice due to stringent protocols and eligibility criteria.[118]

3.2 Justification for the grouped-treatment approach

We performed an observational study using the two-level statistical (grouped-treatment) approach, combining aspects of the individual-level analysis with those of an ecological study. The following section begins with a description of the confounding by

indication issues leading to the decision to measure variables at different units of analysis for this study. Then, both theoretical and empirical explanations are provided to justify the study approach.

To begin with, confounding by indication arises from the general notion that medical providers prescribe medications and perform procedures on patients with the most clinical need for treatment.[119, 120] A similar phenomenon, confounding by disease severity, arises when sicker patients with a poor prognosis are prescribed higher doses of medications and given more treatment. When treatment decisions are made because of medical indications and underlying prognoses that may not be fully accounted for in a model, a purportedly beneficial medication may appear to be positively associated with an adverse outcome.[119] Confounding by indication/disease severity is an especially salient threat to the validity of non-experimental studies of dialysis patients where the substantial morbidity and poor prognoses in this population may thwart the benefits of a medication.[119] As an illustration, statins, prescribed to reduce the rates of cardiovascular events, are frequently prescribed to those perceived to be in greatest clinical need of these medications.[120] Rather than demonstrating a reduction in cardiovascular events, statins may appear to cause them without adequate adjustment for cardiovascular risk factors.[120]

In a RCT, confounding by indication or selection bias is mitigated through the randomization process, guaranteeing that the balance of patients in each arm is due the chance.[117] Throughout the years, there have been substantial advancements in the execution of observational studies, especially in the identification of confounding variables and in the quality of secondary databases like the USRDS.[116]

In this particular study, bias due to confounding by indication/disease severity would likely be present in an individual-level analysis because our data source does not contain PTH, calcium, and phosphorous levels. These clinical variables are assessed as a nephrologist makes decisions to administer vitamin D and they are simultaneously measures used to assess the effect of vitamin D on serum makers post-administration.

There has been growing interest in the use of different analytical approaches to mitigate the effects of confounding by indication in observational studies. Of particular interest, ecological studies have been advanced as a means of addressing the aforementioned confounding issues with investigations into the subject published by researchers Wen and Kramer.[121] To account for confounding by indication bias due to improper control of underlying processes influencing the association between vitamin D dosing practices and fracture risk, a grouped-treatment approach was used, combining aspects of both the ecological and individual-level units of analysis. Since we do not have access to clinical variables like PTH levels influencing the prescription of vitamin D, measures of vitamin D exposure were modeled as ecological variables at the facility-level while covariates and dependent variables were modeled at the individual-level.

Theoretically, the grouped-treatment approach used herein consisted of three variable types: the ecological predictor (X), individual-level covariates (x) and the individual-level outcome (y).[122] The main ecological predictor, X, can have a cross-level effect on y in three ways: 1) X can directly affect y; 2) X can act as an effect modifier and modify the association between x and y; and 3) X can have an indirect effect by affecting x, which then affects y.[122] To futher justify the use of this approach, the differences between ecological and individual-level analyses are described below.

Ecological analyses are characterized by studies with groups as the unit of analysis (both independent and dependent variables measured at the group level and where associations between independent and dependent variables across groups are measured).[123] Selection bias concerns within a particular center are not major concerns when employing an ecological analysis. In contrast, individual-level studies, as the name implies, investigate associations between independent and dependent variables (both measured at the individual-level) across individuals.[123] Both approaches vary in the type of inferences and information generated. Although assessing information on group characteristics, ecologic studies are void of data regarding the cross-classification of individual-level characteristics within groups. For instance, the association between the percentage of drinkers in different rehabilitation groups and hospitalization rates can be assessed in an ecological study but the study will lack information regarding whether drinkers were actually more likely to be hospitalized within specific rehabilitation centers. Contrarily, individual-level studies assess interindividual variation but frequently without assessing the characteristics of the groups that individuals comprise.[123]

At the individual-level, treatment effects can be accurately obtained if using observational data with adequate clinical details and measures of disease severity and comorbidity.[121] Although ecologic studies come with their own issues, an ecologic analysis is preferred for an assessment of the treatment effects of vitamin D because we believe that their advantages (relative immunity from confounding by indication) supersede potential ecological fallacy issues. Furthermore, the proposed study question fits within Wen and Kramer's description of research situations where it is appropriate to use an ecological level key independent variable.[121] Specifically, they should be used when 1) there is limited

evidence of treatment efficacy from a randomized clinical trials; 2) there is limited evidence of treatment effectiveness in clinical practice; 3) confounding by indication is likely in an individual-level analysis; 4) across geographic areas, large variations in the use of the treatment exists; and 5) variations across geographic areas are believed to be due largely to practice style differences. The principal premise is that the use of the treatment is driven by a provider's particular practice style which varies by region, assuming that groups of patients are of similar in prognosis.[124] The challenges of measuring practice style at the patient-level can be overcome with the key independent vitamin D-related variables measured ecologically.

The grouped-treatment approach has been used successfully in epidemiological studies. Using subarachnoid hemorrhage treatment as a case study, Johnston and colleagues compared an individual-level study with all variables at the patient-level, and an ecological study with all variables at an aggregated level, and a grouped-treatment approach to assess the association between in-hospital death and treatment type (endovascular therapy versus surgery).[124] The authors found evidence of confounding by indication in the individual-level analysis given that trends in the individual and ecological models were in opposite directions.[124] To combat this, the authors employed a grouped-treatment approach with the following elements: 1) in-hospital death as a binary, individual-level dependent variable, 2) an ecological independent variable (portion of cases treated by endovascular techniques) as the main predictor, and 3) covariates specified at the individual-level. Unlike the individual-level model, this two-level model suggested a strong association between institutional use of endovascular therapy and reduced in-hospital death risk.[124] Johnston successfully demonstrated that confounding by indication was present at the individual level.

Endovascular therapy, given more to patients with a poor prognosis, resulted in a higher mortality risk and this bias was mitigated by the grouped-treatment approach. The ecological treatment variable bypassed these individual-level treatment selection bias concerns.[124]

The decision to use the grouped-treatment approach in this dissertation was driven by the knowledge that the United States Renal Data System (USRDS) dataset used to assess the association between vitamin D exposure and fracture risk in this work does not contain measures of biochemical parameters like PTH, phosphorous and calcium levels. IV vitamin D is prescribed and indicated for the manipulation of these biochemical markers in the treatment of SHPT among hemodialysis patients. Without these biochemical measures, an investigation of the association between vitamin exposure and fracture risk in an individual-level analysis where all variables are measured at the patient-level would suffer from confounding by indication. Confounding by indication may likely arise because the allocation of IV vitamin D treatment is not randomized but rather prescribed to the patient based primarily on their PTH levels. Confounding by indication in a patient-level analysis would be evident if the treatment, in this case IV vitamin D, influenced PTH levels or any other marker of SHPT that fostered the use of treatment *and* IV vitamin D, at the same time, increased the risk of fracture, our outcome of interest. With the grouped-treatment approach employed in this dissertation, the vitamin D treatment was measured at the facility-level while covariates and the fracture outcome were measured at the patient-level. This approach allowed us to take advantage of the aforementioned relative immunity of ecological studies from confounding by indication with our ecologically measured treatment variable. Simultaneously, the advantages of increased power and precision were realized with outcomes and covariates specified at the individual level.

Lastly, the grouped-treatment approach was employed in this dissertation because it was well-suited for the study of our target population. The grouped-treatment approach allows for pseudo-randomization whereby we assumed that patients received treatment within dialysis facilities in a way that randomized them to different vitamin D prescribing protocols.[125] Hemodialysis patients are very unique in that patients are assigned to the dialysis facility nearest to their home residence and a dialysis facility's vitamin D administration practices does not factor into the decision to attend a particular center. This differs from hospitals, for instance, who may receive more patients with a certain condition because they have a particular expertise or procedure driving their reputation for superior treatment of the condition in question. The grouped-treatment approach has been previously employed successfully in observational studies of hemodialysis patients[95, 126], lending empirical credence to the methodology employed herein. The following chapter provides details of the methods used to assess both study aims presented in this dissertation and explains how we operationalized the grouped-treatment approach in Aim 2.

CHAPTER IV

METHODS

The goals of this retrospective cohort study were: 1) to describe patient-level, facility-level, and state-level trends in the use and dosage of three vitamin D analogs among prevalent hemodialysis patients, and 2) to investigate the association between vitamin D exposure and fracture risk. This section provides a detailed description of the data sources, study design, measurements, and statistical analyses that were used to examine each of the two specific aims. This study was exempt from review by the University of North Carolina Institutional Review Board.

4.1 Data source

Secondary data for this study was derived from the United States Renal Data System (USRDS). Data from years 1999-2008 were used to identify the study population and baseline covariates. The USRDS is a registry that collects, analyzes, and distributes national data on all ESRD patients in the United Sates, irrespective of insurance coverage or age. All Medicare Part A and B claims are also included within the USRDS Standard Analytical Files (SAFs). In the following section, the relevant files within the USRDS are described in detail.

Institutional claims within Medicare Part A are comprised of all inpatient, outpatient, skilled nursing facility, home health agency, and hospice claims. Hospitalization data includes the admission source, length of stay, discharge destination, and associated diagnoses and procedures for each patient. The Inpatient SAF contains final action claims data

submitted by inpatient hospital providers for reimbursement of facility costs. These data include diagnosis (ICD-9 diagnosis), procedure (ICD-9 procedure code), Diagnosis Related Group (DRG), dates of service, reimbursement amount, hospital provider, and beneficiary demographic information. The USRDS maintains these data in two files, an Institutional file with records at the patient-level and an Institutional Claims Detail file with records at the claim level.

Medicare Part B Physician/Supplier claims include durable medical equipment charges along with physician services and supplies. The file also contains final action claims data submitted by non-institutional providers. Examples of non-institutional providers include physicians, physician assistants, clinical social workers, nurse practitioners, independent clinical laboratories, ambulance providers, and free-standing ambulatory surgical centers. Data contained in this file includes diagnosis, procedural codes, dates of service, reimbursement amount, non-institutional provider numbers (e.g., UPIN, PIN, NPI), and beneficiary demographic information. Each observation in this file is at the claim level.

The USRDS Patient File contains information describing patient race, age, date of death, first service date, and other demographic characteristics. Death data are obtained from the CMS-2746 ESRD Death Notification Form, providing the date along with the primary and secondary causes of death for over 99% of patients.[3]

The USRDS Payer History File documents the sequence of payers for each patient including any change in Medicare status and dual Medicare/Medicaid eligibility.[127] Patient transplant events are documented in the USRDS Transplant File. The USRDS Facility File contains dialysis facility-level data derived from the CMS Annual Facility Survey (CMS-2744, hereafter AFS), a survey that all centers are mandated to complete each calendar year.

In addition to facility-level characteristics such as geographic region, the file reports the number of patients being treated at all dialysis facility or treatment center at the end of each calendar year.[3]

The remaining sections of this chapter describe the study design and patient population, followed by a detailed description of the measurements and statistical analyses employed for each aim.

4.2 Study design and cohort selection by aims

Using USRDS data, we conducted a retrospective cohort, intention-to-treat analysis. Generally, the intention-to-treat design results in smaller observed treatment effects compared to observed estimates if all patients adhered to vitamin D therapy, thus tending to bias estimates toward the null.[128] This section describes the study design for each aim. After describing the study design, the process for cohort selection is described, including a detailed explanation by aim of the inclusion and exclusion criteria.

4.2.1 Aim 1

The following section details the cohort selection process and overall study design used for Aim 1.

Aim 1: To investigate patient-level, facility-level, and state-level trends in the use and dosage of three vitamin D analogs among prevalent hemodialysis patients.

Table 1 details the inclusion criteria that were used to define the study population.

Table 1. Summary of Aim 1 cohort selection process

Inclusion criteria
Patients with Medicare as a primary payer throughout the study period
In-center hemodialysis patients
Patients with at least 90 days of hemodialysis following the initiation of renal replacement therapy

A retrospective cohort study was conducted to describe patient-level, facility-level and state-level secular patterns in the use and dosage of IV vitamin D formulations among prevalent hemodialysis patients in the USRDS dataset. To be eligible, patients had to have Medicare as a primary payer at 90 days post hemodialysis initiation. Medicare is considered the secondary payer for the first 30 consecutive months following dialysis initiation for individuals who were not already eligible for Medicare on the basis of age or disability prior to enrollment in the ESRD program.[129] If this requirement was not enforced, patients with Medicare as a secondary payer would have limited or non-existent treatment and event data. Spurious rate calculations would have resulted as these patients contributed follow-up time to the denominator but limited event information to the numerator.[3] Historically, the number of incident hemodialysis patients with Medicare as primary payer has decreased drastically from 95% in 1974 in the earliest years of the ESRD program to 74% in 2009, with the percentage of prevalent hemodialysis patients with Medicare as primary payer at 83% in 2009.[3]

Additionally, patients must be an in-center hemodialysis patient. Renal replacement therapy consists of either kidney transplantation or dialysis, a means of filtering waste from the blood in order to enable the body's regulatory functions.[130] There are two main forms of dialysis, hemodialysis that uses an apparatus to filter blood outside of the body or peritoneal dialysis that uses the lining of the abdomen to filter blood inside the body.[130] Patients electing home hemodialysis with the support of trained health care professionals are provided home treatment 3 to 5 times a week for a period of 3 to 10 hours per session. In contrast, in-center hemodialysis, conducted at the hospital or a free-standing clinic, is administered 3 times a week on alternating days (Mondays, Wednesdays, and Fridays or Tuesdays,

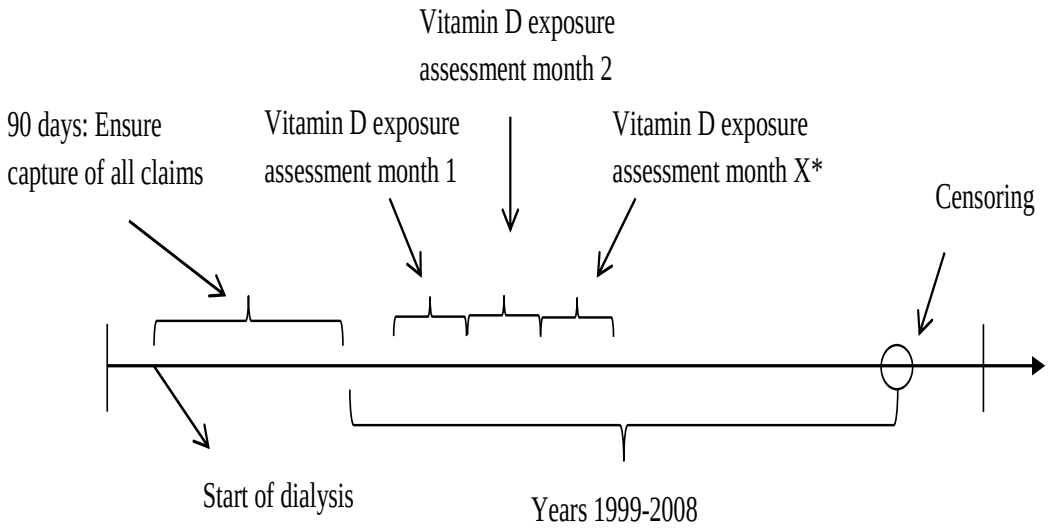
Thursdays, and Saturdays) with dialysis sessions averaging 3.5 to 4 hours.[131] Since patients are administered IV medications during their respective dialysis sessions, only in-center hemodialysis patients were included to avoid any confounding arising from differences in the length of a dialysis session and frequency of medication administration.

Furthermore, the analysis was restricted to only hemodialysis patients to account for potential differences in clinical outcomes and patient characteristics associated with each treatment modality. Many studies have compared a range of outcomes among patients treated with in-center hemodialysis versus those treated with peritoneal dialysis, with conflicting results. For instance, although some studies have documented a survival advantage for peritoneal dialysis patients in the first two years of dialysis[132, 133], others have documented higher mortality rates associated with peritoneal dialysis. [131] Yet still, other studies have found no differences in the risk of death when comparing hemodialysis to peritoneal dialysis patients. A recently published study using robust methodology and USRDS data found no significant differences in mortality risk among the treatment modalities during a 5 year follow-up period.[134] In addition to the discrepancies in the medical literature regarding this topic, there is also evidence that diabetes, age, and comorbidity significantly modify the association between treatment modality and mortality.[135]

Eligible patients were further required to be on hemodialysis for at least 90 days. Data obtained in the initial three months of therapy for an ESRD patient poses substantial difficulties for an investigator. Foremost, in the first 90 days, providers are exploring various treatment modalities and therefore patients are more likely to switch from hemodialysis to peritoneal dialysis. For instance, in 2009, the number of hemodialysis patients decreased by

14% from dialysis initiation to day 90.[3] However, the number of peritoneal and transplant patients increased by 1.4% and 21%, respectively, from dialysis initiation to day 90.[3] Most importantly, the ESRD program entitles Medicare coverage to disabled patients under the age of 65. Although peritoneal or home dialysis patients can bill Medicare immediately, in-center hemodialysis patients under 65 years old are not able to bill Medicare for hospitalizations or dialysis therapy until 90 days post their first dialysis service date.[3] To ensure the capture of all claims for all eligible patients, this 90 day restriction was imposed. Figure 5 depicts the study design for Aim 1.

Figure 5. Study design for Aim 1



*X indicates months 3, 4, etc. of eligibility

Prevalent and incident hemodialysis patients identified in the USRDS database from January 1, 1999 through December 31, 2008 meeting the aforementioned eligibility requirements were included in the analysis. Patients who survived 90 days post dialysis initiation entered the follow-up period where vitamin D exposure (monthly/yearly vitamin D dose and formulation preference) were assessed. Patients were censored if one of the

following events occurred: 1) death, 2) kidney transplantation, 3) Medicare was no longer the primary payer, and 4) switched to peritoneal dialysis. Patients were administratively censored at the last date of available data on December 31, 2008. Patients may have undergone dialysis at multiple facilities during the follow-up period. This may occur for several reasons, including if a patient moved or if a patient transferred facilities because a particular facility's shift offerings were more attractive. We assumed that patients receive care at the dialysis facility in closest geographical proximity to their home residence. Therefore, we assumed that all switches occurred at random and we did not account for patient dialysis facility switches.

4.2.2 Aim 2

Aim 2: To investigate the association between vitamin D exposure and fracture risk by fracture type and among relevant subgroups among incident hemodialysis patients.

Table 2 details the inclusion and exclusion criteria that were used to define the final study population. First, eligible patients were identified. Then, we defined eligible facilities as those that serviced at least 5 eligible patients.

Table 2. Summary of Aim 2 cohort selection process

Inclusion criteria
Patients with Medicare as a primary payer throughout the baseline and follow-up period
Patients with at least 90 days of hemodialysis following the initiation of renal replacement therapy
Incident hemodialysis patients
In-center hemodialysis patients
Patients who survived at least 270 days post-dialysis initiation
Patients with at least 120 days of claims during the 180-day baseline period
Exclusion criteria
Patients younger than 18 years of age at dialysis initiation
Patients who experienced a fracture during the 180-day baseline period
Patients without a facility identified in the dataset
Patients in a facility with <5 eligible patients

The analysis was restricted to patients who initiated dialysis between October 1, 1999 and March 1, 2004. The oldest vitamin D formulation, calcitriol, was released in September 1986. Paricalcitol and doxercalciferol were released over a decade later in April 1998 and June 1999, respectively.[27] Patients were eligible to enter the baseline period on January 1, 2000 given that all three vitamin D formulations were being administered at that time. In March 2004, the FDA approved the use of cinacalcet hydrochloride (Sensipar), the only FDA approved calcimimetic for the treatment of SHPT in dialysis patients and hypercalcemia in patients with parathyroid carcinoma.[136] In May 2004, cinacalcet became commercially available and approximately 10% of patients dialyzed by a large for-profit provider received the drug between August to October 2004.[137] To avoid the effect of possible confounding due to this major therapeutic advancement in the treatment of SHPT, the effect of vitamin D exposure on fracture outcomes was assessed solely in a pre-calcimimetic cohort between January 1, 2000 and May 31, 2004. We assumed very minimal use of cinacalcet in May 2004 because of the lag that generally exists between the date a drug becomes commercially available and its adoption into dialysis treatment practice.

Figure 6. Study design for Aim 2

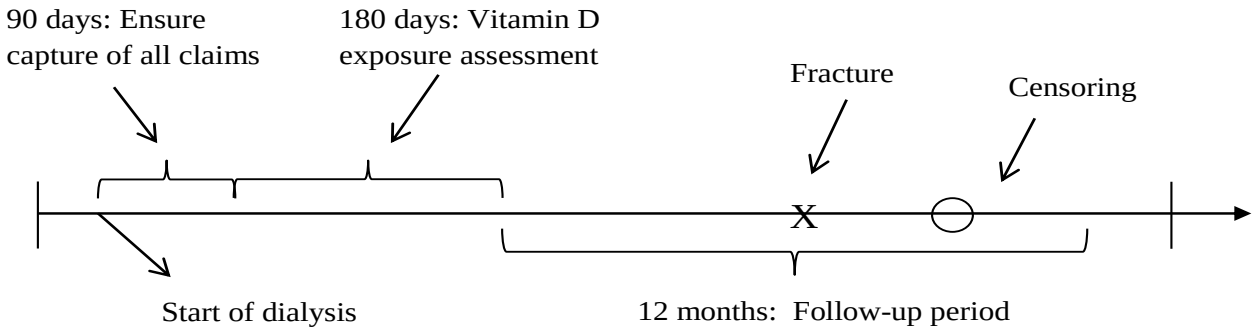


Figure 6 depicts the study design for Aim 2. Following the first 90 days of renal replacement therapy, incident, in-center hemodialysis patients were eligible, using a new-user design. The analysis was restricted to incident dialysis patients to ensure better measurement of factors that may differ systematically between groups of vitamin D users. Identifying patients at a common time point, at dialysis initiation, allows researchers to control for events occurring earlier in therapy that may predict a patient's use of vitamin D and vitamin D dose. Employing a new-user design with an inception cohort of incident hemodialysis patients is advantageous to avoid the considerable bias arising if fracture risk is assumed to vary with time.

Time-dependent biases associated with the inclusion of prevalent patients can be due to several factors. Pharmacologic agents like IV vitamin D have both beneficial and detrimental effects with different induction periods.[138] The inclusion of only incident patients prevents the under-ascertainment of fractures that occurred prior to therapy and before the follow-up period. Also, if prevalent patients were included, there would be no means of accounting for early attrition and mortality of patients most susceptible to fracture events.[138] During the 12 month follow-up period, the association between vitamin D exposure and time to first fracture was assessed with patients censored once any of the following events occured: 1) death, 2) kidney transplantation, 3) loss of Medicare as the primary payer, or 4) a switch to peritoneal dialysis. Patients were administratively censored on May 31, 2004.

A 180 day baseline period to assess covariate values and vitamin D exposure was considered sufficient based on analyses conducted by Teng and colleagues. In a study of 51,037 chronic hemodialysis patients, 83% had started treatment with injectable vitamin D

within 180 days of dialysis initiation.[139] To be eligible, patients must have survived at least 270 days post dialysis initiation. This period includes the first 90 days of dialysis to ensure proper ascertainment of claims and the full 180-day baseline period. Patients were further required to have at least 120 days of claims during the 180-day baseline period in order to ensure a sufficient number of records to assess vitamin D exposure and covariates.

Patients younger than 18 years old were excluded from the analysis. Age was assessed at dialysis initiation. Pediatric and adolescent ESRD patients were excluded because treatment and diagnostic decisions vary substantially with the differing causes of disease, health outcomes, and comorbid conditions in pediatric versus adult dialysis patients.[140] Among the clinical differences between the two patient populations, approximately 45% to 65% of pediatric patients are treated with peritoneal dialysis but only about 13% to 17% of adult ESRD patients are treated with this modality.[140] Whereas the primary causes of ESRD in adults are hypertension and diabetes, the primary cause of the disease in children are cystic, hereditary and congenital diseases.[3] In addition to the clinical challenges, the lack of nephrologists with pediatric specialization may lead to differences in treatment recommendations and outcomes when comparing adults and children.[140]

Hip fractures among younger individuals are extremely rare and likely to be caused by trauma.[141] In children, the incidence of hip fracture is less common compared to adults. Rather than due to physiological processes, pediatric fractures are likely induced by high energy traumas like motor vehicle accidents or falls from a substantial height.[142]

Patients who experienced a fracture during the 180-day baseline period were excluded. The goal of this analysis was to determine the association between vitamin D exposure and a patient's first observed fracture since the end of the baseline period. Having

a prior hip fracture has been associated with a 70% greater adjusted odds ratio (AOR) of hip fracture (AOR=1.70, p=0.02) in a cohort of 12,782 hemodialysis patients across 12 countries.[77] Among the same group of patients, having experienced a hip fracture was highly predictive of incurring a new fracture (RR=4.52, p<0.001). We decided to exclude patients with a prior history of fracture instead of controlling for this variable as a potential confounder because, among other criteria, a potential confounder must not be an effect of the exposure (IV vitamin D in this case) and it must not be a factor in the causal pathway of experiencing a fracture.[117] In this study, having a previous history of fracture is likely in the causal pathway describing the effect of IV vitamin D use and the risk for experiencing a subsequent fracture. Lastly, patients without a corresponding facility identified in the dataset were excluded. Since vitamin D exposure was assessed at the facility-level, an indicator for the corresponding facility for each patient was crucial to allow for the aggregation of the patient-level variables to the facility-level.

4.2.3 Sample size

After employing all eligibility criteria, the cohort selection process was complete. The number of eligible patients for this aim varied over time from approximately 220,000 in 1999 to over 300,000 in 2008. A flowchart diagram for Aim 1 is not presented because of this variability in the number of eligible patients over time.

Figure 7 presents the sample size determination flow chart diagram for Aim 2.

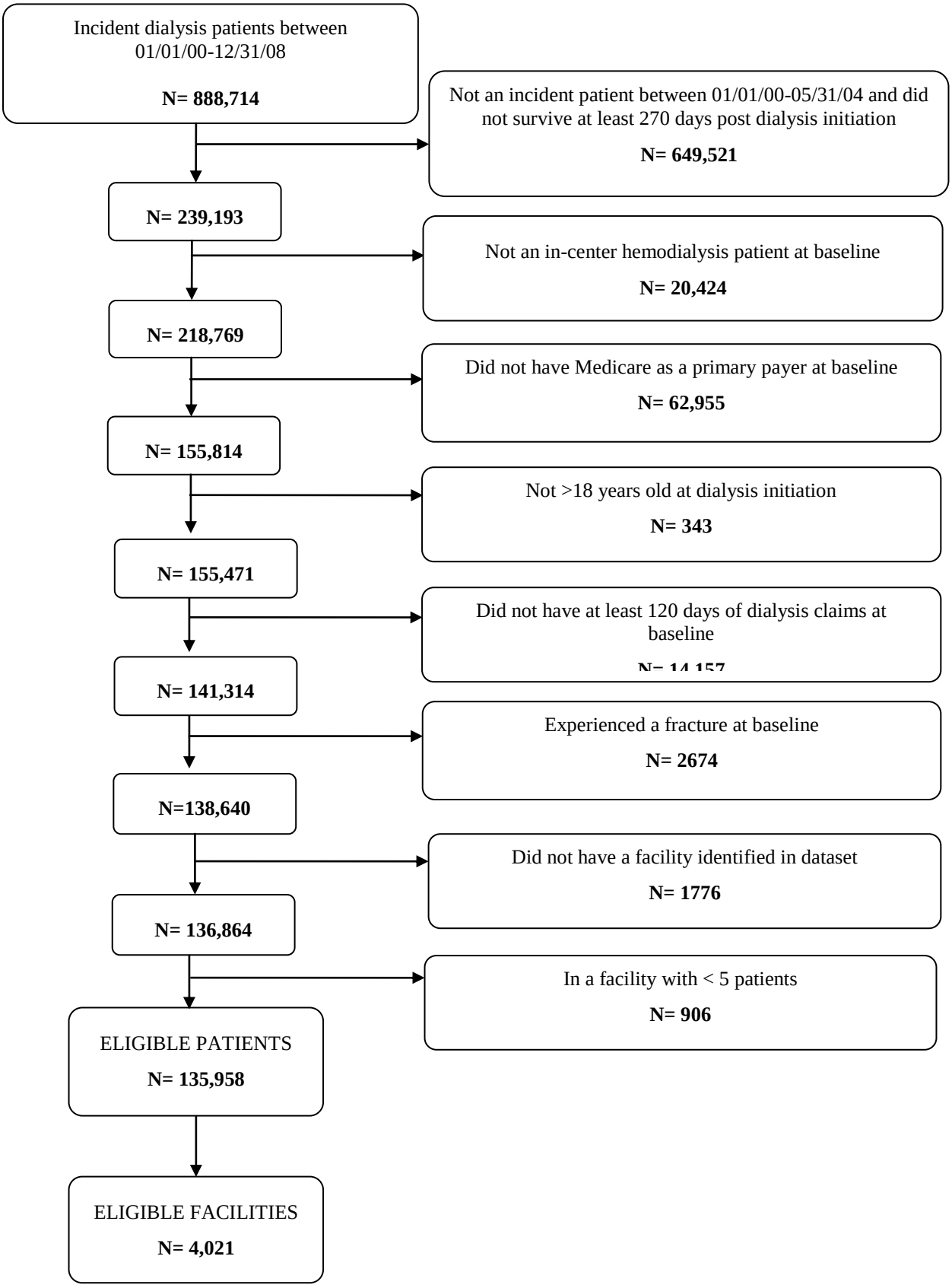


Figure 7. Sample size determination flow chart for Aim 2

4.3 Measurements

This section describes the operationalization of the key measures of vitamin D exposure for Aim 1 and Aim 2, the fracture outcome for Aim 2, and covariates for Aim 2 using USRDS data.

4.3.1 Vitamin D formulations and dose

Table 3 describes the chemical name, dosage form, dosage range, and frequency of administration for each IV vitamin D formulation. According to guidelines, calcitriol doses should range from 0.5-5μg and paricalcitol dosing based on iPTH levels range from 2.5-15μg.[143] Specifically, calcitriol should initially be dosed at 1-2μg, with dose increases of 0.5-1μg at 2-4 week intervals if necessary.[144] Paricalcitol dosed at 2.5–5.0 μg is recommended for iPTH levels of 300–600 pg/mL, 6.0–10 μg, for iPTH levels of 600–1000 pg/mL, and 10–15 μg for iPTH levels greater than 1000 pg/mL.[143] The initial recommended dose of doxercalciferol is 4μg bolus administrations 3 times per week with dose increases of 1-2μg at 8-week intervals if iPTH levels do not reach target ranges.[55]

Table 3. Description of IV vitamin D formulations

Drug	Chemical Name	Dosage Form	Dosage Range[a]	Frequency of Administration[b]
Calcitriol (Calcijex)	1,25-dihydroxyvitamin D_3	1 and 2 μg/mL in 1 mL ampuls	0.5-5 μg	3 times/wk
Paricalcitol (Zemplar)	19-nor-1,25-dihydroxyvitamin D_2	5 μg/mL in 1 and 2 mL vials	2.5-15 μg	3 times/wk
Doxercalciferol (Hectorol)	1α-hydroxyvitamin D_2	2 μg/mL in 1 and 2 mL ampuls	2-8 μg	3 times/wk

Source: Hudson JQ: Secondary hyperparathyroidism in chronic kidney disease: Focus on clinical consequences and vitamin d therapies. *Ann Pharmacother* 40**:** 1584-1593, 2006[143]

Table 4 presents the Healthcare Common Procedure Coding System (HCPCS) codes that were used to identify each formulation within the USRDS. Calcitriol use was identified using HCPCS codes J0635 (1µg) and J0636 (0.1µg). The codes J2500 (5µg) and J2501 (1µg) were used to identify paricalcitol and J1270 (1µg) identified doxercalciferol use. These codes were derived from Medicare Part A institutional claims.

