Parathyroid Hormone Serum Levels and Mortality among Hemodialysis Patients in the Gulf Cooperation Council Countries: Results from the DOPPS (2012-2018)

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Abstract

Background: The prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) has collected data since 2012 in all six Gulf Cooperation Council (GCC) countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates). We report the relationship of PTH with mortality in this largest GCC hemodialysis patient cohort studied to date.

Methods: Data were from randomly selected national samples of hemodialysis facilities in GCC DOPPS phases 5 and 6 (2012-2018). PTH descriptive findings and case-mix adjusted PTH/mortality Cox regression analyses were based on 1825 and 1422 randomly selected hemodialysis patients, respectively.

Results: Mean patient age was 55 years (median dialysis vintage = 2.1 years). Median PTH ranged from 259 pg/mL (UAE) to 437 pg/mL (Kuwait), with 22% having PTH <150 pg/mL, 24% (PTH 150-300), 34% (PTH 301-700), and 20% (PTH >700) pg/mL. Patients with PTH >700 pg/mL were younger, on dialysis longer, less likely to be diabetic, have urine>200 mL/day, prescribed 3.5 mEq/L dialysate calcium, had higher mean serum creatinine and phosphorus levels, lower white blood cell counts, and more likely to be prescribed cinacalcet, phosphate binders, or IV vitamin D. A “U-shaped” PTH/mortality relationship was observed with >2-fold and 1.5-fold higher adjusted HR of death at PTH>700 pg/mL and <300 pg/mL, respectively, compared to PTH 301-450 pg/mL.

Conclusion: Secondary hyperparathyroidism is highly prevalent among GCC hemodialysis patients, with a strong U-shaped PTH/mortality relationship seen at PTH <300 and >450 pg/mL. Future studies are encouraged for further understanding this PTH/mortality pattern in relationship to unique aspects of the GCC hemodialysis population.
Introduction

Parathyroid hormone (PTH) is a major systemic calcium-regulating hormone. Diseases exhibiting elevated PTH levels such as primary and secondary hyperparathyroidism (sHPT) are associated with increased mortality (1-4). High serum PTH, parathyroid gland hyperplasia, and disturbances in mineral metabolism such as hyperphosphatemia are commonly seen in sHPT (5, 6). sHPT can be seen in more than 30% of persons receiving chronic dialysis therapy for end-stage kidney disease (ESKD), but with the prevalence and severity of sHPT varying considerably across countries and hemodialysis (HD) patients.

Chronic kidney disease (CKD) patients affected by mineral bone disorders (MBD) have higher rates of all-cause mortality (3, 7-9), with dialysis patients overall displaying 10- to 100-fold higher mortality than persons in the general population (9-11). Baseline serum PTH levels and, more recently, changes in serum PTH levels over time, have been associated with mortality in dialysis patients (9-11). Substantial differences in PTH levels and their control among HD patients in Japan, western Europe, and black versus non-black HD patients in the US have raised questions regarding potential racial differences in PTH control (12).

Studies examining MBD treatment of dialysis patients in developing countries are extremely limited, especially in the Gulf Cooperation Council (GCC) countries. The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international observational prospective study with detailed data collection of HD care and outcomes across 21 countries (13). The DOPPS provides a unique opportunity for contemporaneous evaluation of MBD control and related outcomes across a diverse set of international health care delivery and financing systems (13).

The DOPPS has shed light on numerous different practices and outcomes for various regions around the world. However, an understanding of the relationship between PTH control and HD
patient outcomes is lacking for the GCC region which has a patient population, diet, and other pertinent factors that differ considerably from those regions that the great majority of prior studies have been based upon. Thus, the role of PTH as a potential predictor of all-cause morbidity and mortality in the GCC HD population warrants investigation to help inform the GCC HD community whether measurement of PTH may provide complementary information for risk stratification of patients, and how best to optimize their care. Hence, this study aims to study the association of serum PTH with all-cause mortality in hemodialysis patients in the GCC population.

**Methods**

**Patients and Data Collection**

Findings are based upon data reported for hemodialysis patients ≥ 18 years old from the participating GCC countries in DOPPS phases 5 (2012-2015) and 6 (2015-2018). As described previously in the GCC-DOPPS study design (14), study patients were selected randomly from a representative sample of randomly selected hemodialysis facilities within each country (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates). In each country, institutional review boards approved the study and informed patient consent was obtained in accordance with national and local requirements. Further details of the GCC-DOPPS study design including number of study sites per GCC country are provided in Pisoni et al (14).

Our study sample was based upon 1346 patients treated at 40 facilities participating in GCC-DOPPS 5, and 928 patients treated at 33 facilities participating in GCC-DOPPS 6. Patients participating in DOPPS 5 were invited to participate in DOPPS 6 if still being treated at the same HD unit. These patients were considered separate patients in analyses since key baseline covariates (e.g., age, dialysis vintage, comorbidities) can differ over the several year time period
between the start of these two study phases. Of these 2274 patients enrolled in GCC DOPPS phases 5 and 6, (a) 423 patients without a PTH measured in the 4 months prior to enrollment and, (b) 26 patients in facilities where the unit of PTH measurement could not be reliably determined were excluded, yielding a studied population of 1825 patients. In mortality analyses, additional exclusions were applied for 8 patients lacking follow-up, and 395 patients having inadequate facility reporting of mortality, resulting in 1422 patients used for mortality analyses. With few exceptions, facilities in the GCC reported using intact PTH assays with lower and upper limits of normal from 10-88 pg/mL.

**Statistical analysis**

Our primary outcome of interest was all-cause mortality and the primary exposure of interest was a patient’s PTH level at enrollment into each DOPPS study phase. Cox regression was used to analyze the association between categories of baseline PTH levels and mortality, stratified by region (Saudi Arabia vs. non-Saudi Arabia). Analyses were not stratified by individual country due to the small number of HD facilities participating in DOPPS in several of the GCC countries. PTH categories used in mortality models were chosen to provide samples of approximately similar sizes across the spectrum of observed PTH values while still retaining cut point values that have been utilized in some prior guidelines (e.g., 150 and 300 pg/mL in KDOQI guidelines). Cox models accounted for facility clustering using robust sandwich covariance estimators and adjusted for potential confounders including age, sex, time (years) on dialysis, body mass index, comorbidities (diabetes, coronary artery disease, cerebrovascular disease, congestive heart failure, and other cardiovascular disease), serum creatinine, and single pool Kt/V. Time at risk started at study enrollment and ended at the time of death, or the earliest of the following censoring events: study end, loss to follow-up, or 7 days after leaving the facility due to kidney
transplantation, switch to home dialysis, recovery of renal function, withdrawal from HD, or transfer to another HD facility. The median follow-up time was 1.4 years. Standard descriptive statistics were used to characterize the patients included in the study.

Overall, missingness for covariates was low (< 10% for the majority of covariates) with the exception of body mass index (17%) and single pool Kt/V (32%). For missing data, we used the Sequential Regression Multiple Imputation Method implemented by IVEware to create 10 imputed datasets (15, 16), and analyzed using the MIAnalyze procedure in SAS/STAT® 9.4.

Results

For the initial prevalent cross-section of patients in each country, median PTH ranged from 259 pg/mL in the UAE to 437 pg/mL in Kuwait (Figure 1). Overall, 22% of patients had a PTH < 150 pg/mL, 24% with a PTH of 150-300, 34% with a PTH of 301-700, and nearly 20% having a PTH > 700 pg/mL. As shown in Figure 1, PTH 600-700 pg/mL occurred in 5% of facilities in Qatar, Saudi Arabia, and UAE, whereas it was 6, 8, and 1% in Kuwait, Bahrain, and Oman, respectively. PTH >700 pg/mL occurred in 14, 17, 23, 26, 27 and 29% in Oman, UAE, Qatar, Bahrain, Saudi Arabia, and Kuwait, respectively.