Table 4. HCPCS codes to identify IV vitamin D formulations

HCPCS Code	Formulation	Dose
J0635	Calcitriol	1µg
J0636	Calcitriol	.1µg
J2500	Paricalcitol	5µg
J2501	Paricalcitol	1µg
J1270	Doxercalciferol	1µg

Source: St. Peter WL, Li S, Liu J, Gilbertson DT, Arneson TJ, Collins AJ: Effects of monthly dose and regular dosing of intravenous active vitamin d use on mortality among patients undergoing hemodialysis. *Pharmacotherapy* 29**:** 154-164, 2009

A dose ratio of 1:4 for calcitriol to paricalcitol has been shown to be effective in treating SHPT without significant variations in phosphorous or calcium levels.[145] A dosing conversion factor of 0.57:1 for doxercalciferol to paricalcitol was found to maintain equivalent suppression of iPTH levels among a cohort of 27 chronic hemodialysis patients.[146] Using these dosing conversions established in clinical practice, the calcitriol-equivalent dosing conversion factor for calcitriol to doxercalciferol was determined to be 1:2.28 (4*calcitriol=paricalcitol; paricalcitol=doxercalciferol/0.57; therefore 4*calcitriol=doxercalciferol/.57).

4.3.2 Vitamin D exposure by aims

Aim 1: Vitamin D exposure measured at the individual, facility and state level

At the individual-level, the following vitamin D exposure variables were assessed: vitamin D use (yes/no) and average vitamin D dose per month. Vitamin D use was measured as a dichotomous variable indicating whether a patient was administered any dose of vitamin D in the respective month of measurement. Vitamin D administration is not accurately captured during hospital stays. Because of this, inpatient days were subtracted from patient time at risk during the month of interest. Patients with zero vitamin D administered during the month or year of interest were classified as a non-vitamin D user for that respective time period. Average vitamin D dose represented the mean dose of any vitamin D formulation administered to patients during the respective month or year of interest. Vitamin D use and average vitamin D dose were measured monthly and yearly for all eligible patients between January 1, 2000 and December 31, 2008.

At the facility-level, the following vitamin D-related variables were assessed: the percentage of vitamin D users per facility per month and average vitamin D dose per patient per month in each facility in the months between January 1, 2000 and December 31, 2008. The percentage of vitamin D users per month within each facility indicated the percentage of patients within a facility administered any dose of vitamin D, irrespective of formulation, in the respective month of analysis. The average vitamin D dose per patient per month in each facility indicated the mean dose of any vitamin D agent, irrespective of formulation, administered to patients in each facility during the respective month of interest. Facility-level vitamin D formulation preference by calendar year was also tabulated (Appendix 4). At the state level, the following measures of vitamin D exposure were assessed: the percentage of vitamin D users per state per year and average vitamin D dose per patient per year within the respective state. Analogous to the facility-level analysis, the unadjusted proportion of

vitamin D users per year was defined as the number of vitamin D users per year in each state divided by the number of eligible dialysis patients in the state of interest. The average vitamin D dose per patient per year in each state indicated the mean dose of any vitamin D formulation administered to all patients per year in the state of interest.

Aim 2: Vitamin D exposure measured as ecological variables at the facility-level

The key measures of vitamin D exposure for Aim 2 were ecological variables measured at the facility-level during the 180-day baseline period: 1) the non-case-mix adjusted proportion of vitamin D users in each facility; 2) the case-mix adjusted proportion of vitamin D users in each facility; 3) the non-case-mix adjusted average vitamin D dose per patient in each facility; 4) the case-mix adjusted average vitamin D dose per patient in each facility; and 5) whether a facility was in the highest quartile of case-mix adjusted average vitamin D dose per patient in each facility. The "case-mix adjusted proportion of vitamin D users" variable and the "case-mix adjusted average vitamin D dose per patient" variable required the use of statistical modeling techniques to create. Therefore, detailed descriptions of both variables are provided in the section entitled "Analyses used to create case-mix adjusted measures of vitamin D exposure." Each measure of vitamin D exposure was modeled separately in regression analyses. A detailed description of each vitamin D-related variable follows.

Foremost, at the individual-level, vitamin D use was a dichotomous variable indicating whether the patient received any dose of vitamin D during the baseline period. When aggregated to the facility-level, the non-case-mix adjusted proportion of vitamin D users within each facility was modeled as a continuous variable measuring the proportion of patients within a facility administered any dose of vitamin D, irrespective of formulation,

during the 180-day baseline period. It is important to emphasize that while vitamin D use (yes/no) at the individual-level is a dichotomous variable, when aggregated to the facility-level, the percentage of vitamin D users within each facility was a continuous variable.

Although this variable measures the number of vitamin D users relative to number of patients in each facility, the variable does not indicate a facility's predilection to prescribe vitamin D. Employing a strategy reported by Tentori and colleagues, the case-mix adjusted proportion of vitamin D users at a facility was estimated to reflect a facility's propensity to prescribe vitamin D.[95] The creation of this variable is described in the "Analyses used to create case-mix adjusted measures of vitamin D exposure" section below.

Furthermore, the non-case-mix adjusted average vitamin D dose per patient in each facility indicated the mean vitamin D dose administered per patient in each facility during the 180-day baseline period, irrespective of vitamin D formulation. Analogous to the case-mix adjusted proportion of vitamin D users, the case-mix adjusted average vitamin D dose per patient in each facility is described in the "Analyses used to create case-mix adjusted measures of vitamin D exposure" section.

The last measure of vitamin D exposure indicated whether a facility was in the highest quartile (75^{th} percentile) of average vitamin D dose per patient. This was based on the distribution of the average vitamin D dose per patient among all eligible facilities. To ameliorate potential multicollinearity issues, each measure of vitamin D exposure was modeled separately in statistical analyses (described in the "Statistical analyses by aims" section).

4.3.3 Fracture outcomes

Table 5 lists the ICD-9 codes that were used to identify fractures by site. Fractures in any diagnoses field in any one of four broad fracture categories were identified: 1) vertebral; 2) pelvis/hip; 3) other [femur, lower leg (tibia, fibula, patella & ankle), ribs/sternum, humerus, scapula & clavicle (shoulder/upper arm), or forearm/wrist]; and 4) any of the above fracture types.

Table 5. Diagnostic codes used to identify fractures

	Fracture Category	*ICD-9 Codes*
1	Vertebral	733.13, 805.xx, 806.xx
2	Pelvis/hip (femoral neck)	733.14, 808.xx, 820.xx
3	Other	Femur: 733.15, 821.xx Lower leg: 733.16, 822.x, 823.xx, 824.xx Ribs/sternum: 807.0x-807.1x, 807.2-807.3 Shoulder/upper arm: 733.11, 810.xx, 811.xx, 812.xx Forearm/wrist: 813.xx, 814.xx
4	Any	Any of the above ICD-9 codes

The four broad categories of fractures delineated in Table 5 represent the most common and most economically burdensome fracture types. Of note, this classification, therefore, excludes the following fractures in the 800-829 fracture series: fractures of the skull and facial bones (800.xx – 804.xx), ill-defined bones of trunk (809.xx), fractures of the metacarpals & phalanges (fingers) (815.xx-817.xx), ill-defined fractures of upper limb (818.xx), multiple fractures of upper limb (819.xx), fractures of tarsal, metatarsals, phalanges (toes) (825.xx – 826.xx), multiple, ill-defined fractures of lower limb (827.xx), multiple fractures of upper and lower limb (828.xx), and unspecified fractures (829.xx).

Some studies of osteoporotic fractures have excluded pathologic fractures under the presumption that these fractures are caused by localized processes such as malignancy or

infection that are not related to the bone disorder of interest.[147] Pathologic fractures were not excluded in this analysis. A study of U.S. Medicare beneficiaries repudiated the rationale for the exclusion of pathologic fractures by demonstrating that epidemiological analyses using administrative data substantially underestimate the burden of fractures with the exclusion.[147]

In contrast to a closed fracture, an open fracture is where the bone breaks and pierces through the skin.[148] Open fractures, classified with ICD-9 codes like 821, 820.3x 820.9, 821.1x, 821.3x, 822.1, and 805.3, have sometimes been excluded from epidemiological analyses because these fractures are generally associated with major trauma.[149, 150] For the purposes of this analysis, both open and closed fractures were assessed because of the difficulty in determining whether a fracture in claims data was induced by disease (or a traumatic fall subsequent to bone disease) or due to a traumatic event like a motor vehicle accident.

The outcome for Aim 2 was fracture risk. To assess fracture risk, the dependent variable, time to first fracture, was measured during the one-year follow-up period immediately following a hospitalization for a fracture event (see "Study design and eligibility criteria by aims" section below). A detailed description of the outcome variable follows.

As delineated in detail in the section below, patient time at risk began at the 181st day following the end of the 180-day baseline period and ended with the occurrence of a censoring event. To assess fracture risk, time-to first fracture was the dependent variable and defined as a continuous measure in Cox proportional hazards models representing the time in days from the end of the baseline period to the date of hospitalization for the first fracture event.

Table 6 presents an overview of the key independent variables and outcome measure for Aim 2.

Table 6. Overview of key independent and outcome variables for Aim 2

Variable	Description	Type	Unit of Analysis
Independent variables measured during 180-day baseline period			
Non-case-mix adjusted proportion of vitamin D users	Proportion of patients within a facility administered any dose of vitamin D	Continuous	Facility-level
Case-mixed adjusted proportion of vitamin D users	Patient and facility case-mix adjusted proportion of patients at a facility prescribed any dose of vitamin D	Continuous	Facility-level
Average vitamin D dose per patient	Mean vitamin D dose administered per patient in each facility	Continuous	Facility-level
Whether a facility is in the highest quartile of case-mix adjusted average vitamin D dose	Whether a facility is in the 75th percentile of case-mix adjusted average vitamin D dose per patient	Dichotomous	Facility-level
Dependent variable measured during 1-year follow-up period post-fracture hospitalization			
Time to first fracture	Time in days from the end of the baseline period to the date of the first fracture event. Time to first fracture is the dependent variable and fracture risk (the probability of fracture among patients in the exposure group relative to those who were not exposed to the key vitamin D variable) is the parameter estimate that results after performing Cox regression analyses	Continuous	Patient-level

4.3.4 Covariates

Covariates were defined a priori and 6 vectors of variables were delineated: demographic characteristics, comorbidities, disease history characteristics, facility

characteristics, functional status markers, and treatment characteristics. Details regarding the coding definition and source file for each variable can be found in Appendix 3. The choice of covariates was based on published literature describing predictors of fractures in both the general and dialysis population. For instance, Jadoul and colleagues substantiated that risk factors for fractures in dialysis patients include female sex, older age, non-black race, and having a prior kidney transplant.[77]

Demographic characteristics

Age, sex, and race described patient demographic characteristics. Age at dialysis initiation, sex, and race were derived from the USRDS Patient File. Patients were assigned to one of four age categories: 18-44, 45-64, 65-74, and ≥ 75 years old. As the modal group, patients 65-74 years old were chosen as the reference category. Several studies have documented an increased incidence of hip fracture with increasing age in both the dialysis and general population.[74, 80]

With regards to sex, women have an estimated 64% greater risk of hip fracture when compared to men and black patients have been reported to have a 62% lower risk in comparison to white patients.[73] In fact, Mitterbauer and colleagues developed a predictive model positing that the independent variables of age and sex sufficiently predict fractures occurring within 1 year of hemodialysis treatment.[76]

Black individuals in the general population have been shown to have increased bone mass in comparison to white individuals and SHPT may actually be a causal factor.[151] The increased bone mass may be attributed to changes in the vitamin D-endocrine system including greater tubular reabsorption of calcium and greater circulating levels of

$1,25(OH)_2D$.[151] Possibly in part due to the increased bone mass observed among blacks, whites have been observed to have the greatest incidence of hip fractures.[80]

Medicaid eligibility at dialysis initiation was categorized as a binary variable. Approximately 22% of new dialysis patients are eligible for Medicaid services; with the rate of eligibility increasing to 32% as the high costs of medical care depletes patient financial resources.[152] It is important to control for Medicaid eligibility given that systematic differences have been documented when Medicaid-enrolled and non-Medicaid incident dialysis patients are compared. Incident ESRD patients with Medicaid coverage are generally younger, female, minority, have functional limitations, or are prone to risk factors associated with adverse health outcomes.[152]

Comorbidities

The presence of comorbid conditions within the ESRD population presents a major therapeutic challenge for nephrologists and they must be controlled for because these conditions independently predict poor patient health outcomes. The analyses controlled for the presence of any of the following comorbid conditions or procedures during the baseline period: acute myocardial infarction (MI), anemia, autoimmune disorder, coronary artery bypass graft (CABG) performed/ stent/ percutaneous transluminal coronary angioplasty (PTCA) placement, cancer, chronic obstructive pulmonary disease (COPD)/asthma, diabetes mellitus, gastrointestinal bleed, human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS), hypertension, hyperthyroidism, ischemic heart disease, liver disease, neurologic disorder, obesity, other heart disorder, peptic ulcer disease, peripheral vascular disease, pneumonia, psychiatric disorder, pulmonary circulation disorder, stroke, and substance use disorder. Patients were categorized as having an autoimmune

disorder at baseline if they had any claim with the diagnoses of inflammatory bowel disease, psoriasis, lupus, or rheumatoid arthritis/collagen vascular diseases. Cardiovascular abnormalities, including ischemic heart disease, hypertension, and peripheral vascular disease, arguably, present the greatest clinical challenge. Table 7 lists the diagnostic codes that were used to identify each type of comorbid condition.

Table 7. Diagnostic codes used to identify comorbidities

Diagnosis	ICD-9 codes
Acute MI	410
HIV/AIDS	042-044
Anemia	280.0-281.9, 385.9
Autoimmune disorder	564.1, 695.4, 696.0-696.1, 710, 710.0, 714, 720, 725
Cancer[a]	140-172, 173.3, 173.9-175.9, 179-199, 200-201, 202.0-202.3, 202.50-203.01, 232.9, 233.0, 233.1, 338.3, 799.4, 203.8, 238.6, 273.3, 300.29, 789.51, 795.82, V10, V67.2
COPD/Asthma	490-496, 505, 506.4
Diabetes mellitus	250
Gastrointestinal bleed	578
Heart-related procedure	CABG/stent/PTCA placement **ICD-9 Codes:** 00.66, 36.06, 36.07 **HCPCS Codes:** 33510-33519 (excluding 33515), 92982, 92985, 92980
Hypertension	401-405 (excluding 402.11,402.91,404.11,404.13,404.91,404.93)[b]
Hyperthyroidism	242
Ischemic heart disease	411-414
Liver disease	070.32, 070.33, 070.54, 456.0, 456.1, 456.20, 456.21, 571.0, 571.2, 571.3, 571.4, 571.5, 571.6, 571.8, 571.9, 572.3, 572.8, V42.7
Neurologic disorder	331.9-332.0, 333.4, 333.5, 334, 335, 340, 341, 345.0, 345.1, 345.4, 345.5, 345.8, 345.9, 348.1, 348.3, 780.3, 784.3

Table 7. Diagnostic codes used to identify comorbidities

Diagnosis	ICD-9 codes
Obese	278.00-278.01
Other heart disorder	402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 420-429, 785.0, V45.0, V53.3, 0932, 7463, 7464, 7465, 7466, V422, V433
Peptic ulcer disease	530.2, 531-534, V12.71
Peripheral vascular disease	440-443, 447.1, 557.1, 557.9, V43.4
Pneumonia	481-486
Psychiatric disorder	295-298
Pulmonary circulation disorder	415-417
Stroke	434.01, 434.11, 434.91, 435-438, V12.54
Substance use disorder	303-305

Source: Brookhart, Freburger, et al. paper that is currently under review

[a] The listed ICD-9 codes identify the following broad types of cancers: *Codes 140-172*= malignant neoplasms of the lip, oral cavity, pharynx, digestive organs, peritoneum, respiratory organs, intrathoracic organs, bone and articular cartilage; *Code 173.3*= malignant neoplasm of skin of other and unspecified parts of face; *Codes 173.9-175.9*= malignant neoplasm of the skin (unspecified), female breast and male breast*; Codes 179-199*= malignant neoplasm of genitourinary organs and other/unspecified sites*; Codes 200-201*= lymphosarcoma, reticulosarcoma, other specified malignant tumors of lymphatic tissue, and Hodgkin's disease; *Codes 202.0-202.3*= nodular lymphoma, mycosis fungoides, and Sezary's disease*; Codes 202.50-203.01*= Letterer-Siwe disease, malignant mast cell tumors, peripheral T cell lymphoma, other lymphomas, other and unspecified malignant neoplasms of lymphoid and histiocytic tissue*; Code 232.9*=carcinoma in situ (unspecified)*; Code 233.0*= carcinoma in situ of the breast*; Code 233.1*= carcinoma in situ of the cervix uteri*; Code 338.3*= neoplasm related pain*; Code 799.4*= cachexia*; Code 203.8*= other immunoproliferative neoplasms*; Code 238.6*= neoplasms of plasma cells*; Code 273.3*= Macroglobulinemia*; Code 300.29*=Other isolated or specific phobias*; Code 789.51*= malignant ascites*; Code 795.82*=elevated cancer antigen 125 *; Code V10*= personal history of malignant neoplasm*; Code V67.2*= cancer chemotherapy follow-up.

[b] These codes are excluded from the definition of hypertension because they define hypertensive heart disease. Because of this, these codes are a part of the "other heart disease" category.

Many of the comorbidities associated with older age are clinically manifested in the ESRD population.[153] The frailty, loss of muscle mass, inactivity, and other indicators of physical decline found in ESRD patients but traditionally intrinsic to older patients, may lead to the 5% to 8% of falls that result in fractures.[154] The prevalence of cardiovascular, pulmonary, gastrointestinal, and other disorders contributing to polymorbidity have been associated with a high incidence of falls and subsequent severe femoral fractures.[154] Acute illnesses like pneumonia have been associated with an increased risk of falls, especially

among older adults.[155, 156] We controlled for psychiatric disorders because conditions such as dementia, depression, and schizophrenia have been associated with an increased risk of fracture.[157]

Disease history characteristics

Primary cause of ESRD and prior history of parathyroidectomy were controlled for as disease history characteristics.

Each patient's primary cause of ESRD was categorized into four groups: diabetes mellitus, hypertension, glomerulonephritis, and other. Diabetes, hypertension, glomerulonephritis and all other causes of ESRD are coded as separate identifiers in claims found in the USRDS Patient File. Diabetes served as the reference category as the most frequent cause of renal failure. The "other" category captured patients whose renal failure was caused by polycystic kidney disease or another genetic or urologic disease.

The leading cause of ESRD in the United States is diabetic nephropathy due to type 2 diabetes followed by hypertension.[158] The cause of ESRD in administrative claims data within the USRDS is a reflection of the physician's clinical understanding of pathophysiology of a patient's renal disease. It should be noted that the clinical diagnoses in administrative forms may not accurately represent the true underlying cause of the progression of renal insufficiency.[159] Establishing the true cause of ESRD is a difficult endeavor given the complexity of the disease. For instance, hypertension is a proven cause of ESRD but hypertension can be a complication of kidney disease as well.[160] Malignant hypertension can induce renal failure while primary renal diseases may cause hypertension.[160] Also, the cause of ESRD may be a series of processes occurring simultaneously including repeated kidney infection, hypertension, and diabetes mellitus.[159]

For this patient, compelling a nephrologist to choose one single underlying cause of disease may lead to errors and may simply reflect the physician's diagnostic preferences.[159] While the validity of the cause of ESRD variable merits further research, it has been shown to be a clinically relevant measure. The primary cause of ESRD has been observed to indicate discrepancies in ESRD mortality rates. For example, compared to patients without diabetes as the primary cause of ESRD, diabetes as a cause of renal failure has been associated with a higher relative risk of mortality (RR 1.55; 95% CI 1.36-1.80; $p<0.001$).[161]

A parathyroidectomy is often the therapeutic modality of last resort among patients whose SHPT is unable to be managed with pharmacological options.[20] Because of this, having had a parathyroidectomy performed provides an important indication of SHPT severity.[20] When compared to matched control subjects, a parathyroidectomy in chronic hemodialysis patients has been associated with a 32% lower risk for hip fracture (95% CI 0.54-0.86; $p=0.001$) and a 31% lower risk for any fracture (95% CI 0.57-0.83; $p<0.001$).[14] Among other possible mechanisms, a parathyroidectomy can act to lower fracture risks in three main ways: 1) a parathyroidectomy can mitigate the effects of high-turnover bone lesions, thereby decreasing long term fracture risk by improving bone quality; 2) a parathyroidectomy induces a swift uptake of phosphorous and calcium by the skeleton which may have a protective effect on fractures; and 3) a parathyroidectomy may lower fracture risk by improving a patient's bone strength and bone mineral density.[14] Table 8 describes the diagnostic and procedural codes that were used to identify parathyroidectomies.

Table 8. Diagnostic and procedural codes used to identify parathyroidectomies

Diagnosis or procedure description	ICD-9 or CPT code
Complete parathyroidectomy	6.81 (ICD-9)
Other parathyroidectomy	6.89 (ICD-9)
Parathyroidectomy or exploration of parathyroid(s)	60500 (CPT)
Parathyroidectomy or exploration of parathyroid(s); re-exploration	60502 (CPT)
Parathyroidectomy or exploration of parathyroid(s); with mediastinal exploration, sternal split or transthoracic approach	60505 (CPT)

Yost Engineering, Inc.: Epicoder. http://healthcare.yostengineering.com/epicoder. Accessed November 15 2011

Facility characteristics

Data regarding all dialysis facilities were derived from the USRDS Facility File and measured during the baseline period. The analysis controlled for the following facility-level covariates: profit status, practice setting, chain affiliation, size, and region.

Facilities were categorized into two groups based on profit-status: for-profit and not-for-profit. There is conflicting evidence regarding the potential effect of facility profit status on patient outcomes. Numerous studies have been conducted under the hypothesis that for-profit dialysis facilities put their patients at risk because they may have an economic incentive to use fewer resources.[162] For instance, Devereaux and colleagues concluded that private for-profit dialysis centers were associated with an increased risk of death (RR 1.08; 95% CI, 1.04-1.13; $p<0.001$).[163] Contrarily, Frankenfield et al. found that facility profit status did not have an effect on intermediate outcomes like hematocrit levels and Brooks and colleagues found no relationship between dialysis center profit status and patient survival.[162,

[164] Although the evidence may be conflicting, it was important to control for the potential impact of facility profit-status on patient outcomes.

Facility practice setting was categorized as freestanding or hospital-based facilities. Hospital-based facilities are located within or are associated with a hospital while freestanding facilities function independently of hospitals. Although providing a greater variety of dialysis services compared to free-standing facilities, hospital-based dialysis facilities tend to be less efficient providers of care given the complex salary and benefit structures associated with hospitals.[165]

According to the USRDS, a chain is defined as a corporation operating 20 or more dialysis facilities in two or more states.[127] The exact number of chains in the USRDS database can thus vary annually with the addition of new facilities and due to chain mergers and acquisitions. Each patient was categorized into one of the top six largest dialysis chains during the study period. The top 3 largest chains were determined based on the number of dialysis facilities affiliated with each chain. Compared to smaller chains and independent facilities, larger dialysis chains may benefit from lower costs due to economies of scale. Dialysis chains may also differ in the quality of care provided to patients, their use of inputs (e.g., number of staff and available dialysis machines), patient-case mix if one chain tends to treat sicker patients, and chains may differ in organizational maturation (learning by doing effects).[166] Facilities were categorized into three groups of small, medium and large based on the number of patients each facility served.

Facilities in the lowest quartile after tabulating each facility's patient volume were considered small (18 or fewer patients), facilities in the highest quartile of patient volume (44 or more patients) were considered large, and facilities in between serving 19-43 patients were

considered medium. Compared to hemodialysis patients in smaller facilities, patients in larger dialysis facilities are more likely black, elderly, dialysis patients for greater than 2 years, and more likely to have adequacy measures (e.g., urea reduction ratio) performed.[164] Both large and small facility size have also been associated with negative health outcomes, however. Adherence to hemodialysis regimens are vital to patient health with skipping dialysis sessions associated with higher hospitalization rates and greater phosphate levels.[167] Small dialysis units, defined in one study as less than 30 patients per unit, have been found to generally have higher patient mortality rates compared to larger facilities, suggesting that small dialysis providers may cater to a disproportionate number of high risk patients.[168]

Four geographical regions (Northeast, Midwest, South, and West) of the US were delineated based on the location of each patient's dialysis facility using Census Bureau Regions and Divisions.[169] Differential rates of fracture have been observed to vary by fracture type and geographical region. Hip fracture rates are generally higher in the southern portion of the US and lower in the north.[15, 170] The reason for the observed regional differences in fracture rates remains unclear but some suggested hypotheses include risk factors that are more prevalent in the south when compared to the north. Some hypotheses include geographical variations in the presence of nutritional deficiencies, sunlight exposure, dietary fluoride consumption, and factors like poverty and rural location that are strongly associated with diet.[170]

The Northeast region consisted of the New England and Mid-Atlantic states of Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont. The Mid-West region consisted of Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota and

Wisconsin. The Southern region consisted of Alabama, Arkansas, Delaware, the District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, and West Virginia. The Western region consisted of Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oklahoma, Oregon, Texas, Utah, Washington and Wyoming.

Functional status markers

The analysis accounted for the presence of a personal assistance aid as a marker of functional status. Table 9 details the procedural codes used to identify claims for wheelchairs, walkers/canes, and modified bathroom equipment including claims for replacement parts for all three technologies. Patients with any claim during the baseline period for any of the three personal assistance technologies were coded as "1" for present in a binary variable.

Table 9. Procedural codes used to identify personal assistance aids

Personal assistance aid	Healthcare Common Procedure Coding System (HCPCS) codes
Use of wheelchair	E0950 – E1228, E1230, E1240 – E1298
Use of walker/cane	E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0105, E0100
Use of modified bathroom equipment	E0240 – E0248

A study of 4,952 dialysis patients within the USRDS found an independent association between the inability to ambulate and the relative risk of hip fracture (RR 1.84; 95% CI 1.10-3.06;p=0.019) but this relationship was not statistically significant in age, gender, and race adjusted analyses.[112] The ability to transfer was independently associated with an increased risk of hip fractures (HR = 3.0, 95% CI = 1.2–7.2) in a study of community dwelling, disabled, older adults.[171]

Treatment characteristics

The presence of a fistula was included as a treatment characteristic. Complications arising from vascular access issues are a leading cause of the morbidity observed in dialysis patients.[172] The vascular access variable accounted for whether a dialysis patient had an arteriovenous fistula (hereafter fistula) placed during the 180-day baseline period. The three primary forms of vascular access are the native arteriovenous fistula, arteriovenous fistula graft and central vein catheter.[172] The presence of a fistula was assessed using the Institutional Claims File and the HCPCS codes in Table 10 below.

Table 10. Procedural codes used to identify fistula creation

Fistula creation	**Healthcare Common Procedure Coding System (HCPCS) codes**
Arteriovenous anastomosis, open; by upper arm cephalic vein transposition	36818
Arteriovenous anastomosis, open; by upper arm basilic vein transposition	36819
Arteriovenous anastomosis, open; by forearm vein transposition	36820
Arteriovenous anastomosis, open; direct, any site (e.g., Cimino type) (separate procedure)	36821
Creation of arteriovenous fistula by other than direct arteriovenous anastomosis (separate procedure); autogenous graft	36825
Creation of arteriovenous fistula by other than direct arteriovenous anastomosis (separate procedure); nonautogenous graft (e.g., biological collagen, thermoplastic graft)	36830

Vascular access is important because early fistula placement is indicative of early nephrology care. Early nephrology care has in turn been associated with better management of comorbid conditions and adequate treatment of disturbances like renal-based anemia.[173]

In comparison to other access types, catheter use is least favorable and has been associated with an increased risk of central venous stenosis, thrombosis, inadequate dialysis, and infections like bacteremia, osteomyelitis, and endocarditis.[174] Among prevalent dialysis patients in Georgia, North Carolina and South Carolina, the adjusted odds of mortality were greater among patients dialyzed with a catheter compared to those dialyzed with a fistula (OR 1.4; 95% CI 1.1-1.9).[174] Fistula use, the preferred access type, compared to grafts, have a higher patency rate, lower rate of infection, and lower cost.[173]

4.4 Statistical analyses by aims

This section begins with a description of the statistical analyses that was used to create the case-adjusted vitamin D ecological variables introduced in the previous section. A description of all statistical analyses used by study aim follows. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

4.4.1 Analyses used to create case-mix adjusted measures of vitamin D exposure

Mixed-effects models were used to create the two case-mixed adjusted key vitamin D exposure variables. The general equation of the mixed-effects model was:

$$Y_{ij} = y_0 + y_1 X + (u_{0j} + e_{ij})$$

In this equation, *i* indicates the patient-level units of observation, *j* indicates the facility-level units of observation, and the subscript 0 indicates a constant term for the corresponding units.[175] The within facility correlation among the patient-level units is indicated by u_{0j}, the random effect.

To estimate the case-mix adjusted proportion of vitamin D users within each facility, we used a mixed-effect logistic regression model, an advantageous method when attempting to account for random variation. The outcome of the mixed-effect logistic regression model was a dichotomous variable indicating whether each patient received any dose of vitamin D during the 180-day baseline period (yes/no). The model adjusted for age (18-44, 45-64, 65-74, and ≥ 75 years old), sex, race (white, black, and other), and primary cause of ESRD (diabetes mellitus, hypertension, glomerulonephritis, and other) as fixed effects. Indicators for each patient's facility were included as random effects.

The case-mix adjusted proportion of vitamin D users at a facility (i.e., the percentage of patients at a facility prescribed vitamin D) was modeled as a normally distributed random intercept that represented the *expected* level of vitamin D treatment at each facility. In other words, an intercept was generated for each facility and that intercept represented the facility-specific vitamin D prescribing rate (the facility-specific case-mix adjusted proportion of vitamin D use). The distributions of the variables were graphed and the correlation between the non-case-mix and case-mix adjusted variables measuring the proportion of vitamin D users within each facility were assessed using a Pearson correlation coefficient (Appendix 5). The distribution of values for the intercept produced from the mixed-effects logistic regression model prior to additional adjustment is depicted in Appendix 9. The number of patients in a facility with each case-mix adjusted measure of vitamin D exposure was graphed (Appendix 6).

To estimate the case-mix adjusted average vitamin D dose per patient in each facility, we used a mixed-effect linear regression model. The outcome of this mixed-effect linear regression model was each patient's average vitamin D dose during the 180-day baseline

period. The model adjusted for age, sex, race, and primary cause of ESRD as fixed effects. Indicators for each patient's facility were included as random effects.

The case-mix adjusted average vitamin D dose per patient in each facility was modeled as a normally distributed random intercept and represented the *expected* average vitamin D dose per patient at each facility during the 180-day baseline period. In other words, an intercept was generated for each facility and that intercept represented the facility-specific vitamin D dosage rate for each patient. The distributions of the variables were graphed and the correlation between the non-case-mix and case-mix adjusted variables measuring the average vitamin D dose per patient within each facility were assessed using a Pearson correlation coefficient (Appendix 5).

A detailed description of all case mix characteristics can be found in the "Covariates" section. Specifically, both models adjusted for age, sex, race, Medicaid eligibility, the presence of various comorbidities (arteriosclerosis heart disease, cancer, cardiac dysrhythmia, cerebrovascular accident/TIA, COPD, congestive heart failure, diabetes, gastrointestinal bleeding, HIV/AIDS, hypertension, liver disease, other cardiac disorders, and peripheral vascular disease), primary cause of ESRD, prior history of parathyroidectomy, facility characteristics (profit status, practice setting, chain affiliation, size and region), use of personal assistance aids, the presence of a fistula, and calendar year.

4.4.2 Aim 1

This section presents an overview of all statistical analyses to be used for Aim 1.

Aim 1: To describe patient-level, facility-level and state-level trends in the use and dosage of three vitamin D analogs among prevalent hemodialysis patients.

Descriptive statistics, stratified by year, vitamin D use, and average vitamin D dose were presented for each major demographic characteristic (e.g. age, race, and sex). Annual percentages of patients treated with vitamin D were charted. The monthly and yearly percentage of patients treated with vitamin D was tabulated by key baseline covariates including age, race, sex and primary cause of ESRD.

Average vitamin D dose per patient at baseline was estimated by dividing the total dose administered to each patient by the total number of eligible patients. For the purposes of this analysis, we focused only on outpatient days at risk. Since we focused on facility practice patterns and to account for missing information during hospitalizations, inpatient hospital days were subtracted from total days at risk for each calendar month. The average annual vitamin D dose per users of each formulation were computed for all study years. Facility vitamin D formulation preference by year was tabulated and the results are presented in Appendix 4. Geographical trends in vitamin D use were described using the SAS PROC GMAP feature to depict the average vitamin D dose administered per patient per year at the state level. The PROC GMAP feature allows SAS users to graph two or three dimensional color maps by combining map and response data.[176]

4.4.3 Aim 2

This section describes the hypotheses for Aim 2, presents an overview of the main statistical approach used and explains the statistical analyses that were used to examine the association between vitamin D exposure and fracture risk.

Aim 2: To investigate the association between vitamin D exposure and fracture risk by fracture type and among relevant subgroups among incident hemodialysis patients.

Null Hypotheses

$H1_0$: There is no association between the non-case-mix proportion of vitamin D users within a dialysis facility and fracture risk.

$H2_0$: There is no association between the case-mix adjusted proportion of vitamin D users within a dialysis facility and fracture risk.

$H3_0$: There is no association between the non-case-mix average vitamin D dose per patient within a dialysis facility and fracture risk.

$H4_0$: There is no association between the case-mix adjusted average vitamin D dose per patient within a dialysis facility and fracture risk.

$H5_0$: There is no association between high case-mix adjusted average vitamin D doses per patient at the facility-level (the 75th percentile) and fracture risk.

Alternative Hypotheses

$H1_a$: The non-case-mix adjusted proportion of vitamin D users within a dialysis facility is negatively associated with fracture risk.

$H2_a$: The case-mix adjusted proportion of vitamin D users within a dialysis facility is negatively associated with fracture risk.

$H3_a$: The non-case-mix adjusted average vitamin D dose within a dialysis facility is negatively associated with fracture risk.

$H4_a$: The case-mix adjusted average vitamin D dose within a dialysis facility is negatively associated with fracture risk.

$H5_a$: High case-mix adjusted average vitamin D doses per patient at the facility-level (the 75^{th} percentile) are negatively associated with fracture risk.

The absolute standardized difference was used to compare baseline characteristics between vitamin D users and non-vitamin D users. Significant imbalance of baseline characteristics between groups was indicated by an absolute standardized difference (ASD) greater than 10.[177] Descriptive statistics were used to describe patient-level demographic and clinical characteristics by quartiles of the case-mix adjusted proportion of vitamin D users measure (Appendices 7 and 8).

Assessing fracture risk

Cox proportional hazards modeling was used to assess the independent association of each vitamin D-related predictor and fracture risk for fracture type and for any fracture. Separate cox proportional hazards models were constructed to assess the association of each-vitamin D exposure with fracture risk by subgroups of age (<65 versus ≥ 65 years old), sex, and race (black versus non-black) (Appendix 14). The dependent variable for all the Cox proportional hazards models was time to first fracture. The general form of the regression equation used was:

$$h_i(t) = h_0(t) + \exp(\beta_1(\text{demographic charactertistics})x_{i1} + \beta_2(\text{comorbidities})x_{i2} + \beta_3(\text{disease history characteristics})x_{i3} + \beta_4(\text{facility characteristics})x_{i4} + \beta_5(\text{functional status marker})x_{i5} + \beta_6(\text{treament history characteristics})x_{i6} + \varepsilon)$$

where i=individual observation, x=covariate, t=time, k=number of covariate[178]

The Cox proportional hazards model, also known as Cox regression, is a semiparametric model that is among the most widely used methods for multivariable survival analysis. It has several advantages in comparison to other approaches including its predecessor, the parametric model.[179] Foremost, Cox regression does not require information

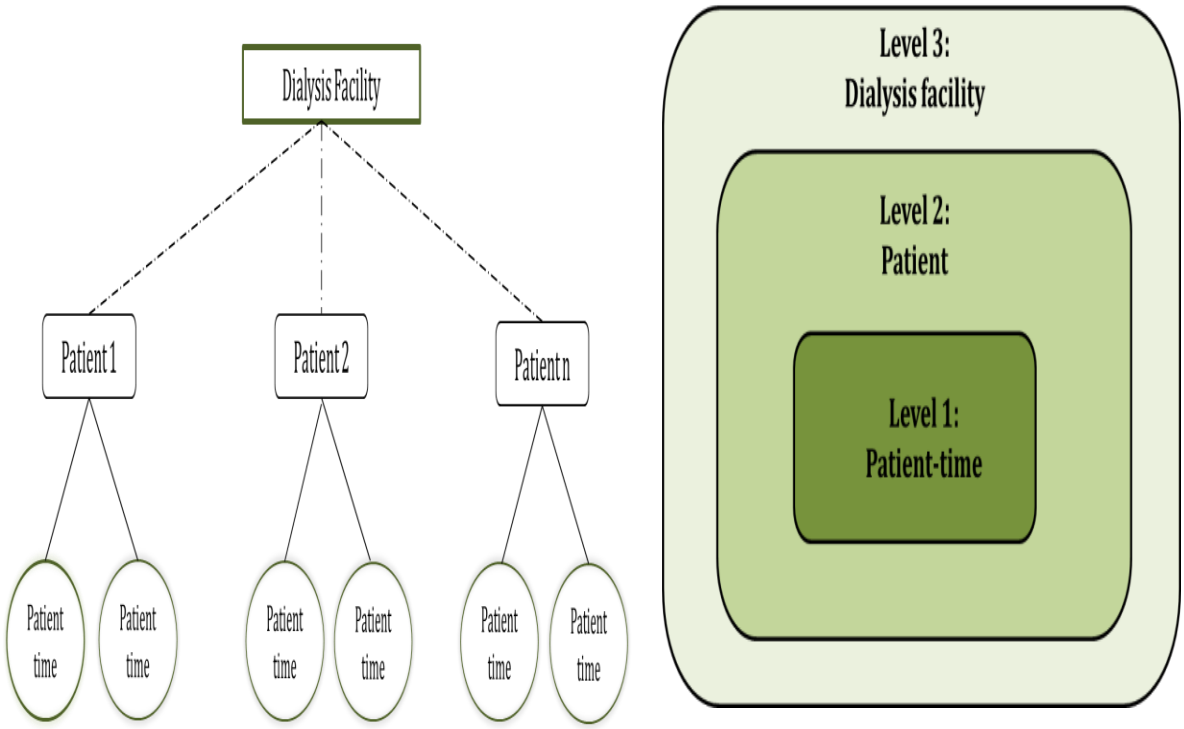
regarding the underlying distribution of survival times such that the same regression model can be used to analyze standard gamma, Weibull, log-normal or any of a range of survival distributions.[179] Secondly, the model allows for the inclusion of time-varying factors within the regression.[179] Moreover, as the name indicates, the hazard function for any two individuals is assumed to be constant, allowing the investigator to estimate necessary parameters without the need to specify a baseline hazard function.[179]

The Efron method was used to handle ties. Ties are defined as instances where two or more patients have the same study time value.[179] Like the Breslow and Exact method, the Efron method assesses the true time ordering of patients with equal study times.[179] The Efron method differs in its use of a numeric approximation to simply derive an estimate rather than assuming ties occurred sequentially or considering all possible orderings.[179] The proportional hazards assumption was verified using the Kolmogorov-type supremum tests based on 1,000 simulations (Appendix 10).

Kaplan-Meier methods were used to derive time to fracture curves depicting interaction between race and vitamin D user status (Appendix 11), sex and vitamin D user status (Appendix 12), and age and vitamin D user status (Appendix 13) at the individual-level. Moreover, it is extremely important to correct for autocorrelated data within a Cox regression. The Cox regression model assumes that independent observations, and, therefore, data from the same unit (patient-level data from individuals grouped within facilities) violates this assumption and engenders several major consequences. At the first level is patient-time data, nested in the patients who in turn are nested within dialysis providers at the third level (Figure 8).[180]

Patient-time refers to the very common repeated measures issue found in longitudinal data where outcome values measured repeatedly over time within the same patient will likely be correlated.[181] A practical example of this phenomenon can be seen in a pre-test/post-test experiment where the pre-test and post-test data are very much correlated because they are being collected from the same individual. With regards to this analysis, a patient's likelihood of experiencing an initial fracture is likely very much correlated with that same patient's likelihood of experiencing a second fracture at a later point in time.

Figure 8. Levels of analysis when studying ESRD population



These "patient-time" issues are nested within patient-level characteristics that have an influence on the outcome of interest. In this case, individual-level factors such as patient frailty, demographic characteristics, and disease history, for instance, all impact that

particular patient's likelihood of experiencing fractures. Patients then regularly attend dialysis facilities. Characteristics associated with the dialysis provider such as their profit-status, number of patients served, and geographic location additionally interact with these patient-level characteristics in predicting one's likelihood of experiencing fractures. If these auto-correlated data issues within a Cox proportional hazards model are ignored, tests of statistical significance may be inaccurate as standard errors would be biased downward while test statistics produced by the model would be biased upward.[179]

In order to avoid the effect of possible clustering, we used a robust sandwich estimate of the covariance matrix.[182] Separate models were constructed to independently model the association between each measure of vitamin D exposure and fracture risk. Each fracture type was a separate outcome.

Results from Cox regression models were expressed as hazard ratios (HR) with their corresponding 95% confidence intervals (CI). Statistical significance was assigned to p-values less than 0.05.

4.5 Sensitivity Analyses

To determine the robustness of our results, sensitivity analyses were performed to assess the effect of varying the value of certain key parameters. Foremost, we assessed results after varying the length of the study period from January 2000-May 2004 to January 2000-December 2008 (Appendix 16). Secondly, for the fracture-related outcomes of Aim 2, the effect of varying the length of the baseline period was examined. We reviewed the length of the exposure period among observational studies investigating the association between IV vitamin D and outcomes among hemodialysis patients (Appendix 18). This provided the

rationale for comparing demographic and clinical characteristics by facility quartile of the case-mix adjusted proportion of vitamin D users (Appendices 19-21). We also assessed the association between IV vitamin D exposure and fracture risk when the length of the baseline period has been changed to 30 days, 90 days, and 365 days, respectively (Appendix 22).

CHAPTER V

STUDY 1 RESULTS: TRENDS AND VARIATIONS IN INTRAVENOUS VITAMIN D USE AMONG HEMODIALYSIS PATIENTS IN THE UNITED STATES

5.1 Overview

Injectable vitamin D agents are commonly used to manage secondary hyperparathyroidism in dialysis patients. Yet, there are little data documenting the trends and geographic variations in the use of these agents in large, representative samples. We sought to describe patterns and variations in the use of vitamin D formulations (calcitriol, paricalcitol, doxercalciferol) in hemodialysis patients. We studied patients in the United States Renal Data System (USRDS) between January1999 and December 2008 with Medicare as a primary payer. Annual percentages of patients treated with each type of formulation were tabulated by race, sex, and age at dialysis initiation. The geographical distribution of vitamin D dose per patient was mapped at the state level. Intravenous vitamin D use has increased sharply from 1999 to 2008 with 83.9% of patients treated with any vitamin D formulation in 2008. The use of calcitriol has declined since 1999, going from being administered in 58.6% of patients in 1999 to 1.8% in 2008.

This chapter presents the results in manuscript form for Aim 1. An overview, introduction, methods, results and discussion of the study are provided. This study sought to describe patient-level, facility-level, and state-level trends in the use and dosage of three vitamin D analogs by relevant patient subgroups. Study 1 was published in the journal Renal Failure in 2013 (Beaubrun AC, Brookhart MA, Sleath B, Wang L, Kshirsagar AV. Trends and Variations in Intravenous Vitamin D Use among Hemodialysis Patients in the United States. Renal Failure. 2013;35(1):1-8).

Paricalcitol was found to be the overwhelmingly preferred formulation during the study years. In 2008, the average dose among black patients was 84% greater than among white patients (136 mcg versus 73.6 mcg). Higher doses of vitamin D were administered to patients in the southern region of the country. Vitamin D use has increased and parallels the rise in use of paricalcitol and doxercalciferol. Given the variations in use and known pharmacologic differences in vitamin D formulations, future research should focus on whether the formulations differentially affect patient outcomes.

5.2 Introduction

Secondary hyperparathyroidism (SHPT), characterized by elevated parathyroid hormone (PTH) levels, is a common complication found in hemodialysis patients.[2] SHPT induced changes in bone histology coupled with increased serum phosphorous and calcium levels, have all been implicated as factors partially responsible for the increased morbidity and mortality observed in hemodialysis patients in comparison to individuals in the general population.[30] The suppression of PTH levels through activated vitamin D therapy has been central to the treatment of SHPT in the dialysis population.[2] Vitamin D therapy helps to maintain appropriate mineral metabolism, prevents bone disease, and minimizes loss of bone strength and fractures.[18] Additionally, treatments for SHPT aim to prevent the numerous extraskeletal complications that may be associated with the high cardiovascular morbidity observed in end-stage renal disease (ESRD).

Currently there are three commonly prescribed intravenous (IV) vitamin D therapies: calcitriol (1α,25-dihydroxyvitamin D3; Calcijex, Abbott Laboratories, North Chicago, IL, USA), paricalcitol (19-nor-1α,25-dihydroxyvitamin D2; Zemplar, Abbott Laboratories) and doxercalciferol (1α-hydroxyvitamin D2; Hectorol, Genzyme). There have been several studies describing patient-level predictors of vitamin D use in the dialysis population.[60, 61] These studies have found that dialysis patients administered vitamin D are generally younger, more likely to be black, and were more likely to have a fistula or graft.[95] However, to date, studies reporting temporal trends in the use of IV vitamin D formulations have been conducted using small sample sizes and none have graphically depicted geographic patterns of vitamin D use.[183]

In the present study, we address this gap in the literature. Using data on US hemodialysis patients in Medicare's ESRD program between January 1, 1999 and December 31, 2008, we report patterns in IV vitamin D dosing and formulation choice over time and across geographic regions.

5.3 Methods

5.3.1 Data source

Data were extracted from the United States Renal Data System (USRDS). The USRDS contains detailed demographic and treatment information including the date of dialysis initiation for all patients beginning renal replacement therapy. All Medicare Part A and B claims are also included within the USRDS dataset, including diagnosis and procedure codes for inpatient and outpatient visits.

5.3.2 Study design and patient population

The study cohort consisted of prevalent hemodialysis patients of all ages between January 1, 1999 and December 31, 2008. Patients were required to have Medicare as a primary payer for the duration of the follow-up period. Patients were eligible if hemodialysis was their initial mode of renal replacement therapy and no adjustments were made to account for any later switches in treatment modality.

5.3.3 Patterns of vitamin D use assessment

Medicare Part A outpatient revenue files were used to identify IV vitamin D administered to hemodialysis patients. Healthcare Common procedure Coding System (HCPCS) J codes were used to identify vitamin D claims. Calcitriol use was identified using HCPCS codes J0635 (1mcg) and J0636 (0.1mcg). The codes J2500 (5mcg) and J2501 (1mcg) were used to identify paricalcitol and J1270 (1mcg) identified doxercalciferol use.

The mean annual vitamin D dose of each formulation per patient was computed for all study years for all patients and by race. A patient was defined as a vitamin D user during each study year if they were administered any dose of any of the three formulations. Variations in IV vitamin D use were assessed according to the annual percentage of patients treated with any vitamin D formulation by race, sex and age at dialysis initiation (<18, 18-34, 35-44, 45-54, 55-64, ≥65). Race was classified as "white" or "black".

To obtain the total and mean annual doses of vitamin D administered to each patient, annual doses of paricalcitol and doxercalciferol administered to each patient were converted to calcitriol-equivalent doses according to conversion ratios derived by St.Peter and colleagues. (4.6:1 for paricalcitol:calcitriol and 3.1:1 for doxercalciferol:calcitriol).[93] Since the administration of vitamin D to hemodialysis patients may not be accurately captured

during hospital stays, annual vitamin D dose during the total number of outpatient days during the year was tabulated. The number of hospitalization days per year per patient remained constant from 1999 to 2008 and, therefore, restricting our exposure period to only outpatient days should not impact our results.

5.3.4 Statistical analyses

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC). Descriptive statistics were used to tabulate the percentage of vitamin D users per year by subgroup, total, and mean annual doses of vitamin D. Geographical trends in vitamin D were described using the SAS PROC GMAP option to depict the mean vitamin D dose administered per patient at the state level. The PROC GMAP feature allows SAS users to graph two or three dimensional color maps by combining map and response data.[176] Geographical trends were presented among the whole eligible patient population of blacks and whites and also among only black patients to elucidate any racial influences on geographical variations in annual vitamin D dose per patient.

This study was exempt from review by the University of North Carolina at Chapel Hill Institutional Review Board.

5.4 Results

Table 11 describes the baseline characteristics of the prevalent hemodialysis cohort in years 1999-2008. The study population consisted of 225,022 patients in 1999 and 315,608 patients in 2008. The mean patient age was consistently 59 years old (SD=17) throughout the 10-year study period. There were 52.0% males in 1999, increasing to 54.3% in 2008. The percentage of white and black patients remained consistent during the 10 year study

period at approximately 57% and 37%, respectively. Diabetes as the primary cause of renal failure increased from 41.1% of the study population in 1999 to 44.7% in 2008 while glomerulonephritis as the primary cause of renal failure decreased from 14.1% of patients to 11.4%. Approximately 29% of all patients reported hypertension as the primary cause of renal failure in all study years.

Table 11. Baseline characteristics of patients between 1999-2008

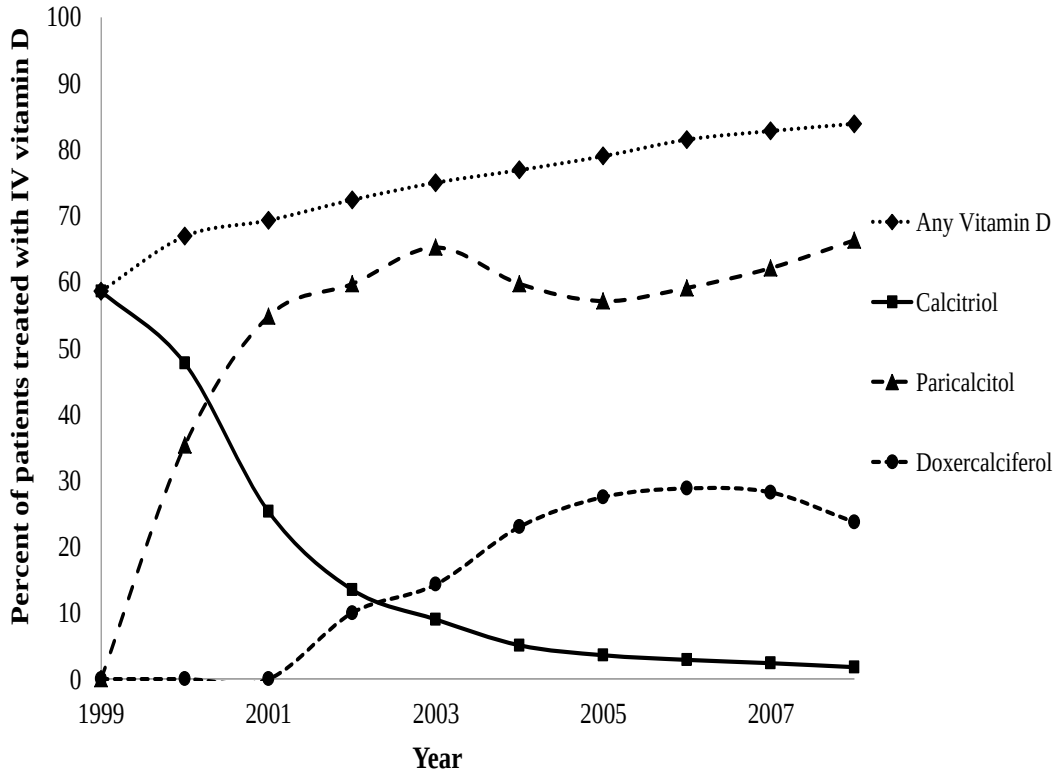
						Cause of ESRD		
Year	**N**	**Mean Age[a] (SD)**	**Male (%)**	**White (%)**	**Black (%)**	**Hypertension (%)**	**Diabetes (%)**	**GN[b] (%)**
1999	225,022	59.0 (17.0)	52.0	56.5	37.8	29.9	41.1	14.1
2000	235,917	59.1 (17.0)	52.2	56.7	37.6	29.6	41.7	13.8
2001	250,940	59.3 (17.0)	52.3	57.0	37.2	29.4	42.5	13.3
2002	268,680	59.6 (17.0)	52.8	57.4	36.9	29.4	42.9	13.0
2003	278,938	59.6 (16.9)	53.0	57.3	36.9	29.4	43.4	12.6
2004	291,255	59.6 (16.9)	53.4	57.2	36.9	29.5	43.7	12.3
2005	301,534	59.5 (16.9)	53.7	57.2	36.7	29.4	44.1	12.1
2006	304,273	59.4 (16.9)	53.9	57.1	36.9	29.3	44.4	11.8
2007	307,919	59.2 (16.9)	54.2	57.0	37.0	29.2	44.5	11.6
2008	315,608	59.1 (16.8)	54.3	57.0	37.0	29.2	44.7	11.4

[a]Age at dialysis initiation
[b]Primary or secondary glomerulonephritis

Figure 9 depicts the annual percentage of patients treated with each vitamin D formulation from January 1999 to December 2008. IV vitamin D use has increased sharply from 1999 to 2008 with 58.6% of patients treated with any vitamin D formulation in 1999 to approximately 84% treated with any vitamin D formulation in 2008. The use of calcitriol has

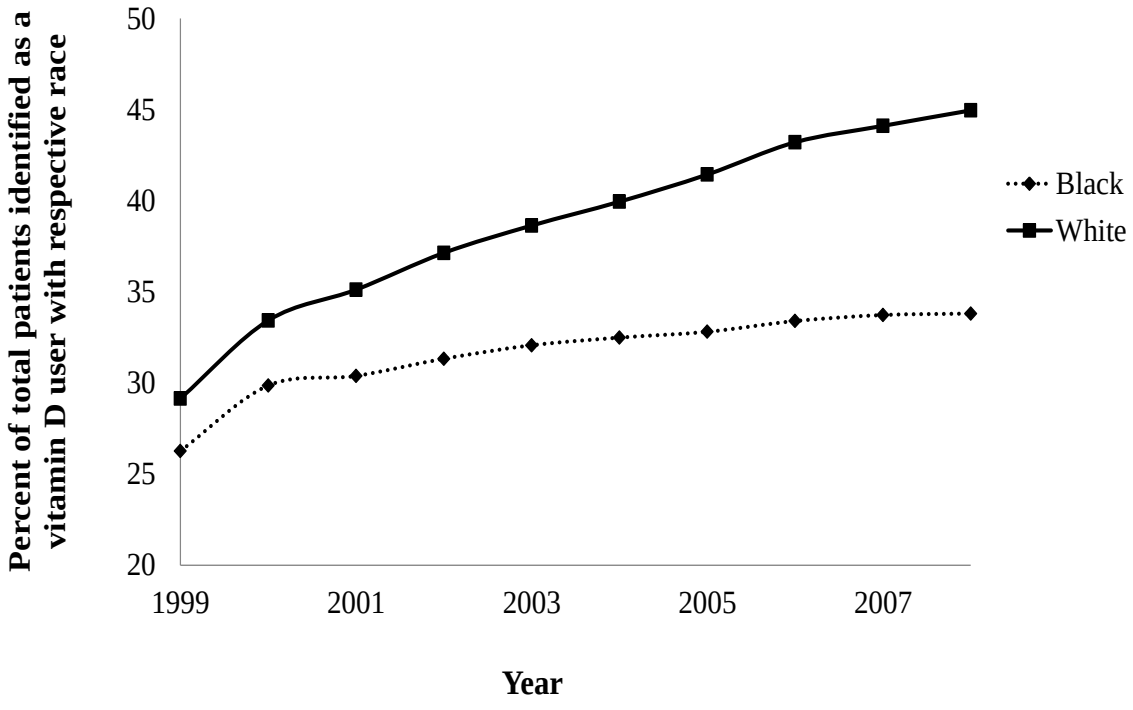
declined since 1999, going from being administered in 58.6% of patients in 1999 to 1.8% in 2008. Paricalcitol was the overwhelmingly preferred formulation. Between 2000 and 2008, the annual percentage of patients administered paricalcitol increased from 35.6% to 66.3%. Paricalcitol use peaked at 65.2% of patients in 2003, declined slightly to 59.7% of patients, then again increased to 66.3% in 2008. Doxercalciferol use in the hemodialysis cohort began in 2002 with 10% of patients administered the drug, steadily increased to a peak of 28.8% of patients treated with doxercalciferol in 2006 and has begun to slightly decline to 23.7% of patients treated in 2008.

Figure 9. Annual percentage of patients treated with intravenous vitamin D by formulation



The annual percentage of patients treated with vitamin D by race is presented in Figure 10. In 1999, approximately 26% of the total patient population was black vitamin D users while 29% of vitamin D users were white. Both the percentage of white and black vitamin D users increased steadily from 1999 to 2008. Approximately 34% of the prevalent patient population was black vitamin D users in 2008 and the percentage of white vitamin D users increased to 45%.

Figure 10. Annual percentage of intravenous vitamin D users by race



Racial variations in vitamin D dose are shown in Table 12. In 1999, when calcitriol was the only IV formulation administered, white patients received an average dose of 47.7 mcg while black patients received approximately 46% more vitamin D at an average dose of 70 mcg. Black patients were administered nearly twice as much vitamin D than white

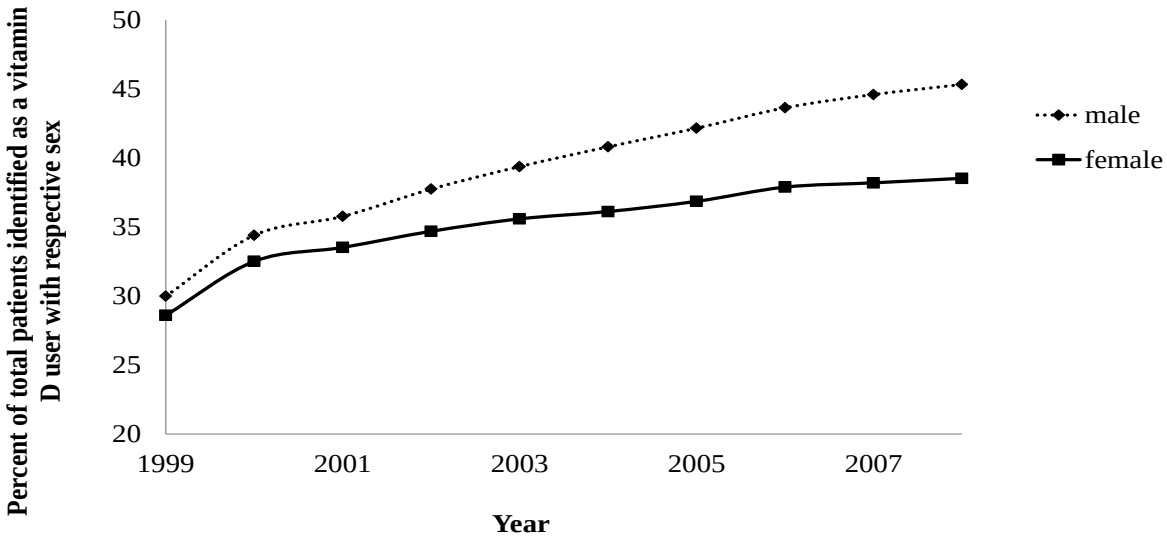
patients annually between 2000 and 2006. In 2007, black patients received 88% more vitamin D than white patients (average dose 129.7 mcg for blacks versus 69.l mcg for whites) and in 2008, black patients received 84% more vitamin D than white patients (average dose 136 mcg versus 73.6 mcg).

Table 12. Mean annual IV vitamin D dose (mcg) administered per patient by race

Year	Race	
	White	Black
1999	47.7	69.6
2000	45.1	92.8
2001	53.0	104.3
2002	59.0	117.7
2003	51.9	113.0
2004	55.6	117.9
2005	61.1	121.4
2006	65.9	127.9
2007	69.1	129.7
2008	73.6	136.0

Figure 11 depicts the annual percentage of patients administered vitamin D by sex. Approximately 30% percent of all patients were male vitamin D users in 1999. In 2008, about 45% of all patients were male vitamin D users.

Figure 11. Annual percentage of intravenous vitamin D users by sex



Approximately 1% of all patients were vitamin D users under 18 years old and this remained constant between 1999 and 2008. Approximately 5% of all patients and 7% were between 18 and 34 years old in 1999 and 2008, respectively. Approximately 12% of patients were vitamin D users between 55 and 64 years old in 1999 and increased to 18% in 2008 while approximately 25% of patients were vitamin D users at least 65 years old in 1999, increasing to 33% in 2008.

Annual trends in the mean dose administered of each vitamin D formulation among the users of that respective formulation are listed in Table 13. The average annual calcitriol dose per calcitriol user has declined over the past decade, reflecting the decreased administration of the formulation. In 1999, on average, 94.9 mcg (SD=3,458) of calcitriol was administered per calcitriol user. In 2008, the average calcitriol dose per calcitriol user was 69.8 mcg (SD=87.6). With regards to paricalcitol, the average annual dose per paricalcitol user increased from 7.97 mcg (SD=4.49) in 1999 to 105 mcg (SD=118) in 2008.

The average annual dose of doxercalciferol per doxercalciferol user also increased steadily from 1999 to 2008.

Table 13. Mean annual IV vitamin D dose (mcg) administered per patient by formulation

Year	Calcitriol Mean Dose (SD)	Paricalcitol Mean Dose (SD)	Doxercalciferol Mean Dose (SD)
1999	94.9 (3,458)	7.8 (4.49)	0.0 (0.0)
2000	74.8 (320.3)	79.5 (431)	0.0 (0.0)
2001	70.6 (216.0)	99.4 (389)	0.0 (0.1)
2002	74.3 (150.3)	108.0 (552)	6.3 (42.9)
2003	81.2 (1,802)	90.6 (144)	8.4 (32.1)
2004	72.6 (146.1)	91.6 (124.8)	89.3 (158)
2005	73.4 (93.2)	95.8 (195)	95.5 (85.7)
2006	78.4 (92.7)	97.0 (110)	103.0 (137)
2007	78.2 (97.2)	96.6 (103)	107.0 (120)
2008	69.8 (87.6)	105.0 (118)	112.0 (111)

Geographical trends in the average annual dose of vitamin D administered per patient among all eligible patients are depicted in Figure 12. In 1999, only 7 states had a mean annual dose of vitamin D per patient greater than 60mcg (South Dakota, Minnesota, Iowa, Kentucky, Delaware, Mississippi, and South Carolina) with patients administered the highest vitamin D doses in South Dakota and Kentucky. In contrast, 18 states had an average annual vitamin D dose per patient greater than 60mcg in 2000 with 4 of the 6 states with average doses between 80mcg and 100mcg clustered in the south (Louisiana, Mississippi, Alabama and South Carolina). The highest doses of vitamin D per patient were administered in California, northeast, and southern region of the country in 2002. In 2002, Delaware, South Carolina, Mississippi and Kansas had an average annual vitamin D dose per patient greater than 100mcg. In 2008, 14 states had a mean yearly vitamin D dose per patient greater than 100 mcg (Connecticut, New Jersey, Delaware, Maryland, Virginia, North Carolina, South Carolina, Tennessee, Georgia, Alabama, Mississippi, Louisiana, Texas, and Illinois). Figure

13 depicts geographical trends in the average annual vitamin D dose per patient among only black patients. When the population was restricted to only black patients, in 2008, only 5 states (Idaho, Montana, Utah, Colorado, and South Dakota) had an average annual vitamin D dose per patient less than 100 mcg.