Patients with PTH levels > 700 pg/mL were younger, had been on dialysis substantially longer, were less likely to be diabetic or have urine>200 mL/day or treated with 3.5 mEq/L calcium dialysate (Table 1). Patients with PTH levels > 700 pg/mL also had higher mean serum phosphorus and serum creatinine levels, lower white blood cell counts, and were much more likely to be prescribed cinacalcet, phosphate binders, and IV vitamin D. A history of
parathyroidectomy prior to study enrollment was indicated for 3-4% of patients who had either low PTH (<150 pg/mL) or high PTH levels (>700 pg/mL) whereas 0-2% of patients had a prior parathyroidectomy among patients with a PTH of 150-700 pg/mL.

Switching patients with higher PTH from oral vitamin D to IV vitamin D appeared to be a common practice, as suggested by the pattern of decline in oral vitamin D only prescription and rise in IV vitamin D prescription in patients with higher PTH (Table 1). Prescription of calcium-containing phosphate binders without co-prescription of sevelamer was substantially lower among patients with higher PTH levels. In contrast, prescription of the non-calcium-containing phosphate binder, sevelamer, or sevelamer in combination with a calcium-containing phosphate binder was markedly higher among patients with higher PTH levels.

Figure 2 shows PTH categories and mortality among GCC-DOPPS hemodialysis patients during the 2012 to 2018 time period. There were 222 deaths from among 1422 participants, resulting in an observed crude mortality rate of 11.4 deaths per 100 patient-years. A “U-shaped” relationship was observed between PTH levels and mortality with a higher adjusted HR of death seen at PTH levels <300 pg/mL and >450 pg/mL compared to PTH values of 301-450 pg/mL (reference group). Compared to this reference group, mortality was >2-fold higher for patients having a PTH >700 pg/mL (HR= 2.04, 95% C.I.:1.42-2.92). Interestingly, mortality also was elevated for patients having a PTH of 150-300 pg/mL (HR= 1.51, 95% C.I.: 1.07-2.13). Similar results were obtained when additionally adjusting for serum albumin, serum calcium, serum phosphate, and residual kidney function (Supplemental Table 1), or excluding the small number of patients (n=26) having a prior parathyroidectomy. Similar results were also observed when treating cardiovascular mortality as the outcome (Supplemental Table 2).
Discussion

Cardiovascular disease (CVD) is the leading cause of death in dialysis patients, with approximately 50% of deaths due to CV causes (17-19). Traditional risk factors for CVD, such as advanced age, hypertension, and smoking, do not fully explain the much higher rate of mortality in dialysis patients versus the non-dialysis population (17). Thus, non-traditional cardiovascular risk factors such as mineral metabolism disorders - in which serum calcium, phosphorus, and PTH levels are elevated - have been shown to be associated with increased cardiovascular mortality and all-cause mortality (20).

Secondary hyperparathyroidism leading to elevated PTH levels is common among advanced CKD patients. This excess PTH can play an important role in development of left ventricular (LV) hypertrophy(21-22), low LV ejection fraction (23), and increased risk of vascular calcification (24-27) in increasing cardiovascular morbidity and mortality risk. However, even with contemporary management approaches, a large percentage of our patients have inadequately controlled PTH, serum phosphorus, and/or calcium levels (12, 28, 29). Among the GCC-DOPPS HD population, the prevalence of high PTH levels is one of the highest reported among the 21 countries participating in the international DOPPS 5 (12, 28, 29, 30). This is especially true for younger patients, a common observation across countries.