Figure 12. Annual intravenous vitamin D dos per patient by state among both white and black patients, 1999-2008

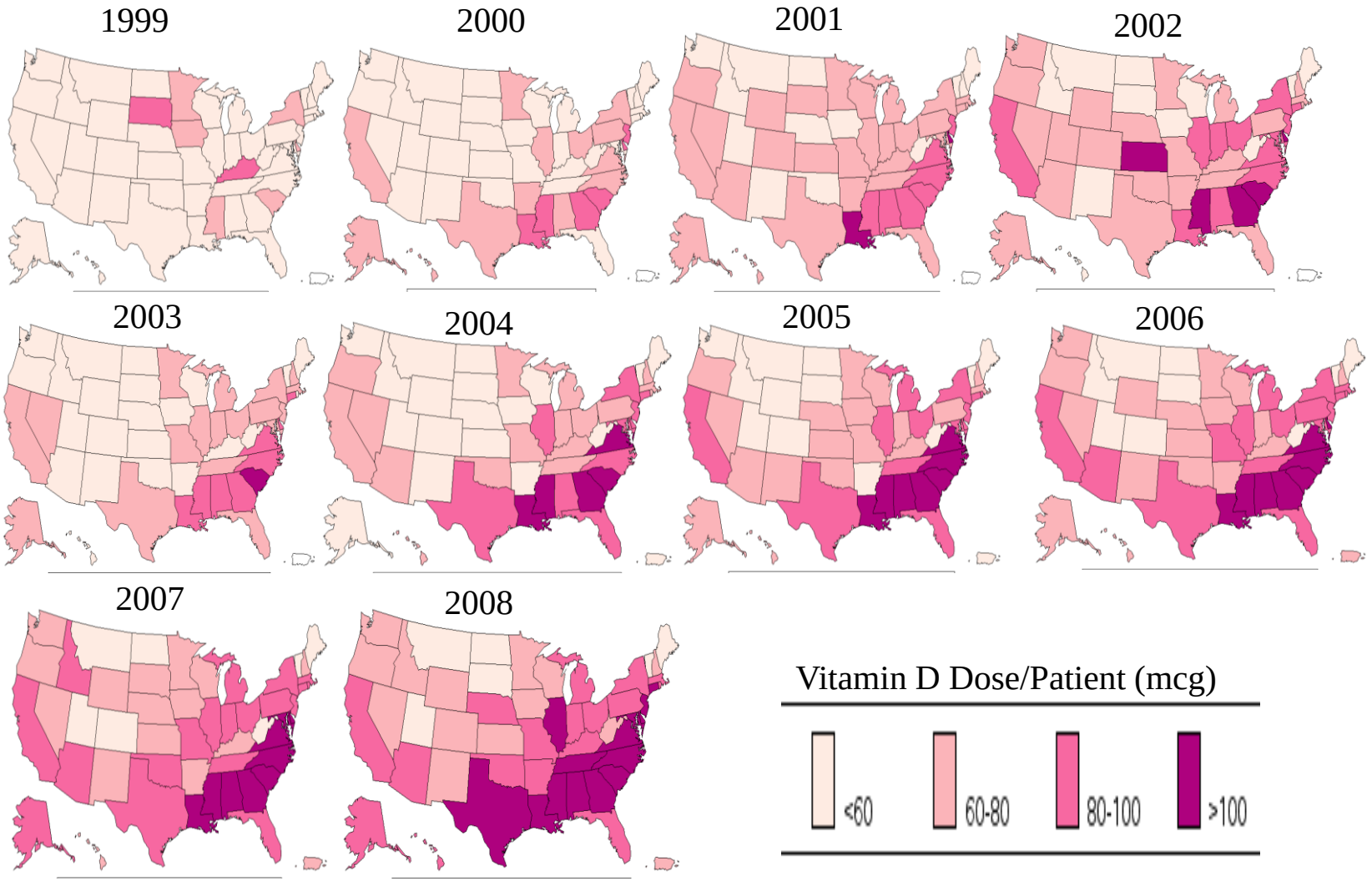
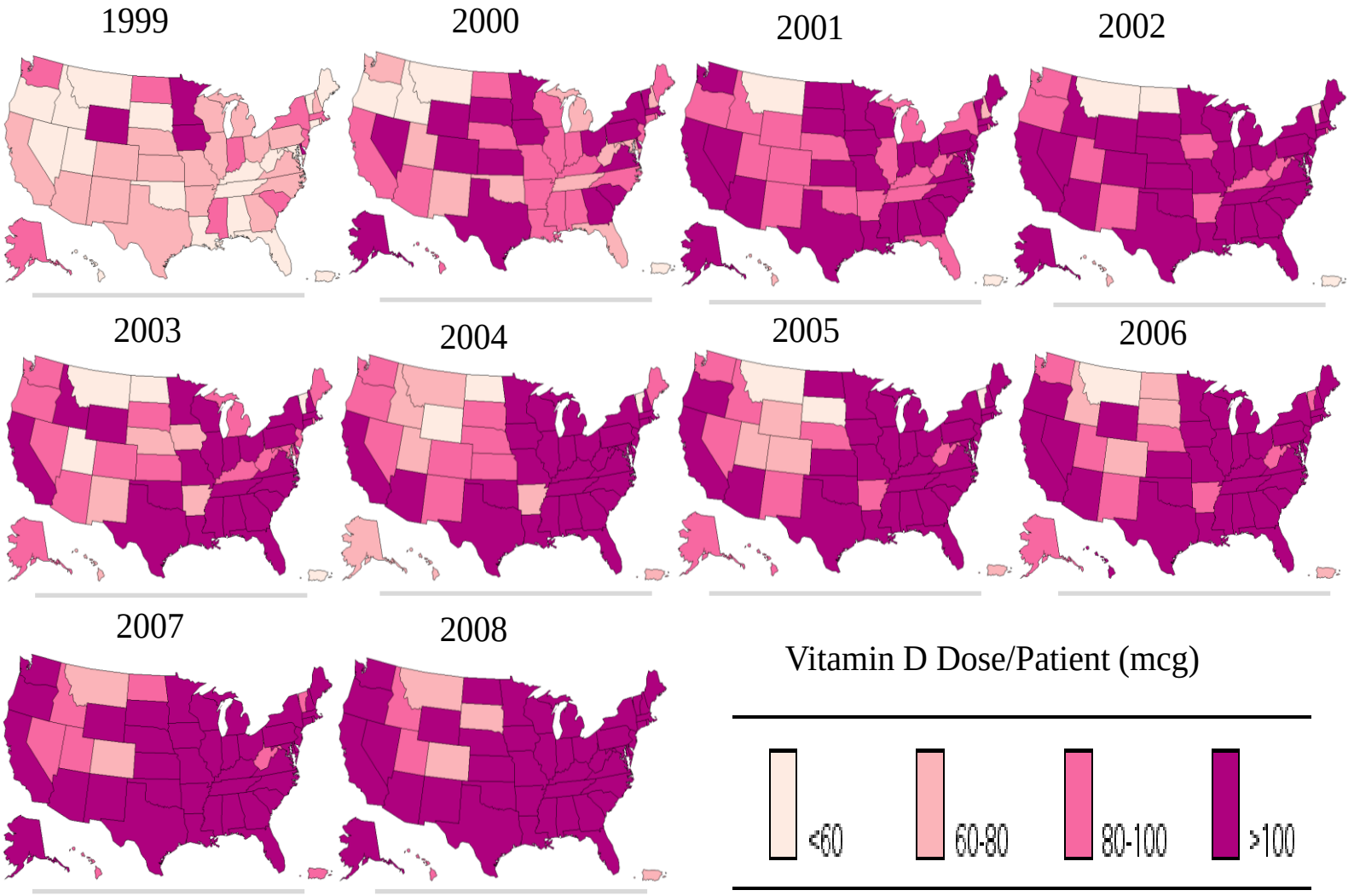


Figure 13. Annual intravenous vitamin D dos per patient by state among only black patients, 1999-2008



5.5 Discussion

This study investigated secular trends and variations in the administration of specific vitamin D analogs in hemodialysis patients. The data suggest that there have been a substantial increase in the use of vitamin D among hemodialysis patients in the United States between 1999 and 2008. As of 2008, approximately 84% of the USRDS population used IV vitamin D. With regards to formulation-specific patterns of utilization, calcitriol use has declined sharply since 1999. In contrast, paricalcitol was the most frequently administered formulation in the United States with 66.3% of patients treated with the analog in 2008. Doxercalciferol use declined steadily since its peak usage of 28.8% of patients in 2006.

The study presented herein is unique in its use of a relatively large population of over 300,000 patients in the most recent years of available data until 2008. It should be noted that the Dialysis Outcomes and Practice Patterns Study (DOPPS), a prospective cohort study of hemodialysis patients in 19 countries, released recent data regarding trends in IV vitamin D formulation use and dose in the US.[183] Unlike this study, however, DOPPS investigators based their observations on a relatively small sample of less than 4,000 US dialysis patients. Consistent with the results of this study, the DOPPS study reported that in August of 2010, 85.3% of the sample used only paricalcitol, 13.6% used only doxercalciferol, and 1.0% used only calcitriol. However, in December 2011, the percentage of patients using only paricalcitol decreased to 55.5%, doxercalciferol users increased to 44.2% and the percentage of calcitriol users was 0.1%.

Clinical differences between the three formulations may explain the changes over time in IV vitamin D formulation choice. The first available vitamin D analog, calcitriol, can effectively lower serum PTH levels.[57] However, calcitriol administered in dialysis patients

has been associated with elevated serum calcium and phosphorous concentrations.[44] The risk of hypercalcemia may increase when calcitriol is used simultaneously with calcium-based phosphorous binders or dialysate with high calcium concentrations.[57] The vitamin D2 analogs, paricalcitol and doxercalciferol, are also considered mainstream therapy among dialysis patients.[57] Both vitamin D2 analogs, like calcitriol, can effectively lower PTH levels but do so with a smaller effect on serum calcium and phosphorous concentrations compared to calcitriol.[57] Several studies have demonstrated equivalent or even superior PTH level suppression with the use of either paricalcitol or doxercalciferol compared to calcitriol.[58]

The preponderance of paricalcitol use within the hemodialysis population as demonstrated by the data, however, does not decrease the need to explore the comparative effectiveness of IV vitamin D agents. A meta-analysis of randomized controlled trials of chronic kidney disease patients demonstrated both potentially beneficial and detrimental effects of vitamin D compounds like paricalcitol and doxercalciferol introduced into the market after calcitriol. Paricalcitol and doxercalciferol vitamin D compounds were shown to significantly reduce PTH levels by about 11pmol/L but they also simultaneously increase phosphorous levels.[58] Reduced PTH levels may correspond to a decrease in patient mortality risk by approximately 5% to 10% over a 3 year span but the increase in phosphorous concentrations may increase mortality by an equivalent amount.[58]

The most striking differences in vitamin D use were found in comparisons of annual vitamin D dose per patient between black and white patients. Although the percentage of black patients receiving vitamin D was less than the percentage of white patients over the past decade, black patients have continued to receive nearly twice as much of the drug in comparison to whites. This greater use is possibly a result of pervasive vitamin D deficiency

associated with individuals with darker pigmented skin. In the general population, 90% of Mexican Americans and nearly all non-Hispanic blacks (97%) currently suffer from vitamin D deficiency.[34] Additionally, black hemodialysis patients generally have higher intact PTH levels in comparison to other races.[19] Gupta and colleagues reported an average PTH level of 641.7 in black and 346.0 in white dialysis patients.[31] Therefore, the greater severity of SHPT among black patients may be associated with the greater vitamin D dose administered to these individuals in comparison to whites.

Our findings are consistent with the finding by Kalantar-Zadeh and colleagues demonstrating that African Americans had twice the odds of receiving a higher dose of paricalcitol (>10µg/week) than other races in a study of ESRD patients in a large dialysis organization.[184] Also, the greater administration of IV vitamin D to black dialysis patients is reflected in cost figures from the 2011 USRDS Annual Data Report. In 2008, IV vitamin costs were 78% greater for black compared to white patients within the prevalent dialysis population with vitamin D costs reaching $1,824 per patient per year for blacks.[3]

Moreover, since 1999, higher doses of vitamin D per patient were found in the southern region of the United States in states like Mississippi, Louisiana, and Alabama. St.Peter and colleagues have also reported geographic variations in injectable drug use among the dialysis population.[185] For instance, the authors found the greatest use of IV iron in Alaska and eastern Texas while the lowest percentages of IV iron were found in the central region of the country.[185] Patient, facility and policy level factors contributing to the geographic differences in injectable drug administration to hemodialysis patients merits further investigation. More research is needed to investigate how the greater administration

of vitamin D doses to black patients or individuals with higher body mass indexes impacts the observed regional differences in vitamin D administration.

The study has important limitations. Since Medicare Part A data within the USRDS is collected primarily for administrative purposes, we can not know whether the amount of vitamin D dose billed actually reflects the amount of vitamin D received for each patient. The dosage reflected in vials billed for a particular formulation may not accurately capture partial doses administered. Also, administration of vitamin D is guided primarily by patient serum PTH levels, a variable not available in the USRDS.

Our data suggest that the frequency and doses of vitamin D are increasing. Patterns of prevalent vitamin D use at different times over a decade, shows that while use of vitamin D in general has increased, calcitriol and doxercalciferol use have both decreased while paricalcitol emerged, at least temporarily, as the dominant formulation. Recent controversy regarding the therapeutic effects of vitamin D in ESRD has sparked interest in the comparative effectiveness and safety of vitamin D formulations. Given the increase in dose and variation in use of these formulations, more research is needed to investigate the comparative differences in patient health outcomes resulting from the use of paricalcitol versus doxercalciferol versus calcitriol.

CHAPTER VI

STUDY 2 RESULTS: INCREASING USE OF INTRAVENOUS VITAMIN D MAY NOT REDUCE FRACTURE RISK AMONG HEMODIALYSIS PATIENTS

6.1 Overview

The administration of intravenous (IV) vitamin D therapy has been central to the treatment of secondary hyperparathyroidism (SHPT) and other bone mineral disorders; however its clinical benefits are not clear. The objective of this analysis was to examine the association between IV vitamin D exposure and fracture risk among hemodialysis patients, by fracture type. A retrospective cohort study was conducted using Medicare claims from the United States Renal Data System. Incident hemodialysis patients between 01/01/2000 and 05/31/2004 who survived at least 90 days post the initiation of dialysis therapy entered a 180-day baseline period where vitamin D exposure was assessed. After the baseline period, the time to the first fracture hospitalization was assessed during a 12-month follow-up period. The key measures of vitamin exposure were ecological variables measured at the facility-level during the baseline period: 1) the proportion of vitamin D users in each facility (derived using mixed-effects logistic regression); and 2) the average vitamin D dose per patient in

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This chapter presents the results in manuscript form for Aim 2. An overview, introduction, methods, results and discussion of the study are provided. This study sought to examine the association between vitamin D exposure and fracture risk by fracture type and among relevant subgroups.

each facility (derived using mixed-effects linear regression). Fractures were identified at the individual-level and grouped into four categories. Multivariable Cox proportional hazard regression models adjusted for demographic, treatment, health status, and facility-level characteristics. A total of 135,958 patients within 4,021 facilities were eligible for cohort inclusion. No significant relation was observed between increasing vitamin D use or increasing vitamin D dose per patient at the facility-level and fracture risk for all fracture types in both crude and multivariable adjusted analyses. Specifically, for any fracture, the hazard ratio (HR) in adjusted models for a facility's proportion of vitamin D users was 1.10 (95% CI 0.86-1.42) while the HR for a facility's average vitamin D dose per patient was 0.99 (95% CI 0.90-1.09). In summary, increasing vitamin D use and increasing average vitamin D dose administered per patient within dialysis facilities did not have an observed beneficial association with fractures.

6.2 Introduction

In the end-stage renal disease (ESRD) population, fractures are common, costly, and associated with increased morbidity and mortality.[74, 80, 81, 88] After experiencing a hip fracture, dialysis patients have a one-year survival rate of approximately 50%[81] and patients experience 3-5 hospitalizations within 1 year of fracture.[189] Secondary hyperparathyroidism (SHPT)-induced variations in bone histology and increased serum phosphorous and calcium levels, have all been implicated as factors in part responsible for the increased fracture risk, morbidity and mortality observed in hemodialysis patients.[30]

Intravenous (IV) vitamin D is widely prescribed to hemodialysis patients for the treatment of SHPT and its use has increased over the past 10 years.[183, 186] In 2008, 84% of

dialysis patients received IV vitamin D.[186] During our study period, IV vitamin D reimbursement was based on the total units of the drug administered, a payment structure prompting large increases in vitamin D dosage and expenditure.[11] With recent changes to reimbursement expected to foster substantial decreases in vitamin D dosage for cost-efficiency purposes[1], it is imperative that we understand whether variations in vitamin D dosage influence important clinical outcomes like fracture risk.

Administration of IV vitamin D has been shown to be effective at suppressing the elevated serum parathyroid hormone (PTH) levels that characterize the SHPT,[5, 30, 187] but the clinical benefit of IV vitamin D in the dialysis population remains unclear. The existing trials of vitamin D are small and have limited follow-up and have mostly focused on the effects of vitamin D on PTH levels.[58] It is unknown whether PTH is an adequate surrogate marker for fracture risk.[88, 112]

To address this gap in the evidence, we conducted a large-scale retrospective study of the effectiveness of IV Vitamin D therapy on fracture risk. We employed a statistical approach that uses variation in vitamin D usage practices across dialysis facilities as the basis of a natural experiment to account for expected strong confounding by indication bias.[124, 188]

6.3 Methods

6.3.1 Data source

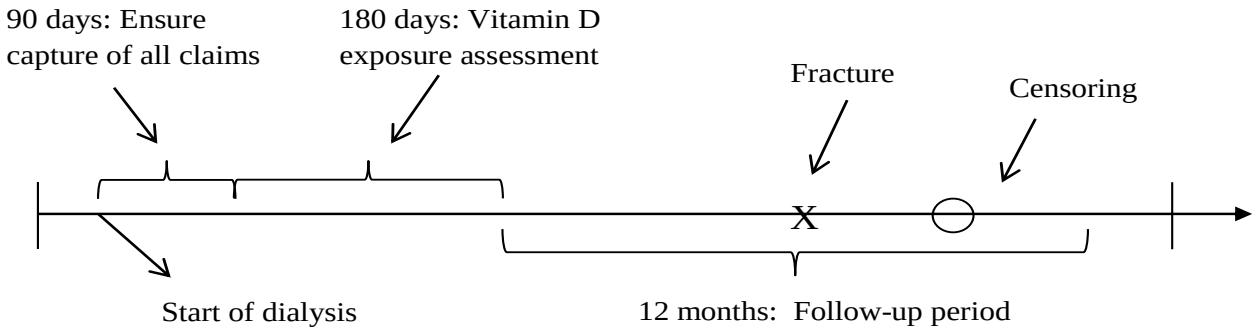
Medicare claims were derived from the United States Renal Data System (USRDS), a registry that collects, analyzes, and distributes national data on all ESRD patients in the United States. All Medicare Part A and B claims are included within the USRDS Standard Analytical Files (SAFs). Institutional claims within Medicare Part A are comprised of all

inpatient, outpatient, skilled nursing facility, home health agency, and hospice claims. Medicare Part B Physician/Supplier claims include durable medical equipment charges along with physician services and supplies. The USRDS Patient File contains information describing patient race, age, date of death, first service date, and other demographic characteristics. The USRDS Facility File contains dialysis facility-level data derived from the CMS Annual Facility Survey (CMS-2744), a survey that all centers are mandated to complete each calendar year. Death data was obtained from the CMS-2746 ESRD Death Notification Form, providing the date of death for over 99% of patients.[3]

6.3.2 Study design and cohort selection criteria

We conducted a retrospective cohort study using USRDS data. Incident, in-center hemodialysis patients within the USRDS dataset between January 1, 2000 and May 31, 2004 who survived at least 90 days post the initiation of dialysis therapy entered a 180-day baseline period where vitamin D exposure and covariates were assessed (Figure 14).

Figure 14. Study design diagram



Patients were eligible if they had Medicare as a primary payer throughout the baseline and follow-up period, had at least 120 days of claims during the baseline period, and if they were older than 18 years of age at dialysis initiation. Patients who experienced a fracture during the baseline period, patients without a facility identified in the dataset and patients in a

facility with less than 5 hemodialysis patients were excluded. After the baseline period, the time to the first fracture hospitalization was assessed during a 12-month follow-up period.

In March 2004, the Food and Drug Administration (FDA) approved the use of cinacalcet hydrochloride[136]. In May 2004, cinacalcet became commercially available and approximately 10% of patients dialyzed by a large for-profit provider received the drug between August to October 2004.[137] To avoid possible confounding effects resulting from the availability of an alternative therapy for SHPT, the association between vitamin D exposure and fracture outcomes was assessed solely in a pre-calcimimetic cohort between January 1, 2000 and May 31, 2004.

6.3.3 Measurement of vitamin D exposure

Vitamin D use was derived from Medicare Part A institutional claims and identified using Healthcare Common Procedure Coding System (HCPCS) codes J0635 (1µg) and J0636 (0.1µg) for calcitriol, J2500 (5µg) and J2501 (1µg) for paricalcitol and J1270 (1µg) for doxercalciferol use. Doxercalciferol and paricalcitol doses were converted to calcitriol-equivalent doses using dosing conversions established in clinical practice (1:2.28 for calcitriol to doxercalciferol and 1:4 for calcitriol to paricalcitol). [145, 146] The key measures of vitamin D exposure were ecological variables measured at the facility-level during the 180-day baseline period: 1) the case-mix adjusted proportion of vitamin D users in each facility; and 2) the case-mix adjusted average vitamin D dose per patient in each facility. Employing a strategy reported by Tentori and colleagues, the case-mix adjusted vitamin D treatment variables reflect a facility's propensity to prescribe vitamin D after accounting for various characteristics that may influence the dose and whether patients within a facility are administered the drug.[95]

Mixed-effects logistic regression was used to estimate the case-mix adjusted proportion of vitamin D users within each facility. The outcome of the model, adjusting for age, sex, race (white, black, or other), and primary cause of ESRD (hypertension, diabetes, or other), was a dichotomous variable indicating whether each patient received any dose of vitamin D during the 180-day baseline period with indicators for each patient's facility included as random effects. Patients were assigned to the dialysis center most used throughout the study period. An intercept was generated for each facility representing the facility-specific vitamin D prescribing rate (the *expected* level of vitamin D treatment at each facility). The case-mix adjusted average vitamin D dose per patient, the *expected* average vitamin D dose per patient at each facility during the baseline period, was estimated using a mixed-effects linear regression model. The outcome of the model was each patient's average vitamin D dose during the 180-day baseline period. The model, similarly, adjusted for age, sex, race, and primary cause of ESRD.

6.3.4 Measurement of fracture outcomes

The outcome variable was the time from the end of the baseline period to the first hospitalization for fracture measured at the individual-level during the 12-month follow-up period. Fractures were identified using International Classification of Diseases, 9th revision (ICD-9) diagnosis codes and grouped into four categories: 1) vertebral; 2) pelvis/hip; 3) other [femur, lower leg (tibia, fibula, patella & ankle), ribs/sternum, shoulder/upper arm (humerus, scapula & clavicle) or forearm/wrist]; and 4) any of the above fracture types. This classification excluded fractures of the hands and feet (due to minimal consequences of these fractures), fractures of multiple areas and of the skull/trunk (likely indicative of severe or blunt trauma), and ill-defined, unspecified factures.

6.3.5 Measurement of Covariates

Relevant confounding variables were ascertained based on published literature investigating predictors of fracture risk in both the dialysis and general population. Age, sex, race (white, black, or other), and primary cause of ESRD were derived at dialysis initiation from the USRDS Patient File. Patients were assigned to one of four age categories: 18-44, 45-64, 65-74, and ≥ 75 years old. As the modal group, patients 65-74 years old were chosen as the reference category. Each patient's primary cause of ESRD was categorized into four groups: diabetes mellitus, hypertension, glomerulonephritis, and other. Diabetes served as the reference category as the most frequent cause of renal failure. The "other" category captured patients whose renal failure was caused by polycystic kidney disease or another genetic or urologic disease. Medicaid eligibility was derived at dialysis initiation from the USRDS Payer File.

The USRDS Medicare Part A and Part B files were searched during the 180-day baseline period for the following comorbid conditions or procedures: acute myocardial infarction (MI), anemia, an autoimmune disorder, cancer, chronic obstructive pulmonary disease (COPD)/asthma, diabetes mellitus, gastrointestinal bleed, a heart-related procedure, human immunodeficiency virus (HIV)/ acquired immunodeficiency syndrome (AIDS), hypertension, hyperthyroidism, ischemic heart disease, liver disease, neurologic disorder, obese, other heart disorder, peptic ulcer disease, peripheral vascular disease, pneumonia, psychiatric disorder, pulmonary circulation disorder, stroke, and substance use disorder. Patients were categorized as having an autoimmune disorder at baseline if they had any claim with the diagnoses of inflammatory bowel disease, psoriasis, lupus, or rheumatoid arthritis/collagen vascular diseases. A heart-related procedure was defined as any claim at

baseline with HCPCS codes in part A or par B indicating that a coronary artery bypass graft (CABG) was performed or that a stent or percutaneous transluminal coronary angioplasty (PTCA) was placed.

Data on all dialysis facilities were derived from the USRDS Facility File and measured during the baseline period. The analysis controlled for the following facility-level covariates: profit status, practice setting, chain affiliation, size, and region. Facilities were categorized into two groups based on profit-status: for-profit and not-for-profit. Facility practice setting was categorized as freestanding (facilities that function independently of hospitals) or hospital-based. Each patient was categorized into one of the top three largest dialysis chains during the study period. Facilities were categorized into three groups of small, medium and large based on the number of patients each facility served. Facilities in the lowest quartile after tabulating each facility's patient volume were considered small (18 or fewer patients), facilities in the highest quartile of patient volume (44 or more patients) were considered large, and facilities in-between serving 19-43 patients were considered medium. Four geographical regions (Northeast, Midwest, South, and West) of the US were delineated based on the location of each patient's dialysis facility using Census Bureau Regions and Divisions.[169]

Prior history of parathyroidectomy, use of personal assistance aids and the presence of a fistula were defined as the presence of a HCPCS code at baseline for any of the respective procedures of interest. The use of personal assistance aids was defined as whether the patient had any claim at baseline for wheelchairs, walkers/canes, and modified bathroom equipment including claims for replacement parts for all three technologies.

6.3.6 Statistical analyses to assess fracture risk

The absolute standardized difference was used to compare baseline characteristics between vitamin D users and non-vitamin D users. Significant imbalance of baseline characteristics between groups was indicated by an absolute standardized difference (ASD) greater than 10.[177]

Unadjusted and adjusted Cox proportional hazard regression analyses were performed to examine the independent association between vitamin D exposure and fracture for each fracture type. Multivariable Cox models adjusted for age, sex, race, Medicaid eligibility, the presence of various comorbidities, primary cause of ESRD, prior history of a parathyroidectomy, facility characteristics, use of personal assistance aids and the presence of a fistula.

Patients were censored once any of the following events occurred: 1) death, 2) kidney transplantation, 3) loss of Medicare as primary payer status, or 4) a switch to peritoneal dialysis. Patients were administratively censored on May 31, 2004. A robust estimate of the standard errors was computed that acknowledged the within-facility clustering of outcomes.[182] All analyses were performed using SAS 9.2 (Cary, NC, USA).

6.4 Results

A total of 135,958 patients within 4,021 facilities were eligible for cohort inclusion. Table 14 describes the demographic and clinical characteristics of the cohort by vitamin D user status. Approximately 60% of the cohort was over 65 years old, 43.4 % were Medicaid eligible, 47.5% were female, with the majority served at a for-profit (79.4%) or freestanding facility (87.1%). The most common comorbidities present were anemia (84.9%),

hypertension (79.9%), diabetes mellitus (59.1%), and a heart disorder (52.2%). Differences were observed with respect to race when comparing vitamin D users to non-vitamin D users. Among vitamin D users, 57.3% were white, 38.0% were black and 4.8% were of another race. Among non-vitamin D users, however, 76.0% were white, 18.5% were black and 5.5% were of another race. Compared to non-vitamin D users, vitamin D users were more likely to be Medicaid eligible or have anemia and less likely than non-users to have ischemic heart disease, peripheral vascular disease or a heart disorder.

Table 14. Demographic and clinical characteristics of cohort by vitamin D user status

Characteristics	All (%)	Vitamin D User (%)	Non-Vitamin D User (%)	Absolute standardized difference
N	135,958	95,705	40,253	-
Age (years)				
18-44	10.3	10.8	9.1	5.7
45-64	29.1	30.3	26.3	8.9
65-74	31.2	30.8	32.3	3.2
>= 75	29.4	28.2	32.3	8.9
Race				
White	62.8	57.3	76.0	40.6**
Black	32.2	38.0	18.5	44.4**
Other	5.0	4.8	5.5	3.3
Female	47.5	48.0	46.4	3.2
Medicaid eligible	43.4	45.6	38.0	15.5**
Comorbidities				
Acute MI	4.5	4.3	5.1	3.8
Anemia	84.9	85.9	82.2	10.1**
Autoimmune disorder	3.4	3.2	3.7	2.7
Cancer	11.2	10.7	12.3	5.0
COPD/Asthma	19.1	18.2	21.3	7.8
Diabetes mellitus	59.1	58.5	60.3	3.7
Gastrointestinal bleed	5.6	5.2	6.3	4.7
Heart-related procedure	2.3	2.4	2.2	1.3
HIV/AIDS	1.1	1.1	1.1	0.0
Hypertension	79.9	79.9	79.9	0.0
Hyperthyroidism	1.0	1.0	0.9	1.0
Ischemic heart disease	38.3	36.8	42.0	10.7**
Liver disease	3.3	3.3	3.4	0.6
Neurologic disorder	7.6	7.2	8.6	5.2
Obese	4.1	4.3	3.6	3.6
Other heart disorder	52.2	50.6	56.0	10.8**
Peptic ulcer disease	3.8	3.7	4.3	3.1
Peripheral vascular disease	25.1	23.7	28.4	10.7**
Pneumonia	10.1	9.2	12.1	9.4

Table 14. Demographic and clinical characteristics of cohort by vitamin D user status

Characteristics	All (%)	Vitamin D User (%)	Non-Vitamin D User (%)	Absolute standardized difference
Psychiatric disorder	4.4	4.1	5.2	5.2
Pulmonary circulation disorder	3.1	3.0	3.4	2.3
Stroke	12.5	11.6	14.8	9.5
Substance use disorder	6.1	6.1	6.1	0.0
Cause of ESRD				
Diabetes mellitus	48.8	48.7	48.9	0.4
Hypertension	30.1	31.0	27.9	6.8
Glomerulonephritis	8.0	7.9	8.2	1.1
Other	13.2	12.4	15.0	7.6
Parathyroidectomy	0.1	0.1	0.0	4.5
For-profit	79.4	82.0	73.2	21.2**
Free-standing	87.1	88.4	84.1	12.5**
Chain				
Chain #1	26.4	27.3	24.3	6.9
Chain #2	14.0	15.2	11.2	11.8**
Chain #3	13.4	14.8	10.1	14.3**
Other chain	46.2	42.7	54.4	23.6**
Facility size				
Small	9.3	8.9	10.4	5.1
Medium	44.3	44.3	44.2	0.2
Large	46.3	46.7	45.4	2.6
Region				
Midwest	22.2	21.1	24.7	8.6
Northeast	17.4	17.3	17.7	1.1
South	44.9	46.0	42.2	7.7
West	15.5	15.6	15.4	0.6
Personal assistance aids	6.2	5.9	6.9	4.1
Fistula	24.9	25.2	24.2	2.3

Abbreviations: Acute MI, acute myocardial infarction; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome

** An absolute standardized difference > 10 indicates significant imbalance of characteristic when comparing vitamin D users to non-vitamin D users

Table 15 shows the observed incidence of fractures by whether, at the individual level, patients were administered any dose of vitamin D at baseline. The overall incidence of any fracture was 51.68 per 1,000 Person-Years (PYs) with the highest incidence rate observed for pelvis/hip fractures at a rate of 26.18 fractures per 1,000 PYs. Fracture incidence was greater among non-vitamin D users compared to vitamin D users overall. The

incidence of vertebral and pelvis/hip fractures among non-vitamin D users was approximately 63.1% and 38.0% greater, respectively, than non-vitamin D users.

Table 15. Fracture rates per 1,000 person-years by vitamin D user status

Fracture Type	All	Vitamin D User	Non-Vitamin D User	Absolute standardized difference
Any fracture	51.68	46.74	63.64	34.5**
Pelvis/hip	26.18	23.56	32.51	20.0**
Vertebral	12.47	10.52	17.16	19.3**
Other[a]	16.78	16.08	18.46	6.3

[a]Other fracture comprised of lower leg, shoulder/upper arm, ribs/sternum, femur, and forearm/wrist fractures

** An absolute standardized difference > 10 indicates a significant imbalance in the characteristic when comparing vitamin D users to non-vitamin D users

No significant relation was observed between the proportion of vitamin D users or the average vitamin D dose per patient at the facility-level and fracture risk for all fracture types in both crude and multivariable adjusted Cox proportional hazard analyses (Table 16) [Full models in Appendices 23-30]. Specifically, for any fracture, the hazard ratio (HR) in adjusted models for a facility's proportion of vitamin D users was 1.10 (95% CI 0.86-1.42) while the HR for a facility's average vitamin D dose per patient was 0.99 (95% CI 0.90-1.09). Analyses modeling the non-case-mix adjusted vitamin D exposure variables and whether a facility was in the highest quartile of case-mix adjusted vitamin D dose generated very similar results (Appendices 15 and 16).

Table 16. Cox models of the association between measures of vitamin D exposure and fracture risk

Fracture Type	Proportion of Vitamin D Users[a]	Average Vitamin D Dose per Patient[b]
	HR (95% CI)[c]	HR (95% CI)
Any		
Crude	1.05 (0.82-1.34)	0.98 (0.87-1.11)
Adjusted[d]	1.10 (0.86-1.42)	0.99 (0.90-1.09)
Pelvis/hip		
Crude	0.96 (0.70-1.33)	1.04 (0.91-1.19)
Adjusted	1.05 (0.74-1.48)	1.05 (0.94-1.16)
Vertebral		
Crude	1.03 (0.65-1.63)	0.70 (0.37-1.34)
Adjusted	1.06 (0.64-1.74)	0.76 (0.41-1.40)
Other[e]		
Crude	1.39 (0.89-2.16)	0.98 (0.87-1.11)
Adjusted	1.33 (0.83-2.13)	0.95 (0.79-1.13)

[a]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[b]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of renal disease

[c]Hazard Ratio (95% CI)

[d]Cox models adjusted for age, sex, race, Medicaid eligibility, comorbidities, primary cause of ESRD, prior history of parathyroidectomy, facility characteristics, use of personal assistance aids, and the presence of a fistula.

[e]Other fracture comprised of lower leg, shoulder/upper arm, ribs/sternum, femur, and forearm/wrist fractures

Subgroup analyses were performed to address potential residual confounding by race, sex, and age (Table 17). There was no statistically significant relation observed between average vitamin D dose per patient and fracture risk for all fracture types among black patients. There was also no statistically significant association between average vitamin D dose per patient and fracture risk for all fracture types in a cohort of only female patients and a cohort of only patients over the age of 65.

Table 17. **Multivariable[a] Cox models of the association between facility-level average vitamin D dose per patient[b] and fracture risk among subgroups**

	Black	Female	Age ≥65 years
	HR (95% CI)[c]	HR (95% CI)	HR (95% CI)
Any	0.91 (0.74-1.12)	0.86 (0.69-1.06)	0.97 (0.85, 1.12)
Pelvis/hip	0.93 (0.71-1.21)	0.85 (0.65-1.11)	1.06 (0.95-1.19)
Vertebral	0.50 (0.07-3.43)	0.47 (0.13-1.71)	0.38 (0.12-1.23)
Other	0.93 (0.72-1.20)	0.91 (0.73-1.15)	0.85 (0.59-1.21)

[a]Cox models adjusted for age (except for the age subgroup analysis), sex (except for the sex subgroup analysis), race(except for the race subgroup analysis), Medicaid eligibility, the presence of comorbidities, primary cause of ESRD, prior history of parathyroidectomy, facility characteristics, use of personal assistance aids, and the presence of a fistula.
[b]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of ESRD
[c]Hazard Ratio (95% CI)

6.5 Discussion

We conducted a large-scale investigation of the association between IV vitamin D use and fracture risk among hemodialysis patients. We found that increasing vitamin D use and increasing average vitamin D dose administered per patient within dialysis facilities did not have an observed beneficial association with fracture risk. Fractures are prevalent in the dialysis population and impose substantial clinical post-fracture consequences including high hospitalizations, mortality, and long-term care facility use.[189] Even in an era of increasing vitamin D use and dosage, fracture incidence rates have remained relatively constant among hemodialysis patients.[190]

Our results are consistent with a meta-analysis by Palmer and colleagues of 76 randomized controlled trials of patients at all stages of renal failure. [58] They concluded that vitamin D was of "unproven efficacy" with regards to mortality, bone pain, vascular calcification, or need for parathyroidectomy with the exception of its effect on some biochemical indexes.[58] None of the clinical trials included, however, were adequately powered to examine the effect of vitamin D therapy on fracture risk and resolution of bone

pain.[191] Despite the limitations of the study (e.g., many of the trials were small and had short follow-up times), the results of the meta-analysis did indeed highlight the weakness of current evidence on pharmacological effects of vitamin D therapy in dialysis patients. Our study helps to address this research gap and circumvented the sample size limitations of previously conducted trials of vitamin D.

Our findings are important given that vitamin D is being prescribed more liberally in dialysis patients in an attempt to manipulate PTH levels.[186] However, we found that aggressive vitamin D use among dialysis facilities did not lead to improved fracture outcomes. In the general population, clinical decision making has relied on consistent evidence from randomized control trials to guide treatment of patient-level outcomes based on biochemical endpoints.[192] For instance, while low-density lipoprotein cholesterol and blood pressure have been demonstrated to be valid predictors of mortality and morbidity in the general population, there is no evidence in the renal population that vitamin D's alteration of biochemical parameters such as PTH affects outcomes like fracture.[58] The hazards of using surrogate markers to target pharmacologic treatments in dialysis patients has been demonstrated in recent years with the controversy regarding whether treating anemia by targeting higher hemoglobin targets with erythropoiesis-stimulating agents resulted in increased cardiovascular complication and mortality risk.[193]

We observed a decreased risk of fractures among vitamin D users in descriptive analyses. However, these associations were not present in Cox regression models adjusting for various demographic, clinical, and health-status related characteristics. Even though black patients received over twice the amount of vitamin D as white patients, our analyses found no association between dose and fracture risk in a homogeneous, all-black patient

subgroup analysis. The heterogeneous pathology of bone disease in ESRD patients contributes greatly to the complexity and uncertainties associated with solidifying the link between vitamin D use, PTH levels, SHPT, bone density, falls, demographic attributes (e.g., race) and fracture risk.

Given the non-experimental design, our study may have been subject to residual confounding from factors like frailty and underlying health status. However, our analysis that examined the effect of facility practice patterns on outcomes was explicitly adopted to minimize confounding by patient-level variables. Given that a dialysis patient's facility is generally chosen based on the facility's geographical proximity to a patient's home residence and is not based on a dialysis facility's SHPT management protocols, facility-level practice variability in the administration of vitamin D creates a potential natural experiment. The grouped-treatment analytic approach presented herein assumed that patients were assigned to dialysis facilities in a manner that effectively randomized them to different vitamin D administration practices.[125] Since we did not have access to clinical variables like PTH levels influencing the prescription of vitamin D, confounding by indication issues at the individual-level were mitigated with IV vitamin D exposure modeled as ecological variables that adjusted for the diversity in patient case-mix within a facility. This approach has been successfully applied in studies of ESRD patients[95, 126] and further incorporates the advantages of increased power and precision with outcomes and covariates specified at the individual-level.[124]

Also, we were unable to capture oral anti-resorptive medication use within the USRDS database but this is a minor limitation. Bisphosphonates are not generally prescribed to dialysis patients because of safety concerns related to toxicity due to impaired renal

excretion[66-68], and bone disease in dialysis patients is often due to SHPT and other forms of renal osteodystrophy.[4]

Medicare claims within the USRDS are collected primarily for administrative purposes and, thus, the amount of vitamin D dose billed may not actually reflect the amount of vitamin D received for each patient. The dosage reflected in vials billed for a particular formulation also may not accurately capture partial doses administered.[186] Furthermore, our definition of fracture, based on ICD-9 codes, may be somewhat misclassified. However, Fisher and colleague's validation of hip fracture claims suggests that fractures in the Medicare population are well-ascertained.[194]

In summary, the increased frequency of IV vitamin D administration and increases in the average vitamin D dose administered to dialysis patients has not yielded any observed reductions in fracture risk. It should be strongly noted, however, our results does not obviate the need to continue to administer vitamin D therapy to ESRD patients given that it has been established that treatment alters serum concentrations of PTH, the primary determinant of bone turnover in patients with ESRD.[195] Our study does not suggest that vitamin D should not be used as it is thought to have many pleiotropic effects, such as reduced risk of cardiovascular events and cancer.[196] We conclude only that vitamin D should not be used with the expectation of reducing fracture risk. Future research is needed to substantiate these results and improve our understanding on how to most appropriately dose IV vitamin, especially within the context of the diversity of patient characteristics in the dialysis population.

CHAPTER VII

DISCUSSION

The broad goal of this dissertation was to examine trends in the use and dosing of IV vitamin D and to examine whether vitamin D exposure was associated with fracture risk among hemodialysis patients. Two manuscripts (Chapters 4 and 5) document the results of this research. In Study 1, we sought to describe patient-level, facility-level, and state-level trends in the use and dosage of three vitamin D analogs among prevalent hemodialysis patients. In Study 2, we sought to investigate the association between vitamin D exposure and fracture risk. This concluding chapter synthesizes the findings from the two manuscripts, discusses clinical and policy implications of our work, highlights the strengths and weaknesses of the analyses, and provides recommendations for future research.

7.1 Summary of findings

In Study 1, we documented an increasing frequency in the prescription of vitamin D and increases in the doses administered to hemodialysis patients. Paricalcitol was the overwhelmingly preferred formulation between 2000 and 2008. While doxercalciferol use only declined slightly from its peak, calcitriol use in the dialysis population is virtually non-existent with less than 2% of patients administered the drug in 2008.

In addition to an increase in the percentage of users administered vitamin D (84% of patients in 2008), the dose of vitamin D given increased steadily over the decade for both

doxercalciferol and paricalcitol. The annual dose per patient administered for calcitriol decreased drastically, reflecting its waning popularity. In this dissertation, the inclusion of variables was guided by Andersen's Behavioral Model of Health Services Use. According to the model, predisposing, enabling and need factors are considered population characteristics that together interact to determine the use of vitamin D, the key health behavior we sought to describe in this study. Temporal trends in vitamin D dosing were explored among the three subgroups of predisposing characteristics available in our dataset (age, sex, and race). We found that racial variations in dose were most poignant with black patients administered over 80% more vitamin D than white patients in 2008.

Region was categorized as an enabling characteristic. Geographical variations in the average vitamin D dose per patient administered were observed with the highest doses of vitamin D found in states clustered in the south and the east. We attempted to decipher whether regional variations were due to the racial distribution of patients in the United States and observed that black patients were given high doses of vitamin D (i.e., greater than 100mcg on average annually) in all but 5 states, suggesting that race may be a contributor to observed geographical dosing differences.

In Study 2, we conducted a large, population-based analysis of the association between vitamin D exposure and fracture risk across various fracture types using Cox proportional hazard regression models. While Study 1 was purely descriptive, the inclusion of variables in Study 2's statistical analyses was also guided by Andersen's Behavioral Model of Health Services Use. A facility's decision to administer vitamin D was considered both a process of care and the use of a medical service under the health behaviors component of the model. Vitamin D treatment at the facility-level was hypothesized to directly,

positively influence our health outcome of interest, fracture risk. However, we found no statistically significant association between facilities with high vitamin D use and patient-level fracture risk for all fracture types including those at the pelvis/hip, vertebrae, and femur. There was also no signification association between the average vitamin D dose per patient within a facility and fracture risk for all fracture types examined. Our key measures of vitamin D exposure were case-mix adjusted, accounting for variations in patient attributes within a facility that may influence the facility's vitamin D treatment decisions. Pelvis/hip fractures were observed to be the most common followed by vertebral fractures.

In individual-level comparisons of predisposing, enabling, and need characteristics, differences between vitamin D users and non-vitamin D users were found (as indicated by an absolute standardized difference greater than 10). Whereas we did not observe imbalance with other predisposing characteristics, we observed significant differences in the racial distribution of vitamin D users versus non-vitamin D users. As for enabling characteristics, significant imbalance was observed between vitamin D users and non-vitamin D users with respect to Medicaid eligibility along with the facility-level factors of profit status (for-profit vs. non-profit), practice setting (hospital-based vs. free-standing), and dialysis chain. Finally, differences between vitamin D users and non-vitamin D users were also found with the presence of the following comorbidities reflecting need characteristics: anemia, ischemic heart disease, other heart disorder, and peripheral vascular disease. We found significant imbalance between vitamin D users and non-vitamin D users with respect to only these comorbidities and there is no plausible explanation in the literature to currently elucidate why vitamin D use would vary by the presence of heart disorders and anemia (ubiquitous among

dialysis patients). The potential association between vitamin D use, anemia, and heart disorders merits further research.

Stratified analyses restricting patients by age, sex, and race were used to examine the association between IV vitamin D use and fracture risk among all the predisposing characteristics. Although we observed that there were more black patients who used vitamin D than those who did not, the relation between vitamin D dose per patient and fracture risk was not significant among a subgroup of only black patients. There also was not a significant relation between vitamin D dose per patient and fracture risk among a population of only female patients or one of only patients older than 65 years. A priori, we hypothesized that IV vitamin D use and dose would be associated with a decreased risk of fracture among black patients, an increased risk of fracture among female patients and an increased risk of fracture among the elderly. Female sex and older age are documented risk factors for fracture among dialysis patients.[77] Black patients, possibly because of greater bone mass, have been observed to be at a lower risk for fracture compared to white patients in both the general and dialysis population.

7.2 Implications

The use of IV vitamin D therapy is ubiquitous among dialysis patients and the dosage of vitamin D therapy administered has steadily increased over time. Medicare policies are hypothesized to be the great catalyst driving the observed, aggressive increase in vitamin D use. Recent changes to Medicare's reimbursement process may greatly impact the use of IV vitamin D therapy among dialysis patients in the future. During the study period explored in this dissertation, dialysis facilities were paid one composite rate by Medicare for routine

dialysis services on a per-treatment basis.[197] Injectable drugs like vitamin D were billed separately on a fee-for-service basis based on the total units of the drug provided to patients.[197] The new ESRD prospective payment system, implemented on January 2011, spawned from concerns that the fee-for-service billing structure for injectable drugs led to high expenditures, inefficiencies and excessive use of erythropoietin stimulating agents and vitamin D.[1] Under the new payment system, routine dialysis services and injectable drugs are billed under one, case-mix adjusted, bundled rate. This provides dialysis facilities with strong financial incentives to manage the administration of IV vitamin D more efficiently.[198] The use of IV vitamin D will likely decline, gradually replaced with the adoption of less expensive oral vitamin D supplementations like generic calcitriol.[199]

Given the expected changes in vitamin D administration with the new payment system, the large variations in vitamin D dosing observed during our study period and documented in Study 1 provided a unique opportunity to investigate the impact of IV vitamin D on a salient clinical endpoint. Vitamin D use and dosage has increased even while fracture incidence rates have remained relatively constant among hemodialysis patients.[190] In Study 2, using the grouped-treatment approach employed by Johnston, Tentori and other researchers,[95, 124] we investigated the association between increasing vitamin D use, increasing vitamin D dose, and fracture risk. The two-level, grouped-treatment approach was applied in this study to combine the advantage of reduced confounding with vitamin D exposure measured at the ecological level and greater variable specification with confounders and outcomes assessed at the patient-level.[124] In contrast, rather than examining the effect of treating an individual dialysis patient with vitamin D, this approach allowed us to answer two questions: 1) "Is treatment at a dialysis facility utilizing IV vitamin D therapy more

frequently associated with reduced fracture risk, regardless of how an individual patient is treated?"; and 2) "Is treatment at a dialysis facility utilizing greater doses of IV vitamin D therapy associated with reduced fracture risk, regardless of the dose given to an individual patient?"

We did not find a statistically significant association between increasing vitamin D use or increasing vitamin D dose at a facility and fracture risk. It would be valid to conclude that, given a choice, there would be no difference in a particular dialysis patient's fracture risk if he or she transferred from a facility with relatively high vitamin D use to one with low vitamin D use. However, given our analytical approach, our results can not indicate whether that same patient should be treated with vitamin D or whether certain doses of vitamin D would alter that patient's fracture risk. The results from this dissertation can not provide guidance regarding who should receive vitamin D therapy; it suggests only that having the option to transfer to a facility with high vitamin D use and dosage may not have any influence on that patient's fracture outcomes. We urge the nephrology community to reevaluate IV vitamin D dosing practices to ensure that any clinical decision to raise the dose of vitamin D for a particular patient is based on sound medical evidence. Our empirical observation that vitamin D use increased drastically during a time of relatively unchanged fracture rates[190] and our statistical analysis of the association between vitamin D exposure and fracture risk strongly suggest that the clinical benefit of vitamin D with respect to fracture risk among hemodialysis should be heavily questioned.

Renewed and wide-ranging interest in the potential beneficial effects of vitamin D may entice nephrologists to incorrectly deem vitamin D a panacea for hemodialysis patients and entertain the use of the drug beyond established indications and guidelines.[95] IV vitamin

D is standard in the treatment of SHPT, regulation of calcium and phosphate levels, and in the management of bone-mineral metabolism disturbances. Vitamin D also has recognized pleiotropic effects including inhibiting the proliferation of cancer cells, defending against microbial infections, and preventing cardiovascular events.[200, 201]

Vitamin D's potential beneficial biological effects on the immune, inflammation, renin–angiotensin systems and various other pathways triggered a number of observational studies that documented a survival advantage for hemodialysis patients administered IV vitamin D.[57, 139] Unfortunately, these analyses failed to properly account for confounding by unmeasured variables like underlying health status. Employing the grouped-treatment approach used in this dissertation and other advanced statistical techniques, Tentori and colleagues did not find a survival advantage among hemodialysis patients administered vitamin D, suggesting that prior observational studies should be interpreted with much caution.[95] Like the caution that should be exercised if deciding to use vitamin D to enhance survival prospects, dialysis healthcare providers should be equally reluctant to administer vitamin D at greater doses in an attempt to manipulate fracture risk.

As the nephrology community awaits the results of well-conducted studies to address the uncertainties regarding the clinical benefit of vitamin D, clinicians and healthcare providers compelled to use vitamin D with the intent of reducing fracture risks should be reminded that there is currently no evidence to substantiate the treatment decision. Results generated from our analysis concurs with a meta-analysis of randomized clinical trials of vitamin D use in dialysis patients concluding that vitamin D had no beneficial effect on patient-level outcomes such as mortality and hospitalization.[58] With respect to vitamin D and fractures among dialysis patients, a meta-analysis of the 4 randomized clinical trials with

fracture as a secondary outcome found that IV vitamin D had no clinical benefit (Effect size 1.0 [0.06, 15.41]).[191]

Given the lack of previous research in this area, findings from this population-based study addresses an important issue facing a growing population of ESRD patients. Fractures are important markers of morbidity among dialysis patients and post-fracture consequences are substantial.[189] The suppression of PTH levels with IV vitamin D therapy has been central to the treatment of SHPT and other bone mineral disorders in renal failure,[187] but the clinical benefit of vitamin D with respect to fractures has yet to be elucidated. The lack of evidence regarding the beneficial effect of vitamin D to curtail the frequency of fractures, however, does not overshadow the years of well-established literature documenting the value of the medication. Our study adds to the cadre of evidence that may be used to guide future research agendas for analysts that might eventually inform decision-making by policymakers and healthcare providers. A summary of recommendations for future research directions is presented in section 7.5.

Moreover, the findings from our descriptive analyses also add to the nephrology literature. Region was observed to be an important enabling factor. The observed state-to-state variations in vitamin D use and dosing practices found in Study 1 are consistent with Freburger and colleagues' observations of the greater use of injectable drugs like erythropoietin stimulation agents and iron among hemodialysis patients in the southeastern region of the United States.[198] Variations in vitamin D use in the dialysis population may be influenced by the same factors that have been found to increase Medicare spending in the general population such as provider profit-seeking behavior, organization of practices, or unmeasured markers of health status.[202] Geographic differences in vitamin D use may also

be due to regional variations in facility practice management or reflective of the trends in demography and Medicare spending observed in the general population.[203, 204] The results from this dissertation provide justification for large-scale analysis of reimbursement policies, scrutiny of factors perpetuating geographical differences and surveys into whether geographic variations in clinical care translate into regional differences in dialysis patient outcomes. We need to better under how enabling characteristics like facility region interact with demographic, clinical, environmental factors to influence variations in facility management of injectable medications.

Also, race was included in our analysis as a predisposing factor partially determining the use of dialysis services and a patient's exposure to vitamin D in dialysis facilities. Racial differences in utilization practices and vitamin D dosing are striking.[186] Black patients receive nearly twice as much vitamin D as white patients, even though the percentage of black patients receiving vitamin D is less than the percentage of white patients receiving the drug.[186] The new Medicare reimbursement system does not include race as a case-mix adjuster and, therefore, the payment system does not sufficiently reflect the higher cost to dialysis facilities to treat black patients.[205] Facility viability and patient access to care may be significantly impacted if the payment system does not incorporate race and other drivers of facility cost differences. However, this consideration is counterbalanced by the need for an appropriate racial classification and a greater understanding of whether racial variations in vitamin D are due to biological mechanisms or reflect discretionary facility practice patterns.[205] The higher PTH levels found in black dialysis patients are among many factors dictating the pathology of renal osteodystrophy in dialysis patients and more studies are needed to ensure that higher vitamin D doses in blacks actually reflect clinical need before

validating these racial dose variations with the payment system.[205] Simultaneously, we need to ensure that racial discrepancies are not due to facility practices that can be readily improved to enhance the quality of care to all dialysis patients of all races.[205]

Finally, falls are an important and potentially modifiable risk factor for fracture.[79] However, there have been very few studies examining fall prevention strategies among dialysis patients. A study of one outpatient hemodialysis center found clinically and statistically significant reductions in the incidence of falls after implementing targeted interventions addressing key risk factors for falls.[206] Although the etiology of falls is multifactorial, risk factors for falls include cognitive impairment with vision, balance, strength, and gait; the presence of environmental dangers within the dialysis facility, and the use of more than four medications.[206, 207] The physical environment of an outpatient hemodialysis center may be hazardous.[79, 206] Potential hazards include loose blood tubing lines, wet floors from water spillage or leakage, elevated scales, and limited visibility due to low ambient lighting to accommodate patient preferences for sleep during dialysis treatment.[206]

There are strategies that hemodialysis facilities may employ to begin to curtail the burden of fractures in their patient population. Outpatient dialysis facilities can begin with a comprehensive assessment to identify patients at high risk for falls.[79] Patients deemed at high risk for falls could be required to use a wheelchair while inside the center, have mandatory assistance with transfers, and scheduled communication with a renal social worker to discuss at-home strategies to reduce the risk of falls.[206] Also, evidence from the general population suggests that reducing the number of medications taken by a patient may decrease the risk of fracture.[79] The high comorbidity burden among dialysis patients is

largely responsible for the widespread polypharmacy observed in this population. A comprehensive medication review, with a keen focus on psychoactive medications, may be beneficial by prompting the discontinuation of superfluous medications. In the general population, the risk of falls has decreased with the gradual discontinuation of benzodiazepines, anticonvulsants, antipsychotics and sleeping pills.[79, 207] With regard to the physical environment of the dialysis center, the impact of replacing elevated scales with in-ground scales and installing tractable floor mats on the risk of falls can be assessed.[79] Other modifiable alterations within the dialysis facility include the routine use of towels around dialysis machines to curb fluid leaks and the installation of rails in patient restrooms.[206]

7.3 Study limitations

This dissertation has limitations. Foremost, despite adjustment for various patient- and facility-level risk factors for fracture risk, residual confounding may still persist. The non-experimental nature of this study compels caution in interpreting study results. Study 2 was limited by the presence of residual confounding from unmeasured factors like bone strength, patient behavior, and nutrition management. For instance, the data did not enable us to account for hypoalbuminemia in our analysis, a factor found to be a strong predictor of high morbidity among dialysis patients.[208]

Another limitation is that death is likely a competing risk in all survival analyses performed. An alternative outcome that alters the probability of the outcome of interest occurring is considered a competing risk.[209] In this study, individuals who had a fracture experienced the outcome of interest at the date of fracture. However, if an individual dies prior to experiencing a fracture but was susceptible to fracture due to IV vitamin D use, death

would have been a competing risk. In the presence of competing risks, traditional Kaplan-Meier and Cox regression estimates may overestimate fracture risk.[209, 210]

A limitation inherent to all administrative claims-based analyses, data from our analyses were derived from claims submitted for reimbursement purposes, not from medical record abstractions or clinical measurements. Misclassification bias may be present in several forms in this analysis. Although studies of Medicare claims have demonstrated adequate ascertainment of fractures,[194] there remains a possibility that some fracture events were missed.

We were able to measure the number of vitamin D units billed for a particular patient but the data do not indicate whether partial doses were delivered to the patient. Also, we could not capture oral vitamin D or bisphosphonate use but this is a minor limitation given that bisphosphonates are not generally prescribed to dialysis patients due to renal safety concerns.[211]

Consistent with prior reports using the grouped-treatment approach[212], we observed relatively wide confidence intervals for the vitamin D ecological variables. However, this can be expected since we are measuring vitamin D treatment with the use of aggregated proxies, causing some loss of precision.

With respect to external validity, the results from this dissertation may not be generalizable to chronic kidney disease patients that are not undergoing dialysis, peritoneal dialysis patient, and patients who do not have Medicare as a primary payer. Also, caution should be taken in generalizing study results to prevalent dialysis patients given the focus on incident dialysis patients who make up only approximately 20% of the total US hemodialysis population.[213]

Lastly, variations in the pathophysiology and severity of comorbid conditions and fractures were not assessed. The addition of the severity grading of various comorbidities did not lead to increased prognostic power in studies of mortality in patients with ESRD,[214] suggesting that this limitation is minor and including the severity of comorbidities in our analyses likely would not have influenced our results significantly.

7.4 Study strengths

The strengths of this dissertation outweigh its limitations. The primary strength of this dissertation was our statistical approach. We attempted to overcome confounding by indication/disease severity (i.e., sicker patients receive more treatment) and other methodological issues commonly present in non-experimental studies conducted at the individual-level with our statistical approach. We adopted a statistical approach aimed at minimizing confounding due to unmeasured variables that directly influence the decision to administer vitamin D and confounding due to the fact that patients prescribed vitamin D may be fundamentally different from those who are not administered the drug. Confounding bias may be attenuated or even eliminated with the use of an ecological, grouped-treatment variable that is related to the patient's treatment but weakly associated with unmeasured patient risk factors.[215]

Researchers have longed cautioned against the use of ecological studies to make inferences at the individual-level in a phenomenon known as the ecologic fallacy.[216] Associations found at an aggregated unit of analysis may not necessarily hold true at the individual-level.[216] However, in the presence of confounding at the individual-level, the relative immunity of ecological studies to confounding by indication may supersede any ecologic fallacy issues if variation in treatment utilization is driven by differences in practice

style.[121, 216] To circumvent the deficits of ecological studies and to take advantage of the relative immunity of the approach from confounding by indication, we employed the grouped-treatment approach. Vitamin D use and dose were aggregated to the dialysis facility-level while covariates and fracture outcomes were measured at the patient-level.[188] Confounding by indication bias was mitigated with the ecological treatment variable and we capitalized on the advantages of increased precision with observed confounders and outcomes at the individual-level.[124]

We recognized that residual confounding may still persist, even after aggregating vitamin D treatment to the facility-level. Our key vitamin D variables may have been confounded by demographic and clinical attributes of patients at a particular facility that may have influenced how that center decided to administer vitamin D. It was important to ensure that our measurement of vitamin D exposure at the facility-level was capturing variations in vitamin D use and dose at a facility, independent of that facility's patient case-mix. A facility's high use of vitamin D may actually reflect a clustering of patient's with a preponderance of characteristics that merit higher vitamin D dosage. For instance, a facility may serve a preponderance of black hemodialysis patients, generally administered higher doses of vitamin D compared to patients of other races.[186] To this end, an additional strength of this dissertation was that we addressed this potential bias by creating case-mix adjusted measures of vitamin D exposure that reflected a facility's propensity to prescribe vitamin D given the facility's patient population.

Our target population of hemodialysis facilities was a considerable strength. The validity of our approach is contingent upon the assumption that the pre-treatment prognosis of patients is not associated with the proportion of patients treated with vitamin D at a

dialysis facility.[212] By way of explanation, the assumption relies on the fact that high-risk patients are not being transferred to particular dialysis facilities because of that facility's vitamin D utilization practices. Studies of dialysis facilities provide a unique opportunity to plausibly fulfill this rather restrictive assumption. Unlike hospitals where patients are most often referred to the hospital most adept at providing the particular procedure or care needed, dialysis patients generally attend the dialysis center in closest geographical proximity to their residence. Therefore, the vitamin D treatment practices of a dialysis facility do not play a role in the decision to attend a particular facility, providing us with the basis for a natural experiment and pseudo-randomization.

Another strength of this dissertation was the use of a proxy for functional status to account for waning underlying health processes that may predict fracture risk. Functional status was estimated using claims for personal assistance aids like wheelchairs, canes, walkers, and modified bathroom equipment. Patients with ESRD experience many of the clinical manifestations of frailty found in patients without kidney disease such as declining physical function, comorbidities, and loss of muscle mass.[153] Adverse outcomes like hospitalizations and death have been shown to be mediated by frailty[153], but few prior studies have attempted to control for its possible effects.

Additionally, this dissertation is unique in its exploration of different subgroups and multiple fracture types. Study 1 explored temporal trends in vitamin D use and dosing by relevant subgroups. Study 2 investigated the association between vitamin D exposure and fracture outcomes by fracture type and relevant subgroups. Unlike our study, the Dialysis Outcomes and Practice Patterns Study (DOPPS), the most contemporary report of IV vitamin D use and dose in the United States, did not report variations in vitamin D use by race, age,

and sex subgroups and used a small sample size of less than 4,000 patients.[183] Studies examining the incidence and factors associated with fracture risk have focused predominantly on hip fracture and were based on selective groups of patients.[73, 74, 77, 82-84] Our study assessed the association between vitamin D exposure and fracture by four fracture categories that represented the most clinically significant and costly types.

Our use of USRDS files is the final major strength of this dissertation. The USRDS captures data on every ESRD patient in the United States and contains the most detailed data on demographic attributes, diagnoses, treatment histories, hospitalizations and dialysis facility services.[217] Our population-based study had a large sample size of over 130,000 patients representing over 4,000 dialysis facilities nationwide.

7.5 Recommendations for future research

The present analysis characterized the association between vitamin D exposure and fracture risk but it was not designed to establish causal inference. A robust clinical trial can confirm the validity of our observed associations but these trials would likely be limited by under-ascertainment of fracture events and questions regarding clinical equipoise. The impracticability of randomized controlled trials warrants the use of robust non-experimental studies to address this salient issue. The following text proposes research questions, corresponding study designs, and data sources that could be employed in non-experimental studies to substantiate our results and address the current gaps in the nephrology literature.

In the absence of clinical trial evidence, the grouped-treatment approach extends the natural experiment methodology commonly found in epidemiology by taking advantage of variations in practice policies to estimate the marginal effect of differences in treatment

selection.[218] As in this dissertation, the grouped-treatment approach (where the main variable of interest is measured ecologically while outcomes are measured at the individual-level) is advantageous in epidemiological studies where individual-level factors like biochemical parameters that determine the decision to prescribe a medication are not readily available in the dataset of interest. An individual-level analysis using a data source with adequate laboratory and biochemical measures could be conducted to substantiate whether there is indeed no association between vitamin D exposure and fracture risk among hemodialysis patients. To this end, one could employ the approach used by Block and colleagues to investigate cardiovascular outcomes among hemodialysis patients. Data from DaVita Inc., the second largest dialysis provider in the United States, could be linked using unique patient identifiers to the Centers for Medicare & Medicaid Services (CMS) ESRD database by the United States Renal Data System (USRDS) through a data licensing agreement.[219]

Unlike using USRDS data alone, merged DaVita and USRDS data contain detailed laboratory values, IV medication use, home medication use, and vascular access information from DaVita while simultaneously providing relevant Medicare claims and hospitalization data from the USRDS for each patient.[219] The DaVita dataset provides two distinct advantages. Firstly, the data contain the important laboratory values of calcium, phosphorus, and PTH levels that are used to guide vitamin D administration. Secondly, merged DaVita and USRDS data would allow researchers to measure exposure to cinacalcet, an oral calcimimetic also used to treat SHPT. Our analysis was restricted to the years prior to the widespread use of cinacalcet to allow us the ability to ascertain the association between vitamin D and fracture risk without the effects of confounding from the administration of a drug also indicated to treat SHPT. A retrospective cohort study using the most recent years

of available data could be conducted to assess the effect of vitamin D exposure on fracture risk with patient-level vitamin D prescription treated as a time-dependent variable. Vitamin D exposure and covariates (e.g., baseline comorbidity, laboratory data, cinacalcet and phosphate binder use) could be measured during a 6-month baseline period. Adjusted time-dependent Cox proportional hazard regression models could be employed to assess 3-year fracture risk and eligible patients would be censored in the event of transfer out of DaVita, renal transplantation or loss to follow-up.