In the present study, a “U-shaped” relationship was seen between PTH and mortality, with mortality risk lowest at PTH levels between 301 and 450 pg/mL and then rising substantially both at PTH levels \( \leq \) 300 pg/mL and \( >450 \) pg/mL. Overall, 25% and 20% of study participants had a PTH >600 and \( >700 \) pg/mL, respectively, while 46% had a PTH \( \leq \) 300 pg/mL, with 22% having a PTH<150 pg/mL. The mortality hazard ratio was nearly 2-fold higher for patients with PTH \( >700 \) pg/mL and approximately 60% higher for patients having a PTH \( \leq \) 300 pg/mL versus
having a PTH of 301-450 pg/mL. Tentori et al’s report from earlier phases of the DOPPS observed the highest mortality risk at serum PTH levels >600 pg/mL (7, 11), although significantly higher risk was also seen at PTH levels as low as 301-450 pg/mL (compared to PTH of 150-300 pg/mL). Furthermore, Kalantar-Zadeh et al (31) found time-updated serum PTH values ≥300 pg/mL to be strongly correlated with higher mortality risk. Moreover, Floege et al recently showed baseline serum PTH concentrations >600 pg/mL to be associated with greater mortality risk [adjusted HR 2.10 (95% CI 1.62–2.73)] versus PTH of 150-300 pg/mL (32, 33). We also found highest mortality risk at high PTH levels of >700 pg/mL (2-fold higher HR of death vs. reference PTH of 301-450 pg/mL) for GCC hemodialysis patients. However, our results suggest modest mortality risks at PTH levels between 450 and 700 pg/mL.

In the present GCC study, it appears that the U-shaped PTH/mortality curve may possibly be uniquely shifted slightly to the right - with the nadir for mortality risk observed at higher PTH levels than seen previously in similarly conducted studies in western Europe, Japan, and the US (2, 32, 34). However, GCC patients on average are approximately 10 years younger (mean age: 55 years) than those in western Europe (67 years), Japan (66 years), and North America (63 years), with GCC HD patients also having a shorter median dialysis vintage (2.2 years) than that of HD patients in Japan (6.6 years), western Europe (3.2 years), and North America (2.8 years) (30). Prior studies have shown younger age and longer dialysis vintage to be strongly correlated with higher PTH levels in HD patients (9,12,35). Furthermore, despite being substantially younger with shorter dialysis vintage, GCC HD patients also have the highest diabetes prevalence, and generally lower cardiovascular comorbidity burden (30). It is conceivable that these substantial differences in demographics, dialysis vintage, and comorbidity burden for GCC HD patients versus those in western Europe, the US, and Japan may affect how elevated PTH
levels influence HD patient survival for HD patients in the GCC versus elsewhere. What is not unique to the GCC is that a U-shaped PTH/mortality relationship has been consistently seen across cohort studies in Latin America and Europe (32, 33, 36), the US (37, 38), and internationally in the DOPPS (11, 39, 40). However, the inflection point at which higher PTH has been significantly associated with increased all-cause mortality varies across studies, ranging from various PTH levels between 300 and 600 pg/mL (9, 11, 31, 37, 29, 41-44) and at PTH >600 pg/mL (7, 11) some of which may also reflect a study’s sample size and PTH reference range.

In addition to the elevated mortality risk for GCC HD patients at high PTH levels, the approximately 1.5-fold higher risk seen at PTH levels <300 pg/mL (versus having a PTH of 301-450 pg/mL) indicates a need for additional research to understand the mechanisms underlying this elevated risk at lower PTH levels. Patients with PTH <300 pg/mL at study entry represented 46% of all GCC HD patients in the current study sample. Prior studies have also shown elevated mortality risks at lower PTH but typically at substantially lower PTH levels [e.g., <50, <100, or <150 pg/mL depending upon the study (7, 9, 35, 45)]. The 22% of GCC HD patients with PTH <150 pg/mL had lower serum phosphorus and serum albumin levels compared to patients in all other PTH categories. However, adjusting for serum phosphorus and albumin levels had little effect on the PTH/mortality associations seen in our current analyses.

Low PTH (<150 pg/dL) has also been shown to be associated with greater use of a higher dialysate calcium bath concentration and inversely associated with black race and vitamin D therapy (9, 46). GCC countries utilize a high dialysate calcium bath to primarily control PTH level. In the current study, a dialysate calcium bath ≥3 mEq/L was used in 86% of patients having a PTH<150 pg/mL compared to 72-74% of patients with PTH >300 pg/mL. This practice
pattern of high calcium dialysate bath, given the potential for excessive treatment contributing to the development of adynamic bone disease, needs to be investigated further. Possibly a change in this practice pattern may help PTH levels return towards the recommended target ranges for some patients currently having a PTH ≤150 pg/mL and avoid possible adynamic bone disease.