Furthermore, a natural extension of the recommended study described above could be an investigation exploring the comparative effectiveness of IV vitamin D formulations with respect to fracture outcomes. In this dissertation, we report the overwhelming use of paricalcitol between 1999 and 2008. However, trends have changed in recent years and contemporary data of hemodialysis patients contend that doxercalciferol and paricalcitol are now being administered at relatively equal frequency, with calcitriol use now virtually non-existent.[183] It is unknown whether the pharmacological differences between these formulations translate into differential effects on important clinical outcomes like fracture risk. Using the aforementioned, linked USRDS and DaVita data, the comparative effectiveness of paricalcitol versus doxercalciferol with respect to fracture risk could be assessed with a retrospective cohort study. A cohort of incident hemodialysis patients could be selected under the new user design. Following a 3-month waiting period for claim ascertainment post-dialysis initiation, vitamin D exposure (use and dosage) could be measured over a 6-month baseline period for patients treated exclusively with either paricalcitol or doxercalciferol. Patients could be followed over 1 or 3 years and censored if they died, switched to another formulation, switched dialysis facilities, or underwent renal

transplantation. Laboratory values could be averaged over the 6-month baseline period and controlled for within Cox proportional hazard regression models along with baseline comorbidity and clinical attribute data.

Cinacalcet, also used to treat SHPT among dialysis patients, is currently covered under Medicare Part D but will be included under the new bundle as of January 2014. Given that financial incentives may compel the substitution of IV vitamin D for the cheaper cinacalcet for certain patient populations in 2014, future studies are needed to investigate the comparative efficacy and safety of vitamin D versus these various therapeutic options with respect to fracture outcomes. The secondary data needed to explore these issues will take years before becoming available to researchers and confirmatory studies will be required to ensure that the bone health of patients with ESRD is not compromised under the new payment system. For now, the independent effect of cinacalcet on fracture risk could be assessed using the methodology published by Frankenfield and colleagues to allow for comparison with studies of vitamin D exposure and to inform future analyses post the 2014 reimbursement policy changes.[220]

Using CMS Medicare Part D data linked to USRDS files, a retrospective cohort study could be conducted with a point-prevalent cohort of adult hemodialysis patients alive between July 1, 2006 and December 31, 2006, the latter months of the calendar year of Medicare Part D's initiation. Patients would then be followed from December 31, 2006 until death, renal transplantation or the last day of available data. Cinacalcet exposure could be defined as a dichotomous, time-dependent variable indicating the presence or absence of a cinacalcet prescription during the study period. Time-varying Cox proportional hazard regression models would assess the effect of cinacalcet prescription on fracture risk with

adjustment for baseline characteristics along with time-varying laboratory and IV vitamin D use.

Lastly, potentially inappropriate use of vitamin D therapy has been observed in an internationally representative sample of dialysis patients where investigators found that vitamin D was potentially overused in up to 46% of patients with low PTH (concentration <100 pg/mL) and potentially underused in up to 34% of patients with high PTH (concentration >400 pg/mL).[221] To understand the appropriateness of vitamin D administration to dialysis patients and to elucidate the relationship between vitamin D use and fracture outcomes, the nephrology community must ensure that treatment decisions are based on current, reliable evidence.

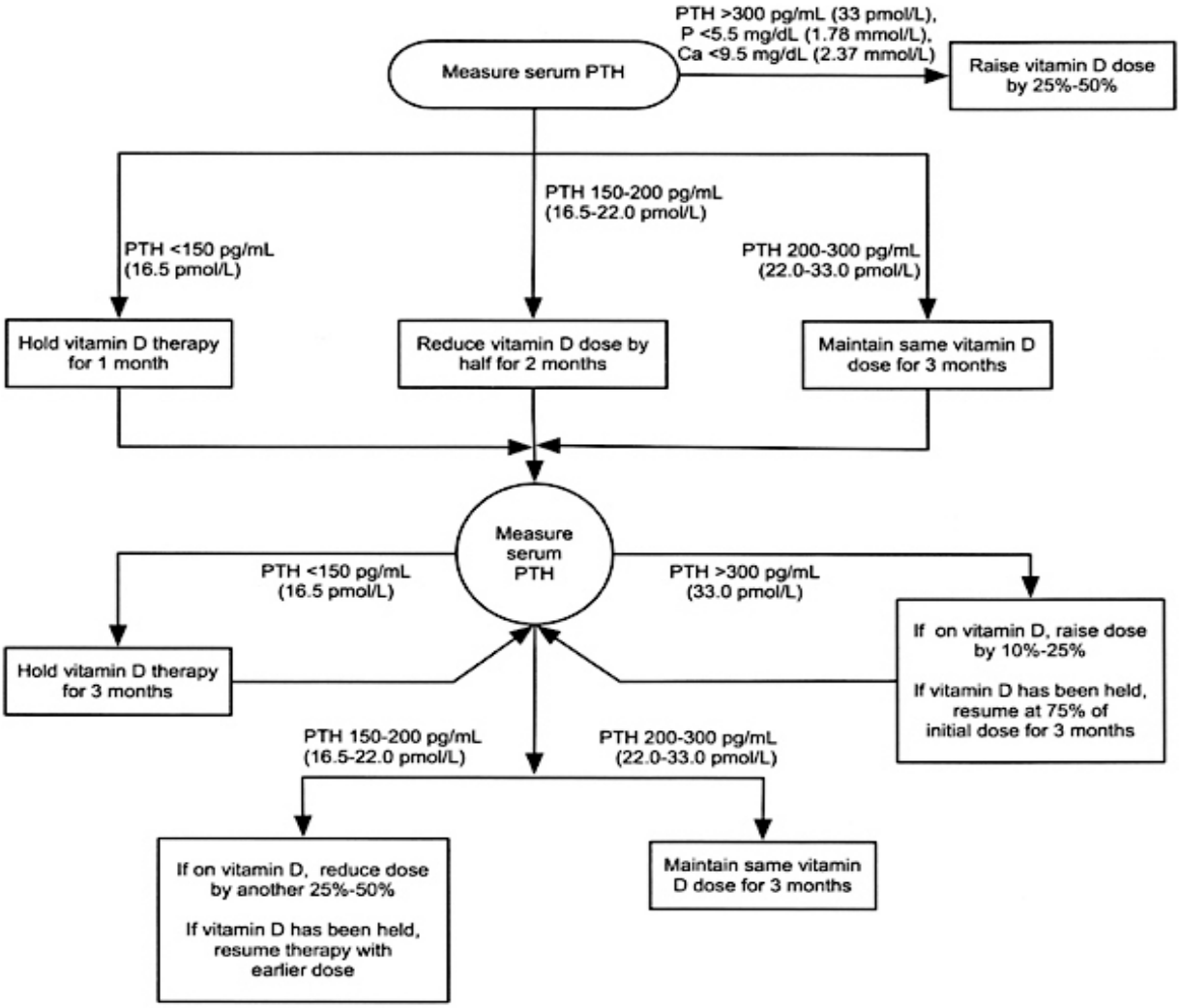
7.6 Conclusion

In conclusion, IV vitamin D use is highly prevalent among hemodialysis patients with both the percentage of users and dosage administered increasing over the past decade. Vitamin D dosing practices varied most poignantly by race and geographical location. Black hemodialysis patients received over twice as much vitamin D as white patients and higher doses of the drug were administered in the southern region of the United States. However, we found that the use of vitamin D in increasing doses was not significantly associated with fracture risk. After employing a statistical approach that mitigates the possible effects of confounding, we found that facilities with a high percentage of vitamin D users and facilities that provided high doses of vitamin D did not have an observed beneficial association with fracture risk, even after adjusting for variations in patient characteristics within dialysis facilities.

The clinical benefit of IV vitamin D with respect to fracture risk has yet to be elucidated. Results from this dissertation begin to address the dearth of large, population-based studies investigating fracture risk among dialysis patients, generally, and serves as the first large-scale examination of the association between vitamin D and fracture risk among hemodialysis patients, to date. The changing reimbursement environment in nephrology fosters an immediate need to understand the impact of varying facility-level vitamin D treatment decisions on patient outcomes given that financial incentives may reduce the administration of the drug. Substantial evidence of vitamin D's pleiotropic effects and its ability to successfully suppress PTH levels reaffirms the need to continue the administration drug given of the prevalence of SHPT in the dialysis patients. However, researchers and clinicians must be simultaneously reminded that vitamin D's benefit currently does not extend past effective manipulation of biochemical parameters. Future investigations are warranted to ensure that vitamin D is appropriately prescribed across dialysis facilities with a growing and diverse hemodialysis patient population.

APPENDICES

Appendix 1. Guidelines for managing vitamin D based on intact parathyroid hormone (PTH) levels

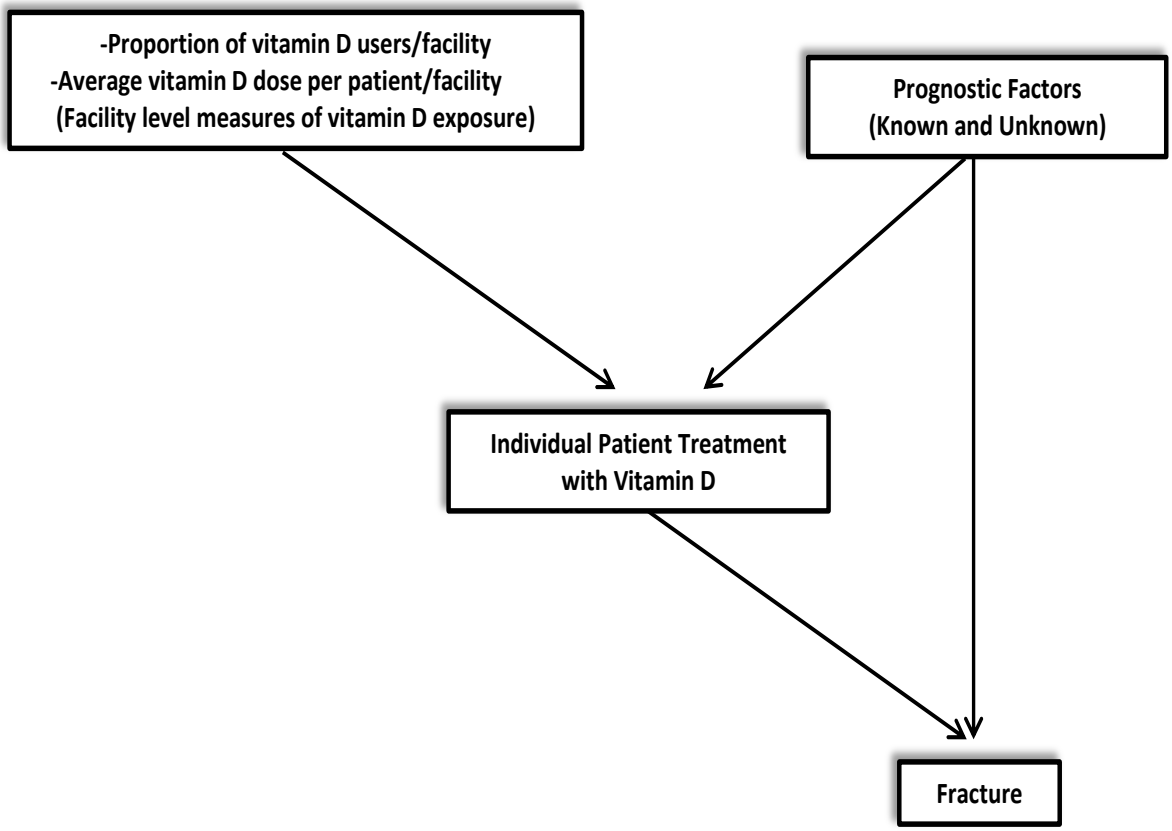


When intact serum PTH is between 300-500 pg/mL (33.0-55.0 pmol/L) and changes on two successive determinations are small (<25%), there is no need to modify vitamin D dose as long as P and Ca are within the desired limits (see Algorithms 3 and 4).

When intact PTH is persistently >500-800 pg/mL (55.0-88.0 pmol/L) and P is 5.5-6.5 mg/dL (1.78-1.94 mmol/L) and/or Ca is 10.2-10.5 mg/dL (2.54-2.62 mmol/L), a trial with a "less calcemic" analog may be warranted for 3-5 months; if such a patient fails to respond, parathyroidectomy may be required.

Source: http://www.kidney.org/professionals/kdoqi/guidelines_bone/Images/Algorithm5L.jpg

Appendix 2. Relationship between vitamin D variables, covariates, and fracture



Adapted from "Schmoor C, Caputo A, Schumacher M. Evidence from Nonrandomized Studies: A Case Study on the Estimation of Causal Effects. *American Journal of Epidemiology.* May 1, 2008 2008;167(9):1120-1129."

Appendix 3. Description of covariates

Variable	Type	Definition	Source
Demographic characteristics			
Age	Categorical transformed into dummies	"Agegrp1"=1 if age is 18≤x≤44 "Agegrp2"=1 if age is 45≤x≤64 "Agegrp3"=1 if age is 65≤x≤74→ ***Reference*** "Agegrp4"=1 if age is ≥75	USRDS Patient File
Sex	Dichotomous	1=male, 0=female	USRDS Patient File
Race	Categorical transformed into dummies	"White"=1 →***Reference*** "Black"=1 "Other_race"=1 if race not white or black, or missing	USRDS Patient File
Medicaid eligibility	Dichotomous	1=eligible, 0=not eligible	USRDS Payer History File
Comorbidities			
Acute MI	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
AIDS	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Anemia	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Autoimmune disorder	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
CABG/stent/PTCA placement	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Cancer	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
COPD/Asthma	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Diabetes mellitus	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Gastrointestinal bleed	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Hypertension	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Hyperthyroidism	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Ischemic heart disease	Dichotomous	1=present, 0=absent	USRDS Institutional

			Claims File
Liver disease	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Neurologic disorder	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Obese	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Other heart disorder	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Peptic ulcer disease	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Peripheral vascular disease	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Pneumonia	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Psychiatric disorder	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Pulmonary circulation disorder	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Stroke	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Substance use disorder	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Disease history characteristics			
Primary cause of ESRD	Categorical transformed into dummies	"Diabetes_cause"=1 if primary cause is diabetes →***Reference*** "Hypertension_cause"=1if primary cause is hypertension "GN_cause"=1 if primary cause is primary or secondary glomerulonephritis "Other_cause"=1 if primary cause is polycystic kidney disease, a urologic disease, or undefined	USRDS Patient File
Prior history of parathyroidectomy	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Facility characteristics			
Profit status	Dichotomous	1=for-profit facility, 0=not for-profit facility	USRDS Facility File

Practice setting	Categorical transformed into dummies	1=free-standing, 0=hospital	USRDS Facility File
Chain affiliation	Categorical transformed into dummies	"Chain_1"=1 → ***Reference*** "Chain_2"=1 "Chain_3"=1 "Chain_4"=1 "Chain_5"=1 "Chain_6"=1	USRDS Facility File
Size	Categorical transformed into dummies	"Small"=1→ ***Reference*** "Medium"=1 "Large"=1	USRDS Facility File
Region	Categorical transformed into dummies	"NE_region"=1 if located in the northeast→***Reference*** "MW_region"=1 if located in the midwest "S_region"=1 if located in the south "W_region"=1 if located in the west	USRDS Facility File
Functional status markers			
Use of personal assistance aids	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File
Treatment characteristics			
Fistula	Dichotomous	1=present, 0=absent	USRDS Institutional Claims File

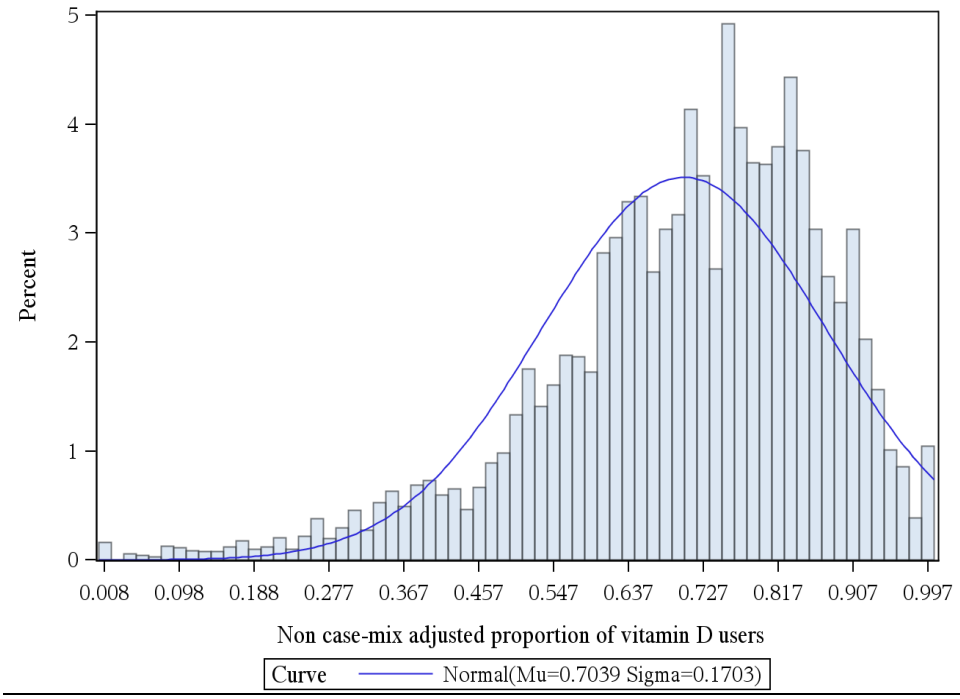
Appendix 4. Facility intravenous vitamin D formulation preference[a] by year

Year	N	Calctriol preferred (%)	Paricalcitol preferred (%)	Doxercalciferol preferred (%)	Mixed preference[b] (%)	No vitamin D administered (%)
1999	3572	97.6	0.0	0.0	0.0	2.4
2000	3783	36.4	17.7	0.0	44.5	1.4
2001	3919	13.4	58.0	0.0	27.4	1.3
2002	4109	6.0	68.5	4.6	20.0	1.1
2003	4257	3.1	70.2	7.4	18.2	1.1
2004	4410	1.7	60.4	20.6	16.3	1.1
2005	4566	1.4	58.6	26.2	13.2	0.8
2006	4683	1.2	58.6	26.2	13.2	0.8
2007	4840	0.7	60.1	24.3	14.1	0.8
2008	5056	0.6	68.4	18.0	12.0	1.0

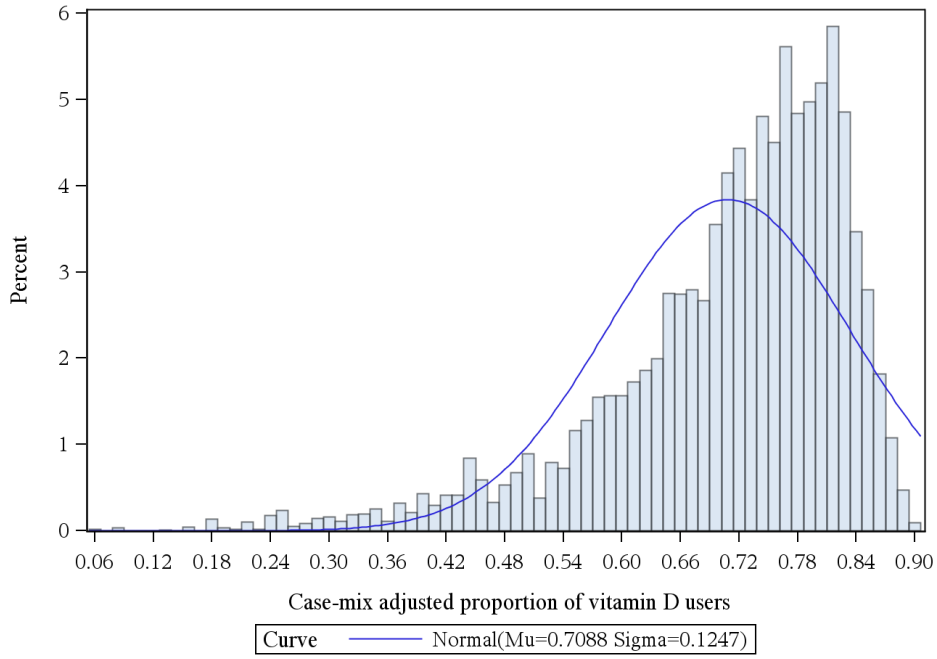
[a]Preference defined as >75% of total vitamin D dose administered in a facility was for particular formulation

[b]Mixed preference defined as no formulation comprised >75% of total vitamin D dose administered in a facility

Appendix 5. Comparative histograms of non case-mix and case-mix adjusted proportion of vitamin D users per facility

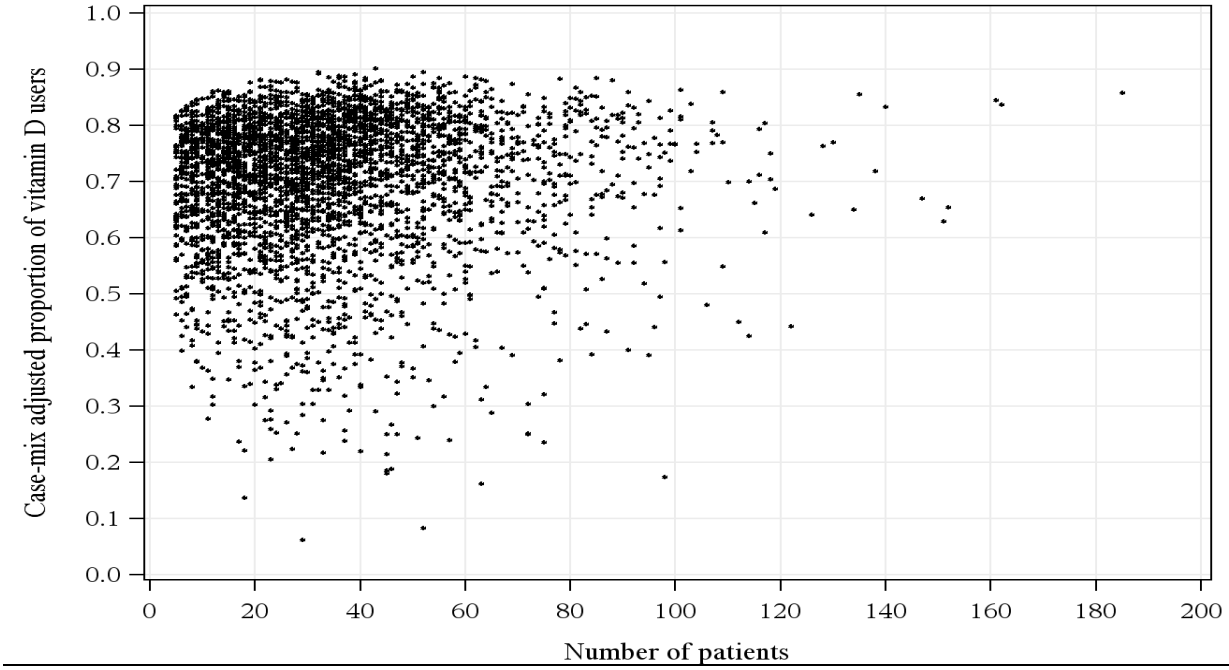


Correlation between non case-mix adjusted and case-mix adjusted proportion of vitamin D users per facility=0.930

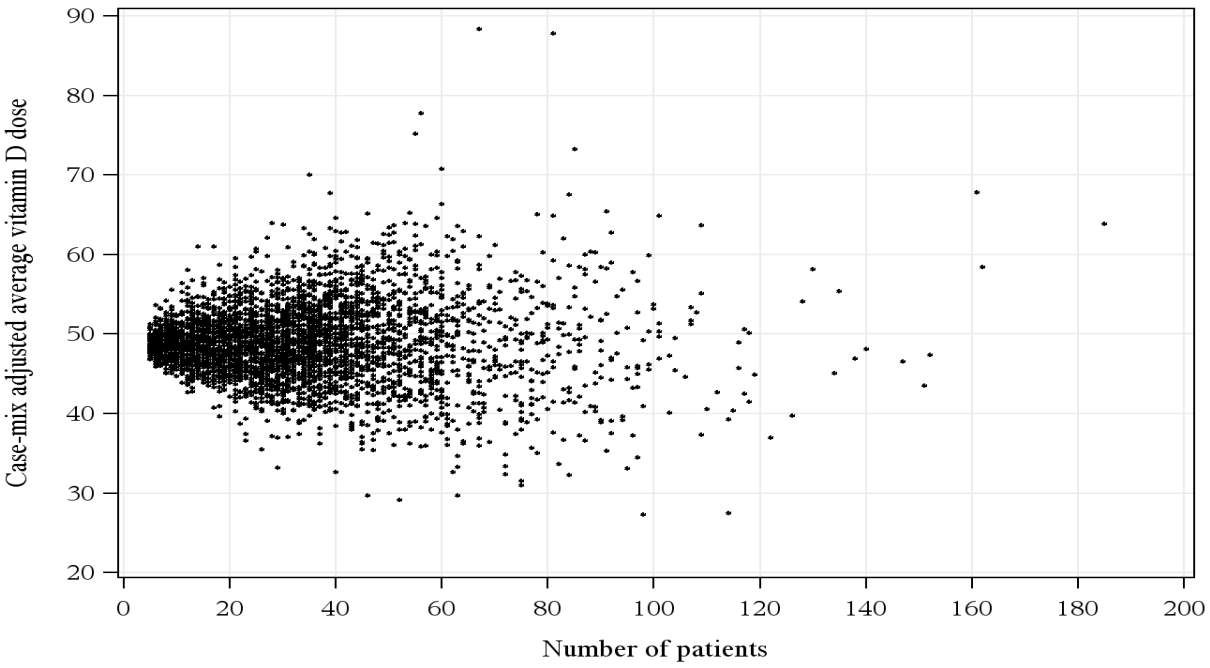


Appendix 6. Number of patients in a facility with each respectivement measure of vitamin D exposure

Case-mix adjusted proportion of vitamin D users



Case-mix adjusted average vitamin D dose per patient



Appendix 7. Demographic and clinical characteristics of cohort by whether patient is in a facility in the lowest versus highest quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Lower Quartile (%)	Upper Quartile (%)	Absolute standardized difference
N	34,000	33,950	
Age (years)			
18-44	10.3	10.3	0.0
45-64	28.8	29.5	1.5
65-74	31.2	31.2	0.0
>= 75	29.7	29.0	1.5
Race			
White	63.5	59.7	7.8
Black	31.2	35.7	9.5
Other	5.3	4.6	3.2
Female	47.1	47.6	1.0
Medicaid eligible	40.4	46.4	12.1**
Comorbidities			
Acute MI	4.6	4.4	1.0
Anemia	1.1	1.1	0.0
Autoimmune disorder	80.0	86.8	18.4**
Cancer	3.4	3.2	1.1
COPD/Asthma	2.3	2.4	0.7
Diabetes mellitus	11.4	11.1	0.9
Gastrointestinal bleed	19.6	18.4	3.1
Heart-related procedure	58.5	59.1	1.2
HIV/AIDS	5.7	5.8	0.4
Hypertension	79.8	79.9	0.2
Hyperthyroidism	1.0	1.1	1.0
Ischemic heart disease	38.2	37.7	1.0
Liver disease	3.3	3.2	0.6
Neurologic disorder	7.6	7.5	0.4
Obese	4.0	4.2	1.0
Other heart disorder	52.3	51.7	1.2
Peptic ulcer disease	3.8	3.9	0.5
PVD	25.1	25.1	0.0
Pneumonia	10.0	10.0	0.0
Psychiatric disorder	4.5	4.3	1.0
PCD	3.2	3.0	1.2
Stroke	12.3	12.2	0.3
Substance use disorder	6.3	5.8	2.1
Cause of ESRD			

Appendix 7. Demographic and clinical characteristics of cohort by whether patient is in a facility in the lowest versus highest quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Lower Quartile (%)	Upper Quartile (%)	Absolute standardized difference
Diabetes mellitus	48.4	48.4	0.0
Hypertension	29.9	31.2	2.8
Glomerulonephritis	8.0	7.7	1.1
Other	13.7	12.6	3.3
Parathyroidectomy	0.1	0.1	0.0
For-profit	63.7	86.4	54.4**
Free-standing	81.5	89.0	21.3**
Chain			
Chain #1	20.3	26.8	15.4**
Chain #2	7.1	16.4	29.2**
Chain #3	6.4	21.4	44.4**
Other chain	66.2	35.4	64.8**
Facility size			
Small	10.1	6.3	13.9**
Medium	44.8	43.9	1.8
Large	45.0	49.8	9.6
Region			
Midwest	28.3	17.8	25.1**
Northeast	13.7	21.5	20.6**
South	46.2	41.9	8.7
West	11.9	18.8	19.2**
Use of personal assistance aids	6.0	6.4	1.7
Fistula	24.7	24.8	0.2
Iron user	85.4	92.7	23.5

Abbreviations: Acute MI, acute myocardial infarction; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome; PVD, peripheral vascular disease; PCD, pulmonary circulation disorder

** An absolute standardized difference > 10 indicates significant imbalance of characteristic when comparing vitamin D users to non-vitamin D users

Appendix 8. Demographic and clinical characteristics of cohort by whether patient is in each quartile of case-mix adjusted proportion of vitamin D users

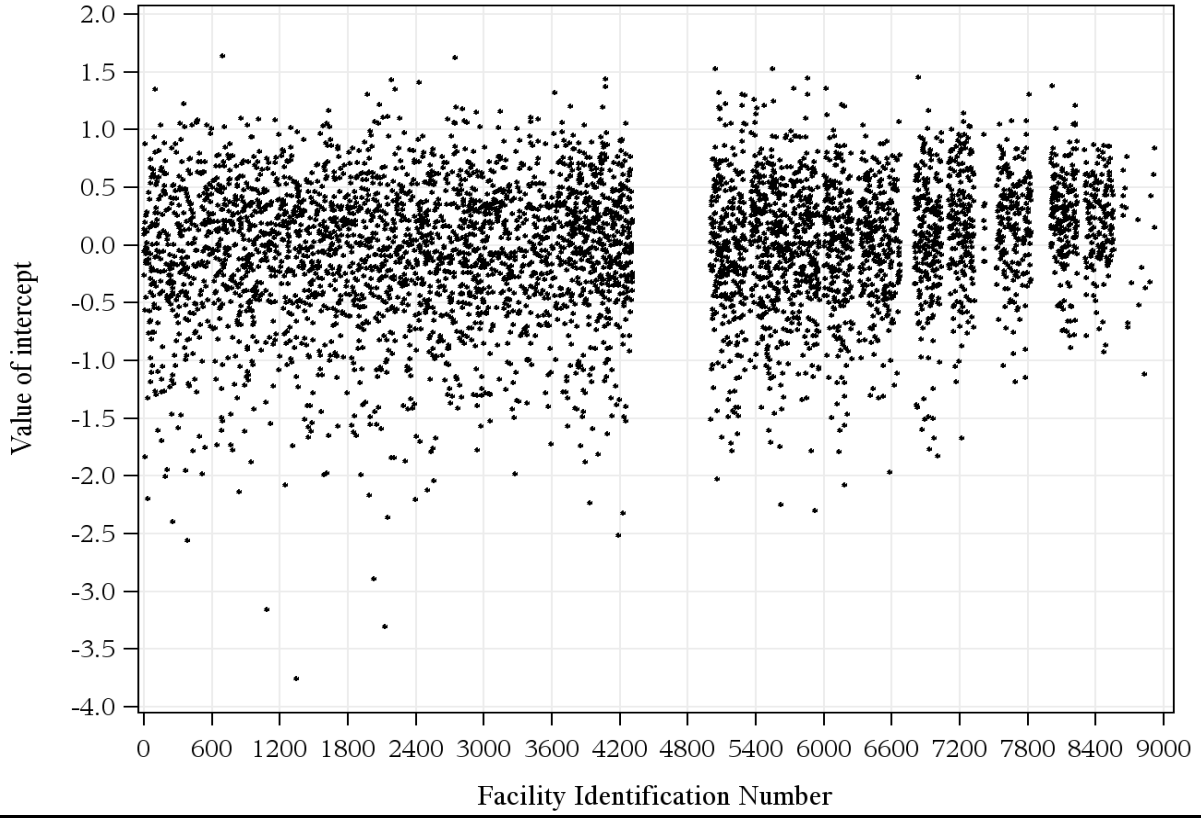
Characteristics	Quartile 1 [<25%] (%)	Quartile 2 [25-50%) (%)	Quartile 3 [50-75%] (%)	Quartile 4 [>75%] (%)
N	34,000	33,987	34,021	33,950
Age (years)				
18-44	10.3	10.4	10.0	10.3
45-64	28.8	29.0	29.1	29.5
65-74	31.2	31.3	31.2	31.2
>= 75	29.7	29.3	29.7	29.0
Race				
White	63.5	65.0	63.1	59.7
Black	31.2	29.7	32.2	35.7
Other	5.3	5.3	4.7	4.6
Female	47.1	47.4	48.0	47.6
Medicaid eligible	40.4	42.3	44.3	46.4
Comorbidities				
Acute MI	4.6	4.6	4.5	4.4
Anemia	1.1	1.2	1.1	1.1
Autoimmune disorder	80.0	86.8	85.8	86.8
Cancer	3.4	3.4	3.6	3.2
COPD/Asthma	2.3	2.3	2.3	2.4
Diabetes mellitus	11.4	11.1	11.0	11.1
Gastrointestinal bleed	19.6	19.3	19.1	18.4
Heart-related procedure	58.5	59.9	58.8	59.1
HIV/AIDS	5.7	5.4	5.3	5.8
Hypertension	79.8	79.7	80.1	79.9
Hyperthyroidism	1.0	0.8	0.9	1.1
Ischemic heart disease	38.2	38.9	38.6	37.7
Liver disease	3.3	3.2	3.7	3.2
Neurologic disorder	7.6	7.6	7.8	7.5
Obese	4.0	3.9	4.2	4.2
Other heart disorder	52.3	52.6	52.2	51.7
Peptic ulcer disease	3.8	3.7	4.0	3.9
PVD	25.1	25.1	25.0	25.1
Pneumonia	10.0	10.2	10.0	10.0

Appendix 8. Demographic and clinical characteristics of cohort by whether patient is in each quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Quartile 1 [<25%] (%)	Quartile 2 [25-50%) (%)	Quartile 3 [50-75%] (%)	Quartile 4 [>75%] (%)
Psychiatric disorder	4.5	4.4	4.5	4.3
PCD	3.2	3.1	3.2	3.0
Stroke	12.3	12.8	12.8	12.2
Substance use disorder	6.3	6.3	6.0	5.8
Cause of ESRD				
Diabetes mellitus	48.4	49.3	49.1	48.4
Hypertension	29.9	29.2	29.9	31.2
	8.0	8.2	8.0	7.7
Glomerulonephritis				
Other	13.7	13.3	13.0	12.6
Parathyroidectomy	0.1	0.1	0.1	0.1
For-profit	63.7	82.2	85.3	86.4
Free-standing	81.5	88.0	90.1	89.0
Chain				
Chain #1	20.3	30.6	27.8	26.8
Chain #2	7.1	15.5	17.2	16.4
Chain #3	6.4	9.0	16.7	21.4
Other chain	66.2	44.9	38.2	35.4
Facility size				
Small	10.1	11.0	10.0	6.3
Medium	44.8	43.6	44.9	43.9
Large	45.0	45.5	45.1	49.8
Region				
Midwest	28.3	20.0	22.8	17.8
Northeast	13.7	19.3	15.1	21.5
South	46.2	46.2	45.3	41.9
West	11.9	14.5	16.8	18.8
Use of personal assistance aids	6.0	6.2	6.3	6.4
Fistula	24.7	25.2	24.9	24.8
Iron user	85.4	92.0	92.4	92.7

Abbreviations: Acute MI, acute myocardial infarction; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome; PVD, peripheral vascular disease; PCD, pulmonary circulation disorder

Appendix 9. Intercept generated from mixed-effects logistic regression model used to create the case-mix adjusted proportion of vitamin D users per facility



Appendix 10. Supremum tests[a] of proportional hazards assumption for association between case-mix adjusted measures of vitamin D exposure and fracture outcomes

Outcome	Case-mix Adjusted Proportion of VD Users[b]		Case-mix Adjusted Average Vitamin D Dose per Patient[c]	
	Max absolute Value	P-Value	Max absolute Value	P-Value
Any fracture	52.00	0.368	83.61	0.087
Pelvis/hip	41.35	0.227	46.94	0.285
Vertebral	32.52	0.123	21.02	0.763
Other[d]	38.74	0.113	54.74	0.022

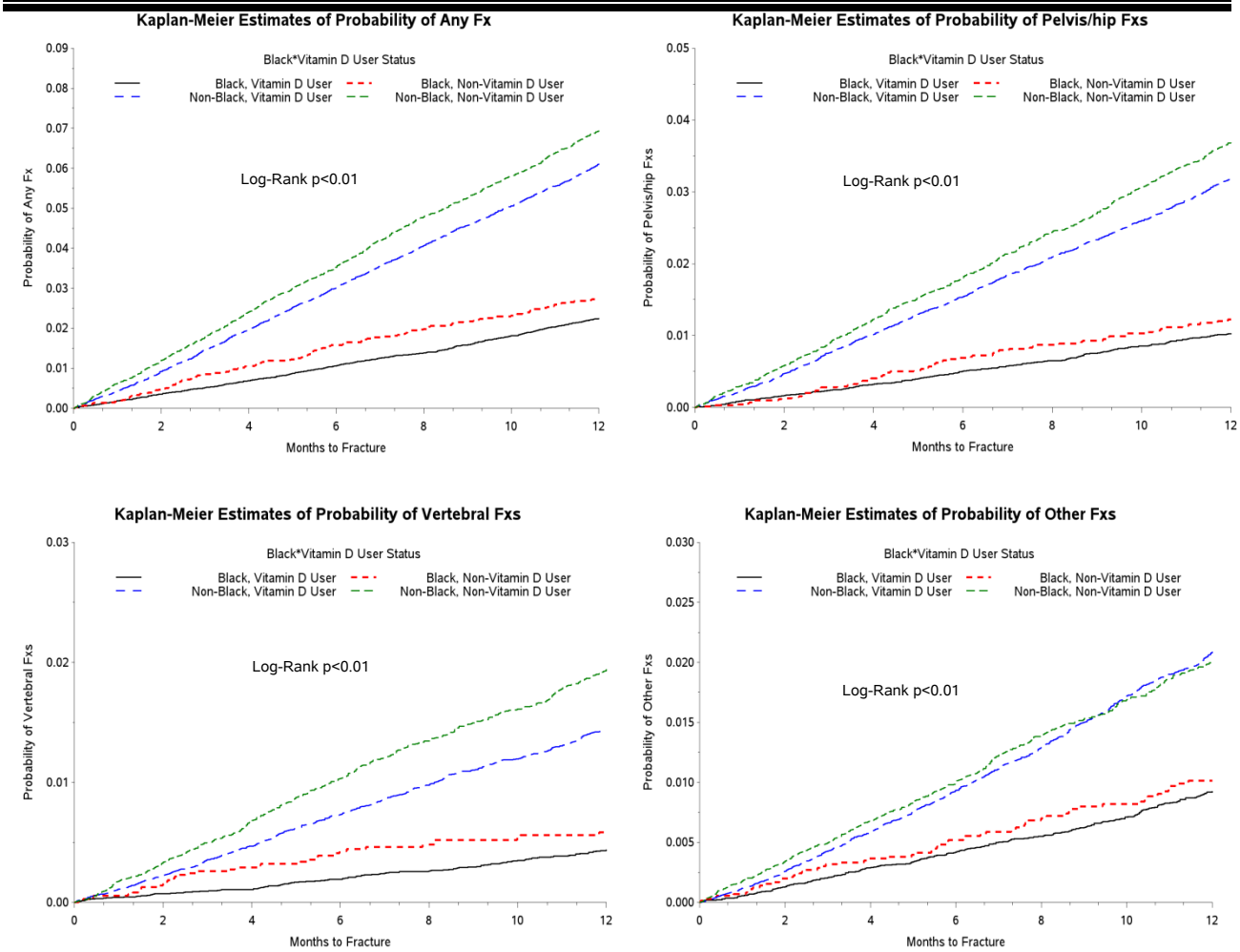
[a]A non-significant p-value suggests that there was no sufficient evidence that the proportional hazards assumption was violated

[b]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

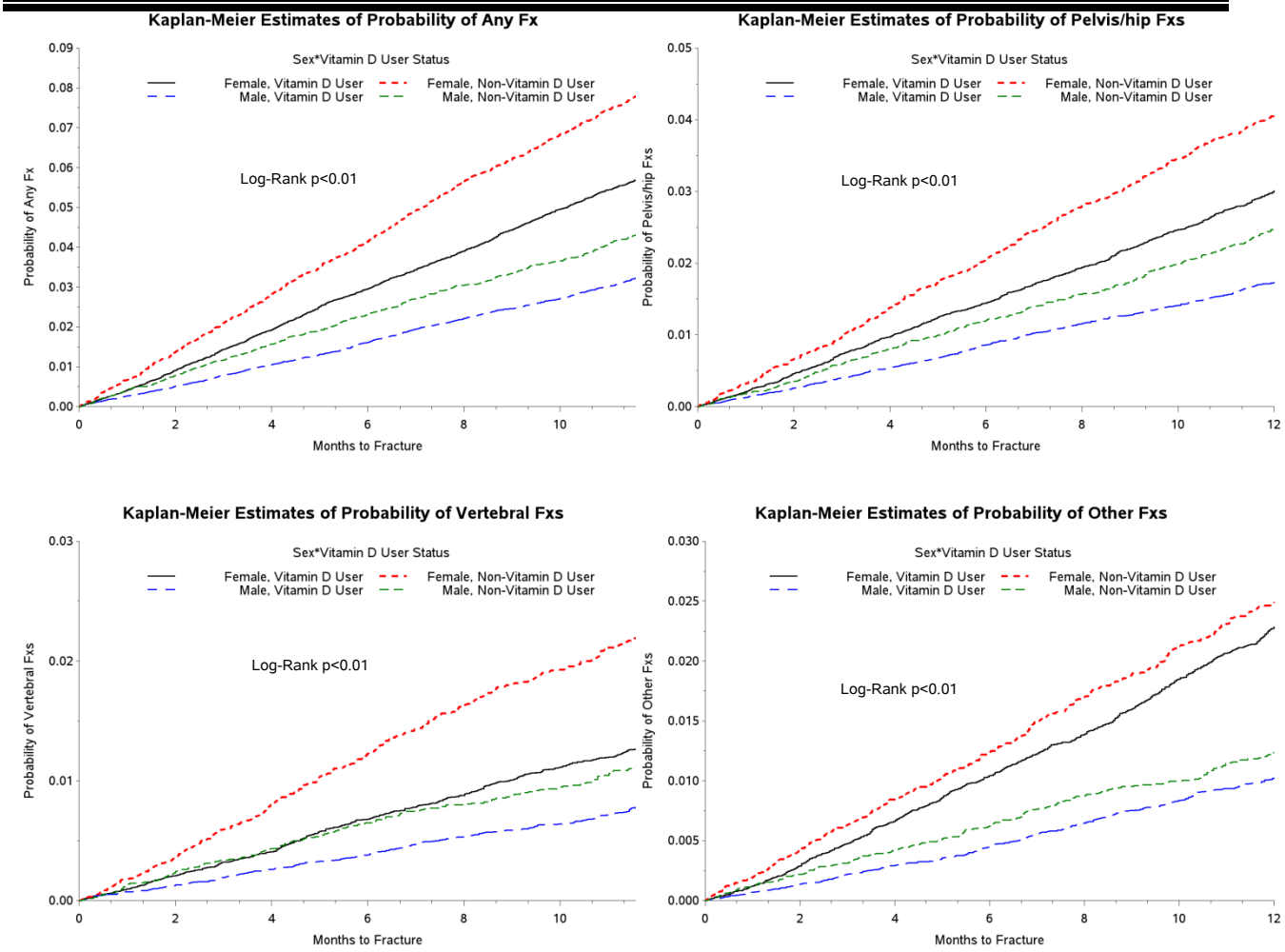
[c]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of renal disease

[d]Other fracture comprised of lower leg, shoulder/upper arm, ribs/sternum, femur, and forearm/wrist fractures

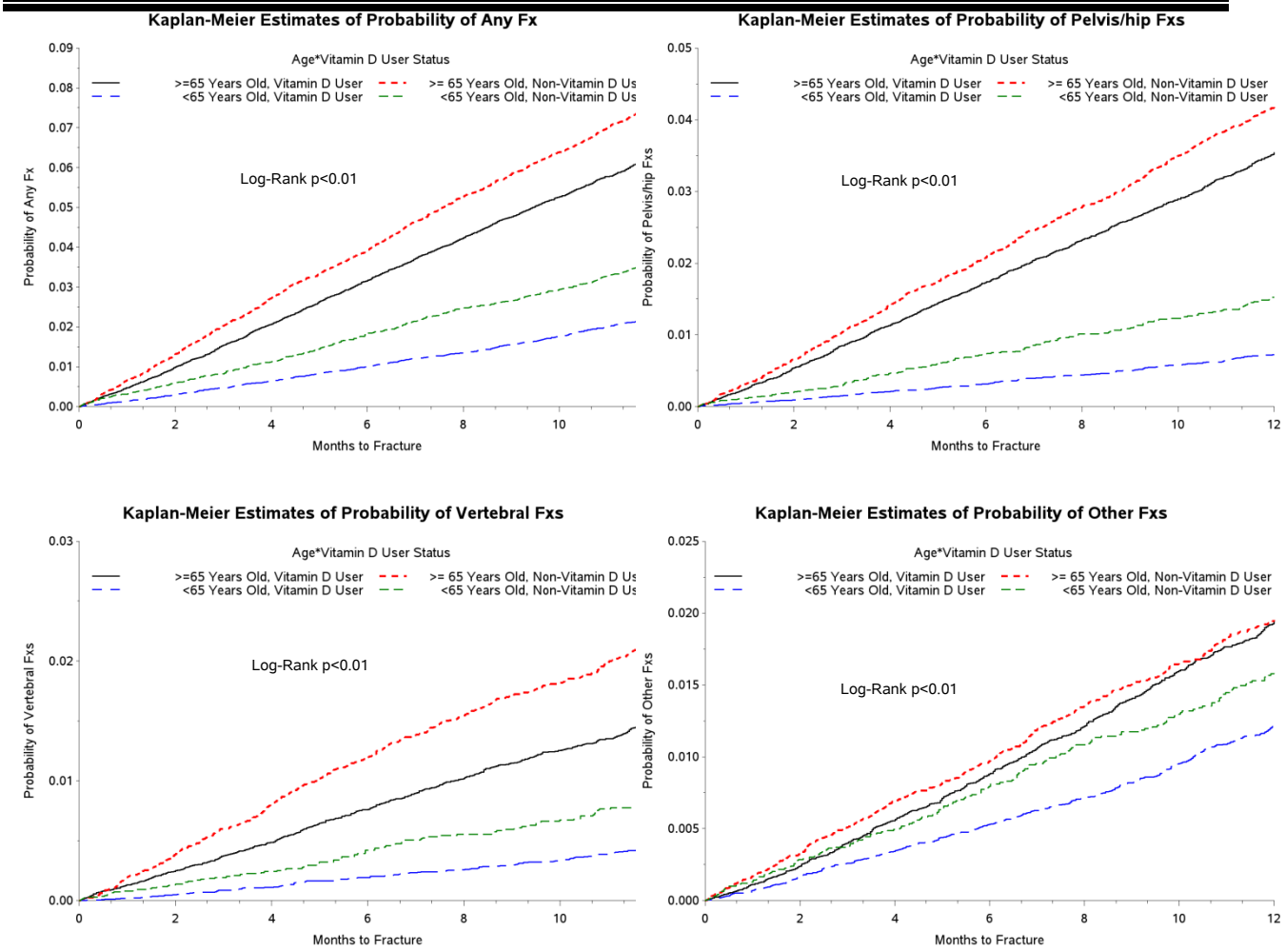
Appendix 11. Kaplan-Meier time to fracture curves by race*vitamin D user status



Appendix 12. Kaplan-Meier time to fracture curves by sex*vitamin D user status



Appendix 13. Kaplan-Meier time to fracture curves by age*vitamin D user status



Appendix 14. Multivariable[a] Cox models of the association between facility-level case-mix adjusted average vitamin d dose per patient[b] and fracture among subgroups (Years 2000-2004)

	Non-Black	Male	Age <65 years
	HR (95% CI)[c]	HR (95% CI)	HR (95% CI)
Any	1.02 (0.92-1.12)	1.16 (1.06-1.28)**	1.06 (0.90-1.25)
Pelvis/hip	1.08 (0.98-1.19)	1.25 (1.15-1.36)**	0.99 (0.64-1.54)
Vertebral	0.84 (0.52-1.35)	1.04 (0.79-1.37)	1.12 (0.93-1.36)
Other	0.98 (0.81-1.18)	1.05 (0.83-1.34)	1.07 (0.91-1.27)

[a]Cox models adjusted for age (except for the age subgroup analysis), sex (except for the sex subgroup analysis), race(except for the race subgroup analysis), Medicaid eligibility, the presence of comorbidities, primary cause of end-stage renal disease, prior history of parathyroidectomy, facility characteristics, use of personal assistance aids, and the presence of a fistula.

[b]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of ESRD

[c]Hazard Ratio (95% confidence interval)

**p<0.01

Appendix 15. Cox models of the association between non-case-mix adjusted measures of vitamin D exposure and fracture risk (Years 2000-2004)

Fracture Type	Proportion of VD Users	Average Vitamin D Dose per Patient
	HR (95% CI)[a]	HR (95% CI)
Any		
Crude	0.66 (0.56-0.78)**	0.77 (0.49-1.20)
Adjusted[b]	1.10 (0.92-1.31)	1.00 (0.97-1.02)
Pelvis/hip		
Crude	0.57 (0.46-0.71)**	0.84 (0.38-1.88)
Adjusted	0.98 (0.77-1.25)	1.00 (0.98-1.03)
Vertebral		
Crude	0.62 (0.45-0.84)**	0.52 (0.38-0.70)**
Adjusted	1.08 (0.75-1.55)	0.95 (0.87-1.05)
Other[c]		
Crude	0.93 (0.69-1.25)	0.81 (0.65-1.02)
Adjusted	1.40 (1.00-1.94)**	0.99 (0.96-1.02)

[a]Hazard Ratio (95% confidence interval)
[b]Cox models adjusted for age, sex, race, Medicaid eligibility, comorbidities, primary cause of end-stage renal disease, prior history of parathyroidectomy, facility characteristics, use of personal assistance aids, and the presence of a fistula.
[c]Other fracture comprised of lower leg, shoulder/upper arm, ribs/sternum, femur, and forearm/wrist fractures
** $p<0.05$

Appendix 16. Cox models of the association between being in a facility in the highest quartile of case-mix adjusted average vitamin D dose per patient[a] and fracture risk (Years 2000-2004)

Fracture Type	Facility in Highest Quartile
	HR (95% CI)[b]
Any	
Crude	0.97 (0.91-1.04)
Adjusted[b]	1.03 (0.97-1.10)
Pelvis/hip	
Crude	0.99 (0.90-1.08)
Adjusted	1.05 (0.96-1.15)
Vertebral	
Crude	0.89 (0.78-1.01)
Adjusted	0.94 (0.83-1.08)
Other[c]	
Crude	0.99 (0.89-1.10)
Adjusted	1.03 (0.93-1.15)

[a]Cox models adjusted for age, sex, race, Medicaid eligibility, comorbidities, primary cause of end-stage renal disease, prior history of parathyroidectomy, facility characteristics, use of personal assistance aids, and the presence of a fistula.
[b]Hazard Ratio (95% confidence interval)
[c]Other fracture comprised of lower leg, shoulder/upper arm, ribs/sternum, femur, and forearm/wrist fractures

Appendix 17. Sensitivity analysis: Cox models of the association between measures of vitamin d exposure and fracture risk (Years 2000-2008)

Fracture Type	Proportion of Vitamin D Users[a]	Average Vitamin D Dose per Patient[b]
	HR (95% CI)[c]	HR (95% CI)
Any		
Crude	0.84 (0.70-1.00)	0.97 (0.89-1.07)
Adjusted[d]	0.88 (0.74-1.06)	1.02 (0.94-1.10)
Pelvis/hip		
Crude	0.81 (0.64-1.03)	0.98 (0.86-1.12)
Adjusted	0.85 (0.66-1.09)	1.03 (0.92-1.14)
Vertebral		
Crude	0.76 (0.55-1.06)	0.81 (0.60-1.10)
Adjusted	0.77 (0.54-1.11)	0.88 (0.66-1.17)
Other[e]		
Crude	0.99 (0.75-1.30)	1.01 (0.85-1.20)
Adjusted	1.02 (0.76-1.38)	1.03 (0.86-1.23)

[a]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[b]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of renal disease

[c]Hazard Ratio (95% confidence interval)

[d]Cox models adjusted for age, sex, race, Medicaid eligibility, comorbidities, primary cause of end-stage renal disease, prior history of parathyroidectomy, facility characteristics, use of personal assistance aids, and the presence of a fistula.

[e]Other fracture comprised of lower leg, shoulder/upper arm, ribs/sternum, femur, and forearm/wrist fractures

Appendix 18. Description of length of intravenous vitamin D exposure measurement period in observational studies of hemodialysis patients

First Author, Year	Data Source	Patient population	Study design	Main Predictor	Outcome	Length of vitamin D exposure measurement period	Relevant notes?
Dobrez, 2004	Records from major dialysis provider	Incident HD patients	Retrospective cohort	IV vitamin D use	Hospitalizations /Hospital days	A minimum of 60 days of HD and a minimum of 10 IV vitamin D injections	-
Kilpatrick, 2011	Records from major dialysis provider	Incident HD patients	Case-crossover	IV vitamin D use	Hypercalcemia/ hyperphosphate-mia	60 days	-
Shinaberger, 2008	Records from major for-profit dialysis provider	All HD patients	Retrospective cohort	IV vitamin D use	All-cause mortality	90 days	-
Teng, 2003	Records from major for-profit dialysis provider	All HD patients	Retrospective cohort	IV vitamin D use	All-cause mortality	Varied: Time between index date and censoring event whereby patient used one IV vitamin D drug exclusively	Base-line laboratory values represent the mean value during the 3 months before initiation of treatment with vitamin D

Appendix 18. Description of length of intravenous vitamin D exposure measurement period in observational studies of hemodialysis patients

First Author, Year	Data Source	Patient population	Study design	Main Predictor	Outcome	Length of vitamin D exposure measurement period	Relevant notes?
Teng, 2005	Records from major for-profit dialysis provider	Incident HD patients	Retrospective cohort	IV vitamin D use	All-cause mortality	Vitamin D measured as a time-varying variable.	73% of those who were eventually treated with injectable vitamin D had started within 90 d of initiating chronic hemodialysis, 83% had started within 180 d, and 93% had started within 365 d
Tentori, 2006	Records from major non-profit dialysis provider	Incident HD patients	Retrospective cohort	IV vitamin D use	All-cause mortality	Varied: 30 days & 90 days	-
Tentori, 2009	Dialysis Outcomes and Practice Patterns Study (DOPPS)	All HD patients	Retrospective cohort	IV/oral vitamin D use	All-cause mortality	Vitamin D prescription (yes/no) measured as a time-varying varying in the last week of the prior 4-	-

Appendix 18. Description of length of intravenous vitamin D exposure measurement period in observational studies of hemodialysis patients

First Author, Year	Data Source	Patient population	Study design	Main Predictor	Outcome	Length of vitamin D exposure measurement period	Relevant notes?
						month interval	
Wolf, 2008	Accelerated Mortality on Renal Replace-ment (ArMORR)	Incident HD patients	Retrospective cohort	Race & ethnicity /IV vitamin D use	All-cause mortality	IV vitamin D analyzed as a time-dependent covariate and calculated from the average dosage over each calendar quarter standardized to the total number of calendar quarters of follow-up. All other covariates collected at dialysis	Among all patients, 77% were treated with vitamin D beginning at a median of day 16 (interquartile range 9 to 43 d) after initiating dialysis and continuing for a median duration of 270 d (interquartile range 126 to 348 d), or 77% of the total follow-up period.

Appendix 18. Description of length of intravenous vitamin D exposure measurement period in observational studies of hemodialysis patients

First Author, Year	Data Source	Patient population	Study design	Main Predictor	Outcome	Length of vitamin D exposure measurement period	Relevant notes?
						initiation	
Zhang, 2012	U.S. Renal Data System (USRDS)	Incident HD patients	Retrospective cohort	IV epoetin, IV iron, and IV vitamin D use	All-cause mortality	90 days	-

Abbreviations: HD, hemodialysis; IV intravenous

Appendix 19. Sensitivity analysis where baseline period changed to 30 days: Demographic and clinical characteristics of cohort by whether patient is in a facility in the lowest or highest quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Lower Quartile (%)	Upper Quartile (%)	Absolute standardized difference
N	42,474	42,476	-
Age (years)			
18-44	9.6	9.5	0.3
45-64	26.7	27.2	1.1
65-74	31.4	31.5	0.2
>= 75	32.2	31.8	0.9
Race			
White	67.2	62.5	9.9
Black	27.7	33.0	11.5
Other	5.1	4.6	2.3
Female	47.2	47.7	1.0
Medicaid eligible	35.6	40.7	10.5
Comorbidities			
Acute MI	1.3	1.3	0.0
Anemia	0.6	0.5	1.4
Autoimmune disorder	59.0	68.2	19.2**
Cancer	1.3	1.2	0.9
COPD/Asthma	0.4	0.4	0.0
Diabetes mellitus	5.0	4.8	0.9
Gastrointestinal bleed	8.4	7.5	3.3
Heart-related procedure	36.7	36.3	0.8
HIV/AIDS	1.6	1.7	0.8
Hypertension	41.4	38.9	5.1
Hyperthyroidism	0.3	0.4	1.7
Ischemic heart disease	15.7	15.1	1.7
Liver disease	1.5	1.1	3.5
Neurologic disorder	2.9	2.6	1.8
Obese	1.2	1.2	0.0
Other heart disorder	25.4	24.2	2.8
Peptic ulcer disease	1.0	1.1	1.0
PVD	9.1	8.8	1.1
Pneumonia	3.1	2.9	1.2
Psychiatric disorder	1.4	1.4	0.0
PCD	0.9	0.9	0.0
Stroke	5.0	4.9	0.5
Substance use disorder	1.5	1.5	0.0

Cause of ESRD			
Diabetes mellitus	47.7	47.9	0.4
Hypertension	29.9	31.1	2.6
Glomerulonephritis	7.7	7.7	0.0
Other	14.7	13.3	4.0
Parathyroidectomy	0.0	0.0	.
For-profit	63.0	87.5	59.2**
Free-standing	79.6	90.0	29.3**
Chain			
Chain #1	20.7	27.0	14.8**
Chain #2	6.2	19.4	40.3**
Chain #3	5.5	22.9	51.5**
Other chain	67.6	30.7	79.4**
Facility size			
Small	9.1	5.0	16.1**
Medium	43.5	47.5	8.0
Large	47.4	47.5	0.2
Region			
Midwest	27.7	20.1	17.9**
Northeast	15.8	17.9	5.6
South	44.7	42.3	4.8
West	11.9	19.7	21.5**
Use of personal assistance aids	1.8	1.9	0.7
Fistula	6.8	7.0	0.8

Abbreviations: Acute MI, acute myocardial infarction; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome; PVD, peripheral vascular disease; PCD, pulmonary circulation disorder

** An absolute standardized difference > 10 indicates significant imbalance of characteristic when comparing vitamin D users to non-vitamin D users

Appendix 20. Sensitivity analysis where baseline period changed to 90 days: Demographic and clinical characteristics of cohort by whether patient is in a facility in the lowest or highest quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Lower Quartile (%)	Upper Quartile (%)	Absolute standardized difference
N	39,387	39,395	
Age (years)			
18-44	9.9	9.9	0.0
45-64	27.8	28.5	1.6
65-74	31.3	31.4	0.2
>= 75	31.0	30.3	1.5
Race			
White	65.7	60.5	10.8**
Black	29.4	35.2	12.4*
Other	4.9	4.2	3.4
Female	47.3	47.9	1.2
Medicaid eligible	38.0	43.4	11.0**
Comorbidities			
Acute MI	2.9	2.8	0.6
Anemia	0.9	0.8	1.1
Autoimmune disorder	72.7	80.0	17.2**
Cancer	2.3	2.3	0.0
COPD/Asthma	1.2	1.2	0.0
Diabetes mellitus	8.7	8.3	1.4
Gastrointestinal bleed	14.6	13.3	3.8
Heart-related procedure	51.6	51.5	0.2
HIV/AIDS	3.4	3.5	0.5
Hypertension	66.2	65.3	1.9
Hyperthyroidism	0.5	0.7	2.6
Ischemic heart disease	28.7	28.1	1.3
Liver disease	2.3	2.2	0.7
Neurologic disorder	5.5	5.3	0.9
Obese	2.6	2.6	0.0
Other heart disorder	41.1	40.3	1.6
Peptic ulcer disease	2.5	2.3	1.3
PVD	18.0	17.3	1.8
Pneumonia	6.5	6.2	1.2
Psychiatric disorder	3.0	2.9	0.6
PCD	1.9	1.9	0.0
Stroke	9.1	8.9	0.7
Substance use disorder	3.9	3.6	1.6
Cause of ESRD			

Appendix 20. Sensitivity analysis where baseline period changed to 90 days: Demographic and clinical characteristics of cohort by whether patient is in a facility in the lowest or highest quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Lower Quartile (%)	Upper Quartile (%)	Absolute standardized difference
Diabetes mellitus	48.3	48.2	0.2
Hypertension	30.0	31.2	2.6
Glomerulonephritis	7.7	7.6	0.4
Other	14.0	13.0	2.9
Parathyroidectomy	0.0	0.0	.
For-profit	63.6	87.2	57.0**
Free-standing	80.3	89.7	26.6**
Chain			
Chain #1	20.1	25.8	13.6**
Chain #2	6.5	19.2	38.7**
Chain #3	5.8	21.1	46.0**
Other chain	67.6	33.9	71.6**
Facility size			
Small	9.6	5.5	15.6**
Medium	43.7	44.4	1.4
Large	46.7	50.1	6.8
Region			
Midwest	27.7	19.5	19.4**
Northeast	15.8	18.7	7.7
South	46.0	43.4	5.2
West	10.5	18.4	22.6**
Use of personal assistance aids	3.9	3.8	0.5
Fistula	16.4	16.8	1.1

Abbreviations: Acute MI, acute myocardial infarction; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome; PVD, peripheral vascular disease; PCD, pulmonary circulation disorder

** An absolute standardized difference > 10 indicates significant imbalance of characteristic when comparing vitamin D users to non-vitamin D users

Appendix 21. Sensitivity analysis where baseline period changed to 365 days: Demographic and clinical characteristics of cohort by whether patient is in a facility in the lowest or highest quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Lower Quartile (%)	Upper Quartile (%)	Absolute standardized difference
N	24,846	24,823	
Age (years)			
18-44	10.9	11.2	1.0
45-64	30.3	31.9	3.5
65-74	31.3	31.0	0.6
>= 75	27.5	26.0	3.4
Race			
White	62.9	58.6	8.8
Black	31.7	36.7	10.6**
Other	5.5	4.7	3.6
Female	46.9	47.5	1.2
Medicaid eligible	42.6	49.9	14.7**
Comorbidities			
Acute MI	7.1	7.1	0.0
Anemia	1.3	1.3	0.0
Autoimmune disorder	87.6	92.2	15.3**
Cancer	4.6	4.9	1.4
COPD/Asthma	4.2	4.3	0.5
Diabetes mellitus	14.5	14.2	0.9
Gastrointestinal bleed	25.7	24.5	2.8
Heart-related procedure	63.9	65.3	2.9
HIV/AIDS	8.8	9.3	1.7
Hypertension	89.7	90.3	2.0
Hyperthyroidism	1.7	1.6	0.8
Ischemic heart disease	48.1	48.1	0.0
Liver disease	4.4	4.9	2.4
Neurologic disorder	10.8	10.8	0.0
Obese	6.2	6.7	2.0
Other heart disorder	64.3	64.0	0.6
Peptic ulcer disease	6.1	6.6	2.1
PVD	34.4	34.8	0.8
Pneumonia	15.6	15.7	0.3
Psychiatric disorder	6.5	6.1	1.6
PCD	5.0	4.8	0.9
Stroke	16.9	17.4	1.3
Substance use disorder	9.6	9.0	2.1
Cause of ESRD			

Appendix 21. Sensitivity analysis where baseline period changed to 365 days: Demographic and clinical characteristics of cohort by whether patient is in a facility in the lowest or highest quartile of case-mix adjusted proportion of vitamin D users

Characteristics	Lower Quartile (%)	Upper Quartile (%)	Absolute standardized difference
Diabetes mellitus	49.0	48.7	0.6
Hypertension	28.9	31.2	5.0
Glomerulonephritis	8.6	8.2	1.4
Other	13.5	11.9	4.8
Parathyroidectomy	0.1	0.2	2.6
For-profit	64.7	84.8	47.6**
Free-standing	81.8	88.3	18.3**
Chain			
Chain #1	21.3	25.8	10.6**
Chain #2	8.5	15.3	21.1**
Chain #3	6.8	21.0	41.9**
Other chain	63.5	37.9	53.0**
Facility size			
Small	10.3	8.5	6.2
Medium	44.4	39.8	9.3
Large	45.3	51.7	12.8**
Region			
Midwest	26.2	18.0	19.9**
Northeast	15.1	20.5	14.2**
South	45.6	41.9	7.5
West	13.1	19.6	17.6**
Use of personal assistance aids	10.0	10.6	2.0
Fistula	32.7	33.7	2.1

Abbreviations: Acute MI, acute myocardial infarction; ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome; PVD, peripheral vascular disease; PCD, pulmonary circulation disorder

** An absolute standardized difference > 10 indicates significant imbalance of characteristic when comparing vitamin D users to non-vitamin D users

Appendix 22. Sensitivity analysis: Cox models of the association between measures of vitamin D exposure and fracture risk after adjusting for relevant covariates- Varying length of baseline to 30 days, 90 days, and 365 days

Fracture Type	Proportion of Vitamin D Users[a] HR (95% CI)[c]	Average Vitamin D Dose per Patient[b] HR (95% CI)
Length of baseline=30 days		
Any	0.88 (0.72-1.09)	1.10 (0.87-1.38)
Pelvis/hip	0.88 (0.66-1.16)	1.36 (1.02-1.80)**
Vertebral	0.82 (0.57-1.18)	0.02 (0.00-17.99)
Other[e]	0.89 (0.61-1.31)	0.61 (0.26-1.44)
Length of baseline=90 days		
Any	0.99 (0.80-1.23)	1.02 (0.97-1.07)
Pelvis/hip	1.04 (0.78-1.39)	1.14 (1.08-1.19)**
Vertebral	0.91 (0.62-1.36)	0.58 (0.17-1.95)
Other	1.03 (0.70-1.52)	0.77 (0.51-1.16)
Length of baseline=365 days		
Any	0.99 (0.72-1.34)	1.01 (0.94-1.09)
Pelvis/hip	0.75 (0.49-1.15)	0.96 (0.84-1.09)
Vertebral	0.70 (0.38-1.28)	1.01 (0.87-1.16)
Other	1.92 (1.09-3.36)**	1.05 (0.97-1.14)

** $p<0.05$

[a]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[b]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[c]Hazard Ratio (95% CI)

[d]Cox models adjusted for age, sex, race, Medicaid eligibility, comorbidities, primary cause of ESRD, prior history of parathyroidectomy, facility characteristics, use of personal assistance aids, and the presence of a fistula.

[e]Other fracture comprised of lower leg, shoulder/upper arm, ribs/sternum, femur, and forearm/wrist fractures

Appendix 23. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and vertebral fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted proportion of vitamin D users	1.03 (0.65- 1.63)	0.911	1.06 (0.64- 1.74)	0.827
Age (years)[Reference: 65-74]				
18-44			0.35 (0.25- 0.50)	<0.01
45-64			0.55 (0.46- 0.66)	<0.01
>= 75			1.45 (1.28- 1.65)	<0.01
Female			1.89 (1.68- 2.13)	<0.01
Race [Reference: White]				
Black			0.35 (0.29- 0.42)	<0.01
Other			0.83 (0.63- 1.09)	0.177
Comorbidities				
Medicaid eligible			0.86 (0.75- 0.98)	0.026
Acute MI			1.10 (0.86- 1.41)	0.431
Anemia			1.08 (0.92- 1.26)	0.376
Autoimmune disorder			1.67 (1.32- 2.12)	<0.01
Cancer			1.44 (1.24- 1.67)	<0.01
COPD/Asthma			1.15 (0.99- 1.32)	0.066
Diabetes mellitus			1.05 (0.91- 1.22)	0.492
Gastrointestinal bleed			1.33 (1.07- 1.65)	0.011
Heart-related procedure			1.03 (0.72- 1.45)	0.886
HIV/AIDS			1.57 (0.70- 3.53)	0.271
Hypertension			1.01 (0.87- 1.18)	0.851
Hyperthyroidism			0.82 (0.48- 1.40)	0.467
Ischemic heart disease			1.05 (0.93- 1.20)	0.437
Liver disease			1.83 (1.39- 2.41)	<0.01
Neurologic disorder			0.97 (0.78- 1.21)	0.816
Obese			0.75 (0.54- 1.05)	0.094
Other heart disorder			1.43 (1.25- 1.64)	<0.01
Peptic ulcer disease			1.12 (0.86- 1.45)	0.406
Peripheral vascular disease			0.88 (0.77- 1.00)	0.053
Pneumonia			1.16 (0.97- 1.39)	0.093
Psychiatric disorder			0.94 (0.70- 1.25)	0.655
Pulmonary circulation disorder			1.18 (0.89- 1.56)	0.241
Stroke			0.93 (0.79- 1.10)	0.414
Substance use disorder			1.10 (0.84- 1.44)	0.497

Appendix 23. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and vertebral fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			1.09 (0.92- 1.28)	0.311
Glomerulonephritis			0.99 (0.77- 1.28)	0.959
Other			1.27 (1.05- 1.53)	0.012
Parathyroidectomy			1.02 (0.15- 6.98)	0.987
For-profit			1.08 (0.87- 1.34)	0.490
Free-standing			0.97 (0.76- 1.23)	0.802
Chain [Reference: Chain #1]				
Chain #2			0.77 (0.63- 0.93)	<0.01
Chain #3			0.81 (0.66- 0.99)	0.038
Other chain			0.88 (0.75- 1.02)	0.096
Facility size [Reference: Small]				
Medium			1.05 (0.85- 1.29)	0.655
Large			0.96 (0.78- 1.19)	0.720
Region [Reference: Northeast]				
Midwest			1.04 (0.88- 1.24)	0.622
South			1.06 (0.89- 1.26)	0.503
West			1.21 (1.00- 1.46)	0.055
Use of personal assistance aids			1.29 (1.05- 1.57)	0.013
Fistula			1.17 (1.03- 1.33)	0.015

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;

[a]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[b]Hazard Ratio (95% confidence interval)

Appendix 24. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and vertebral fractures

	Model 1		Model 2	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted average vitamin D dose/patient	0.70 (0.37- 1.34)	0.285	0.76 (0.41- 1.40)	0.378
Age (years)[Reference: 65-74]				
18-44			0.35 (0.25- 0.50)	<0.01
45-64			0.55 (0.46- 0.66)	<0.01
>= 75			1.45 (1.29- 1.65)	<0.01
Female			1.89 (1.68- 2.13)	<0.01
Race [Reference: White]				
Black			0.35 (0.29- 0.42)	<0.01
Other			0.83 (0.63- 1.08)	0.169
Comorbidities				
Medicaid eligible			0.86 (0.75- 0.98)	0.026
Acute MI			1.10 (0.86- 1.40)	0.435
Anemia			1.08 (0.92- 1.27)	0.362
Autoimmune disorder			1.67 (1.32- 2.12)	<0.01
Cancer			1.44 (1.24- 1.67)	<0.01
COPD/Asthma			1.14 (0.99- 1.32)	0.067
Diabetes mellitus			1.05 (0.91- 1.22)	0.490
Gastrointestinal bleed			1.33 (1.07- 1.65)	0.011
Heart-related procedure			1.03 (0.72- 1.46)	0.882
HIV/AIDS			1.57 (0.70- 3.53)	0.271
Hypertension			1.02 (0.87- 1.18)	0.845
Hyperthyroidism			0.82 (0.48- 1.41)	0.471
Ischemic heart disease			1.05 (0.92- 1.20)	0.443
Liver disease			1.83 (1.39- 2.41)	<0.01
Neurologic disorder			0.97 (0.78- 1.21)	0.814
Obese			0.75 (0.54- 1.05)	0.095
Other heart disorder			1.43 (1.25- 1.64)	<0.01
Peptic ulcer disease			1.12 (0.86- 1.45)	0.406
Peripheral vascular disease			0.88 (0.77- 1.00)	0.054
Pneumonia			1.16 (0.97- 1.39)	0.093
Psychiatric disorder			0.94 (0.70- 1.25)	0.650
Pulmonary circulation disorder			1.18 (0.89- 1.56)	0.241
Stroke			0.93 (0.79- 1.10)	0.415
Substance use disorder			1.10 (0.84- 1.44)	0.500

Appendix 24. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and vertebral fractures

	Model 1		Model 2	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			1.09 (0.93- 1.28)	0.306
Glomerulonephritis			0.99 (0.77- 1.28)	0.965
Other			1.27 (1.06- 1.53)	0.011
Parathyroidectomy			1.02 (0.15- 7.04)	0.981
For-profit			1.09 (0.88- 1.35)	0.420
Free-standing			0.97 (0.76- 1.23)	0.780
Chain [Reference: Chain #1]				
Chain #2			0.77 (0.63- 0.94)	0.010
Chain #3			0.82 (0.67- 1.00)	0.048
Other chain			0.87 (0.75- 1.02)	0.082
Facility size [Reference: Small]				
Medium			1.05 (0.85- 1.29)	0.656
Large			0.96 (0.78- 1.19)	0.724
Region [Reference: Northeast]				
Midwest			1.04 (0.87- 1.23)	0.664
South			1.05 (0.89- 1.25)	0.546
West			1.21 (1.00- 1.46)	0.056
Use of personal assistance aids			1.29 (1.05- 1.57)	0.013
Fistula			1.17 (1.03- 1.33)	0.015

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;

[a]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of renal disease

[b]Hazard Ratio (95% confidence interval)

Appendix 25. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and pelvis/hip fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted proportion of vitamin D users	0.96 (0.70- 1.33)	0.809	1.05 (0.74- 1.48)	0.789
Age (years)[Reference: 65-74]				
18-44			0.23 (0.16- 0.31)	<0.01
45-64			0.51 (0.44- 0.57)	<0.01
>= 75			1.85 (1.69- 2.02)	<0.01
Female			1.80 (1.66- 1.95)	<0.01
Race [Reference: White]				
Black			0.38 (0.34- 0.43)	<0.01
Other			0.70 (0.56- 0.87)	<0.01
Comorbidities				
Medicaid eligible			0.92 (0.83- 1.01)	0.073
Acute MI			1.02 (0.85- 1.22)	0.872
Anemia			1.01 (0.91- 1.13)	0.813
Autoimmune disorder			1.11 (0.90- 1.36)	0.332
Cancer			1.10 (0.99- 1.22)	0.091
COPD/Asthma			1.05 (0.96- 1.16)	0.303
Diabetes mellitus			1.13 (1.02- 1.25)	0.023
Gastrointestinal bleed			1.08 (0.92- 1.27)	0.323
Heart-related procedure			0.85 (0.65- 1.11)	0.241
HIV/AIDS			1.56 (0.84- 2.91)	0.163
Hypertension			0.95 (0.85- 1.06)	0.371
Hyperthyroidism			1.19 (0.85- 1.66)	0.304
Ischemic heart disease			1.11 (1.01- 1.21)	0.022
Liver disease			1.36 (1.09- 1.71)	<0.01
Neurologic disorder			1.10 (0.95- 1.27)	0.199
Obese			0.50 (0.38- 0.67)	<0.01
Other heart disorder			1.17 (1.07- 1.27)	<0.01
Peptic ulcer disease			1.19 (0.99- 1.43)	0.057
Peripheral vascular disease			1.04 (0.95- 1.14)	0.424
Pneumonia			1.00 (0.88- 1.14)	0.979
Psychiatric disorder			1.26 (1.06- 1.49)	<0.01
Pulmonary circulation disorder			1.03 (0.84- 1.28)	0.751
Stroke			1.18 (1.06- 1.32)	<0.01
Substance use disorder			1.40 (1.17- 1.68)	<0.01

Appendix 25. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and pelvis/hip fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			1.05 (0.94- 1.16)	0.411
Glomerulonephritis			0.91 (0.76- 1.08)	0.284
Other			1.15 (1.01- 1.32)	0.036
Parathyroidectomy			2.26 (0.84- 6.08)	0.107
For-profit			1.00 (0.88- 1.14)	0.984
Free-standing			1.11 (0.94- 1.30)	0.209
Chain [Reference: Chain #1]				
Chain #2			0.88 (0.77- 1.01)	0.067
Chain #3			0.94 (0.82- 1.08)	0.378
Other chain			0.97 (0.87- 1.08)	0.563
Facility size [Reference: Small]				
Medium			0.95 (0.83- 1.09)	0.461
Large			0.90 (0.79- 1.03)	0.130
Region [Reference: Northeast]				
Midwest			1.03 (0.91- 1.16)	0.685
South			1.08 (0.96- 1.21)	0.208
West			1.08 (0.94- 1.24)	0.292
Use of personal assistance aids			1.25 (1.09- 1.44)	<0.01
Fistula			1.12 (1.02- 1.23)	0.014

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;

[a]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[b]Hazard Ratio (95% confidence interval)

Appendix 26. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and pelvis/hip fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted average vitamin D dose/patient	1.04 (0.91- 1.19)	0.598	1.05 (0.94- 1.16)	0.386
Age (years)[Reference: 65-74]				
18-44			0.23 (0.16- 0.31)	<0.01
45-64			0.51 (0.44- 0.57)	<0.01
>= 75			1.85 (1.69- 2.02)	<0.01
Female			1.80 (1.66- 1.95)	<0.01
Race [Reference: White]				
Black			0.38 (0.34- 0.43)	<0.01
Other			0.70 (0.56- 0.87)	<0.01
Comorbidities				
Medicaid eligible			0.92 (0.83- 1.01)	0.073
Acute MI			1.02 (0.85- 1.22)	0.871
Anemia			1.01 (0.91- 1.13)	0.807
Autoimmune disorder			1.11 (0.90- 1.36)	0.333
Cancer			1.10 (0.99- 1.22)	0.091
COPD/Asthma			1.05 (0.96- 1.16)	0.303
Diabetes mellitus			1.13 (1.02- 1.25)	0.023
Gastrointestinal bleed			1.08 (0.92- 1.27)	0.321
Heart-related procedure			0.85 (0.65- 1.11)	0.241
HIV/AIDS			1.56 (0.84- 2.91)	0.163
Hypertension			0.95 (0.85- 1.06)	0.369
Hyperthyroidism			1.19 (0.85- 1.66)	0.302
Ischemic heart disease			1.11 (1.01- 1.21)	0.022
Liver disease			1.36 (1.09- 1.71)	<0.01
Neurologic disorder			1.10 (0.95- 1.28)	0.199
Obese			0.50 (0.38- 0.67)	<0.01
Other heart disorder			1.16 (1.07- 1.27)	<0.01
Peptic ulcer disease			1.19 (0.99- 1.43)	0.058
Peripheral vascular disease			1.04 (0.95- 1.14)	0.425
Pneumonia			1.00 (0.88- 1.14)	0.977
Psychiatric disorder			1.26 (1.06- 1.49)	<0.01
Pulmonary circulation disorder			1.03 (0.84- 1.28)	0.750
Stroke			1.18 (1.06- 1.32)	<0.01
Substance use disorder			1.40 (1.17- 1.68)	<0.01

Appendix 26. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and pelvis/hip fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			1.04 (0.94- 1.16)	0.413
Glomerulonephritis			0.91 (0.76- 1.08)	0.282
Other			1.15 (1.01- 1.32)	0.036
Parathyroidectomy			2.26 (0.84- 6.09)	0.107
For-profit			1.00 (0.88- 1.14)	0.987
Free-standing			1.11 (0.94- 1.30)	0.219
Chain [Reference: Chain #1]				
Chain #2			0.88 (0.77- 1.01)	0.066
Chain #3			0.94 (0.82- 1.08)	0.375
Other chain			0.97 (0.87- 1.08)	0.538
Facility size [Reference: Small]				
Medium			0.95 (0.83- 1.09)	0.460
Large			0.90 (0.79- 1.03)	0.131
Region [Reference: Northeast]				
Midwest			1.03 (0.91- 1.16)	0.691
South			1.08 (0.96- 1.21)	0.213
West			1.08 (0.94- 1.24)	0.291
Use of personal assistance aids			1.25 (1.09- 1.44)	<0.01
Fistula			1.12 (1.02- 1.23)	0.014

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;

[a]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of renal disease

[b]Hazard Ratio (95% confidence interval)

Appendix 27. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and other fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted proportion of vitamin D users	1.39 (0.89- 2.16)	0.143	1.33 (0.83- 2.13)	0.235
Age (years)[Reference: 65-74]				
18-44			0.71 (0.56- 0.90)	<0.01
45-64			0.91 (0.80- 1.04)	0.174
>= 75			1.27 (1.13- 1.43)	<0.01
Female			2.12 (1.91- 2.36)	<0.01
Race [Reference: White]				
Black			0.44 (0.39- 0.50)	<0.01
Other			0.61 (0.47- 0.80)	<0.01
Comorbidities				
Medicaid eligible			1.07 (0.95- 1.19)	0.255
Acute MI			0.81 (0.64- 1.04)	0.103
Anemia			1.07 (0.93- 1.23)	0.368
Autoimmune disorder			1.31 (1.04- 1.65)	0.024
Cancer			1.11 (0.96- 1.29)	0.162
COPD/Asthma			1.05 (0.93- 1.19)	0.442
Diabetes mellitus			1.09 (0.95- 1.25)	0.201
Gastrointestinal bleed			1.25 (1.03- 1.52)	0.027
Heart-related procedure			0.96 (0.69- 1.33)	0.811
HIV/AIDS			0.99 (0.49- 1.99)	0.967
Hypertension			1.12 (0.97- 1.30)	0.126
Hyperthyroidism			1.04 (0.67- 1.61)	0.867
Ischemic heart disease			1.02 (0.91- 1.13)	0.787
Liver disease			1.49 (1.17- 1.89)	<0.01
Neurologic disorder			1.24 (1.04- 1.47)	0.014
Obese			1.18 (0.95- 1.47)	0.124
Other heart disorder			1.31 (1.17- 1.46)	<0.01
Peptic ulcer disease			0.95 (0.74- 1.22)	0.703
Peripheral vascular disease			0.94 (0.84- 1.06)	0.302
Pneumonia			1.03 (0.88- 1.21)	0.732
Psychiatric disorder			1.11 (0.89- 1.38)	0.352
Pulmonary circulation disorder			1.06 (0.82- 1.37)	0.651
Stroke			1.07 (0.92- 1.24)	0.392
Substance use disorder			1.23 (1.00- 1.53)	0.054

Appendix 27. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and other fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			0.74 (0.65- 0.85)	<0.01
Glomerulonephritis			0.58 (0.46- 0.74)	<0.01
Other			0.86 (0.72- 1.02)	0.080
Parathyroidectomy			0.00 (0.00- 0.00)	<0.01
For-profit			1.08 (0.91- 1.29)	0.394
Free-standing			1.08 (0.87- 1.33)	0.482
Chain [Reference: Chain #1]				
Chain #2			0.87 (0.74- 1.03)	0.096
Chain #3			1.00 (0.85- 1.17)	0.987
Other chain			0.97 (0.85- 1.10)	0.610
Facility size [Reference: Small]				
Medium			1.02 (0.86- 1.21)	0.840
Large			0.89 (0.75- 1.06)	0.206
Region [Reference: Northeast]				
Midwest			1.06 (0.91- 1.24)	0.433
South			0.87 (0.75- 1.01)	0.070
West			0.96 (0.80- 1.14)	0.605
Use of personal assistance aids			1.32 (1.11- 1.56)	<0.01
Fistula			0.97 (0.87- 1.09)	0.623

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;

[a]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[b]Hazard Ratio (95% confidence interval)

Appendix 28. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and other fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted proportion of vitamin D users	0.97 (0.82- 1.15)	0.736	0.95 (0.79- 1.13)	0.563
Age (years)[Reference: 65-74]				
18-44			0.71 (0.56- 0.89)	<0.01
45-64			0.91 (0.80- 1.04)	0.171
>= 75			1.27 (1.13- 1.43)	<0.01
Female			2.12 (1.91- 2.36)	<0.01
Race [Reference: White]				
Black			0.44 (0.39- 0.51)	<0.01
Other			0.61 (0.47- 0.79)	<0.01
Comorbidities				
Medicaid eligible			1.07 (0.96- 1.19)	0.244
Acute MI			0.81 (0.64- 1.04)	0.101
Anemia			1.07 (0.93- 1.23)	0.339
Autoimmune disorder			1.31 (1.04- 1.65)	0.023
Cancer			1.11 (0.96- 1.29)	0.162
COPD/Asthma			1.05 (0.93- 1.19)	0.445
Diabetes mellitus			1.09 (0.95- 1.25)	0.201
Gastrointestinal bleed			1.25 (1.03- 1.52)	0.027
Heart-related procedure			0.96 (0.70- 1.33)	0.816
HIV/AIDS			0.99 (0.49- 1.99)	0.969
Hypertension			1.12 (0.97- 1.30)	0.124
Hyperthyroidism			1.04 (0.67- 1.61)	0.853
Ischemic heart disease			1.01 (0.91- 1.13)	0.792
Liver disease			1.49 (1.17- 1.90)	<0.01
Neurologic disorder			1.24 (1.04- 1.47)	0.014
Obese			1.19 (0.95- 1.47)	0.123
Other heart disorder			1.31 (1.17- 1.46)	<0.01
Peptic ulcer disease			0.95 (0.74- 1.22)	0.707
Peripheral vascular disease			0.94 (0.84- 1.06)	0.302
Pneumonia			1.03 (0.88- 1.21)	0.728
Psychiatric disorder			1.11 (0.89- 1.38)	0.358
Pulmonary circulation disorder			1.06 (0.82- 1.37)	0.654
Stroke			1.07 (0.92- 1.24)	0.391
Substance use disorder			1.23 (0.99- 1.53)	0.056

Appendix 28. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and other fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			0.74 (0.65- 0.85)	<0.01
Glomerulonephritis			0.58 (0.46- 0.74)	<0.01
Other			0.86 (0.72- 1.02)	0.081
Parathyroidectomy			0.00 (0.00- 0.00)	<0.01
For-profit			1.11 (0.93- 1.32)	0.251
Free-standing			1.06 (0.86- 1.31)	0.564
Chain [Reference: Chain #1]				
Chain #2			0.87 (0.74- 1.03)	0.109
Chain #3			1.01 (0.86- 1.19)	0.883
Other chain			0.96 (0.84- 1.09)	0.486
Facility size [Reference: Small]				
Medium			1.02 (0.86- 1.21)	0.824
Large			0.90 (0.76- 1.07)	0.223
Region [Reference: Northeast]				
Midwest			1.06 (0.90- 1.23)	0.492
South			0.86 (0.75- 1.00)	0.051
West			0.96 (0.81- 1.14)	0.621
Use of personal assistance aids			1.32 (1.11- 1.56)	<0.01
Fistula			0.97 (0.87- 1.09)	0.626

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;

[a]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of renal disease

[b]Hazard Ratio (95% confidence interval)

Appendix 29. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and any fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted proportion of vitamin D users	1.05 (0.82- 1.34)	0.722	1.10 (0.86- 1.42)	0.447
Age (years)[Reference: 65-74]				
18-44			0.40 (0.34- 0.48)	<0.01
45-64			0.65 (0.59- 0.71)	<0.01
>= 75			1.56 (1.47- 1.67)	<0.01
Female			1.88 (1.77- 1.99)	<0.01
Race [Reference: White]				
Black			0.40 (0.37- 0.44)	<0.01
Other			0.70 (0.61- 0.82)	<0.01
Comorbidities				
Medicaid eligible			0.95 (0.89- 1.01)	0.126
Acute MI			0.95 (0.83- 1.09)	0.474
Anemia			1.05 (0.96- 1.13)	0.288
Autoimmune disorder			1.29 (1.12- 1.47)	<0.01
Cancer			1.21 (1.12- 1.31)	<0.01
COPD/Asthma			1.08 (1.01- 1.16)	0.027
Diabetes mellitus			1.10 (1.02- 1.19)	0.011
Gastrointestinal bleed			1.20 (1.07- 1.35)	<0.01
Heart-related procedure			0.91 (0.75- 1.09)	0.301
HIV/AIDS			1.25 (0.81- 1.94)	0.313
Hypertension			1.00 (0.93- 1.08)	0.984
Hyperthyroidism			1.03 (0.79- 1.33)	0.837
Ischemic heart disease			1.08 (1.01- 1.15)	0.021
Liver disease			1.53 (1.32- 1.78)	<0.01
Neurologic disorder			1.12 (1.01- 1.24)	0.029
Obese			0.83 (0.71- 0.97)	0.018
Other heart disorder			1.26 (1.18- 1.34)	<0.01
Peptic ulcer disease			1.10 (0.96- 1.25)	0.175
Peripheral vascular disease			0.98 (0.92- 1.05)	0.552
Pneumonia			1.05 (0.95- 1.15)	0.326
Psychiatric disorder			1.16 (1.02- 1.31)	0.022
Pulmonary circulation disorder			1.07 (0.92- 1.23)	0.380
Stroke			1.09 (1.00- 1.18)	0.050
Substance use disorder			1.26 (1.11- 1.42)	<0.01

Appendix 29. Cox models of the association between the case-mix adjusted proportion of vitamin D users[a] and any fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			0.97 (0.90- 1.05)	0.441
Glomerulonephritis			0.81 (0.71- 0.93)	<0.01
Other			1.08 (0.98- 1.19)	0.118
Parathyroidectomy			1.03 (0.38- 2.74)	0.958
For-profit			1.02 (0.92- 1.12)	0.751
Free-standing			1.09 (0.97- 1.23)	0.155
Chain [Reference: Chain #1]				
Chain #2			0.87 (0.79- 0.95)	<0.01
Chain #3			0.94 (0.86- 1.04)	0.214
Other chain			0.96 (0.89- 1.04)	0.286
Facility size [Reference: Small]				
Medium			1.00 (0.91- 1.10)	0.958
Large			0.92 (0.83- 1.01)	0.094
Region [Reference: Northeast]				
Midwest			1.05 (0.96- 1.15)	0.267
South			1.01 (0.93- 1.10)	0.752
West			1.07 (0.96- 1.18)	0.215
Use of personal assistance aids			1.26 (1.14- 1.40)	<0.01
Fistula			1.09 (1.02- 1.16)	0.012

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;

[a]Case-mix adjusted using mixed-effects logistic regression adjusting for age, sex, race and cause of renal disease

[b]Hazard Ratio (95% confidence interval)

Appendix 30. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and any fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Case-mix adjusted proportion of vitamin D users	0.98 (0.87- 1.11)	0.767	0.99 (0.90- 1.09)	0.831
Age (years)[Reference: 65-74]				
18-44			0.40 (0.34- 0.48)	<0.01
45-64			0.65 (0.59- 0.71)	<0.01
>= 75			1.57 (1.47- 1.67)	<0.01
Female			1.88 (1.77- 1.99)	<0.01
Race [Reference: White]				
Black			0.40 (0.37- 0.44)	<0.01
Other			0.70 (0.61- 0.82)	<0.01
Comorbidities				
Medicaid eligible			0.95 (0.89- 1.02)	0.131
Acute MI			0.95 (0.83- 1.09)	0.472
Anemia			1.05 (0.96- 1.13)	0.273
Autoimmune disorder			1.29 (1.12- 1.47)	<0.01
Cancer			1.21 (1.12- 1.31)	<0.01
COPD/Asthma			1.08 (1.01- 1.16)	0.027
Diabetes mellitus			1.10 (1.02- 1.19)	0.011
Gastrointestinal bleed			1.20 (1.07- 1.35)	<0.01
Heart-related procedure			0.91 (0.75- 1.09)	0.302
HIV/AIDS			1.25 (0.81- 1.94)	0.312
Hypertension			1.00 (0.93- 1.08)	0.980
Hyperthyroidism			1.03 (0.79- 1.33)	0.827
Ischemic heart disease			1.08 (1.01- 1.15)	0.022
Liver disease			1.53 (1.32- 1.78)	<0.01
Neurologic disorder			1.12 (1.01- 1.24)	0.029
Obese			0.83 (0.71- 0.97)	0.018
Other heart disorder			1.26 (1.18- 1.34)	<0.01
Peptic ulcer disease			1.10 (0.96- 1.25)	0.174
Peripheral vascular disease			0.98 (0.92- 1.05)	0.552
Pneumonia			1.05 (0.95- 1.15)	0.325
Psychiatric disorder			1.16 (1.02- 1.31)	0.023
Pulmonary circulation disorder			1.07 (0.92- 1.23)	0.382
Stroke			1.09 (1.00- 1.18)	0.049
Substance use disorder			1.25 (1.11- 1.42)	<0.01

Appendix 30. Cox models of the association between the case-mix adjusted average vitamin D dose per patient[a] and any fractures

	Crude		Multivariable	
Covariates	**HR (95% CI)[b]**	**p**	**HR (95% CI)**	**p**
Cause of ESRD [Reference: Diabetes Mellitus]				
Hypertension			0.97 (0.90- 1.05)	0.443
Glomerulonephritis			0.81 (0.71- 0.93)	<0.01
Other			1.08 (0.98- 1.19)	0.118
Parathyroidectomy			1.03 (0.39- 2.75)	0.950
For-profit			1.02 (0.93- 1.13)	0.626
Free-standing			1.08 (0.96- 1.22)	0.177
Chain [Reference: Chain #1]				
Chain #2			0.87 (0.79- 0.96)	<0.01
Chain #3			0.94 (0.86- 1.04)	0.240
Other chain			0.95 (0.88- 1.03)	0.238
Facility size [Reference: Small]				
Medium			1.00 (0.91- 1.10)	0.950
Large			0.92 (0.84- 1.02)	0.099
Region [Reference: Northeast]				
Midwest			1.05 (0.96- 1.14)	0.292
South			1.01 (0.93- 1.10)	0.815
West			1.07 (0.96- 1.18)	0.211
Use of personal assistance aids			1.26 (1.14- 1.40)	<0.01
Fistula			1.09 (1.02- 1.16)	0.012

Abbreviations: Acute MI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ESRD, end-stage renal disease; HIV/AIDS, human immunodeficiency virus / acquired immunodeficiency syndrome;
[a]Case-mix adjusted using mixed-effects linear regression adjusting for age, sex, race and cause of renal disease
[b]Hazard Ratio (95% confidence interval)

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