Treatment of HD patients with PTH-controlling medications appeared to be as high or higher in the GCC when compared with other DOPPS international regions of Europe, Japan, and North America (30). Percent of cinacalcet use (almost 60% among those with >700 pg/mL) was higher in the GCC than in any of these three international regions and use of active vitamin D (60%) was higher than in Europe but slightly lower than reported for North America and Japan (30). Previous studies have found that vitamin D receptor activators (VDRA) are associated with greater survival in maintenance hemodialysis patients in some studies (31, 47, 48-50) but with no meaningful association when using an instrumental variable approach (7, 39). PTH levels were strongly and positively associated with IV vitamin D and cinacalcet use in the current study, suggesting general appropriateness in prescribing vitamin D therapy and calcimimetics in response to a patient’s PTH level (9) and suggest possibly higher PTH levels prior to initiating hemodialysis.

There are several limitations of this study. Our observational study design limits causal inference due to possible residual confounding despite the factors accounted for in our analyses. Furthermore, analyses were based upon a single-baseline PTH value which has been applied in numerous prior research studies internationally but inherently may not represent long-term PTH control for a given patient. Relatedly, our study design could not inform how different approaches to sHPT management impact mortality outcomes for GCC HD patients. Despite
these limitations, our study has strong points including: (1) being the largest GCC HD patient cohort studied to date regarding PTH control and mortality; and (2) the study is based on randomly-selected patients and dialysis centers within each GCC country.

**Conclusion**

Secondary hyperparathyroidism is highly prevalent among HD patients in the GCC and associated with increased all-cause mortality. This high prevalence of high PTH levels in GCC HD patients is seen despite ample treatment with PTH controlling medications and patients having a relatively short dialysis vintage overall, raising questions regarding how well PTH is managed prior to dialysis in the GCC. Our findings indicate that HD patients who achieved PTH levels of 301-450 pg/mL had a lower subsequent mortality risk compared to patients having PTH ≤300 pg/mL or >450 pg/mL. This nadir for mortality risk is uniquely at somewhat higher PTH levels than seen previously in similarly conducted studies in western Europe, Japan, and the US, and may be influenced by the differences in patient characteristics of GCC HD patients versus other international regions. Altogether, these findings should be considered within the contexts of overall MBD control, and benefits to life prognosis, maintenance of daily living activities, and quality of life from a patient-centered care perspective. Randomized controlled trials are needed to demonstrate whether treatments aimed at achieving specific PTH levels impact patient survival.
Disclosures

Fouly reports receiving salary from his company, Amgen, during the conduct of the study which was supported by Amgen. In addition, Dr. Fouly's company, Amgen, has licensed patents for cinacalcet and etelcalcetide which are drugs used to treat secondary hyperparathyroidism and thus related to the topic of this paper.

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Supplemental Materials Table of Contents

- **Supplemental Table 1**: PTH categories and mortality: effect of progressive adjustment, GCC DOPPS (2012-2018)
- **Supplemental Table 2**: PTH categories and cardiovascular mortality in the GCC DOPPS (2012-2018)
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**Table 1:** Patient characteristics and treatments, by PTH category in the GCC DOPPS (2012-2018)

| Characteristic                              | Baseline PTH, pg/mL |
|---------------------------------------------|---------------------|
|                                             | < 150           | 150-300 | 301-450 | 451-700 | > 700<sup>a</sup> |
| **Demographics**                            |                  |        |        |        |              |
| Sample patients, N (row %)                  | 407 (22%)        | 431 (24%) | 339 (19%) | 290 (16%) | 358 (20%)    |
| Age, years                                  | 56.7 (15.7)     | 57.9 (15.8) | 56.1 (15.6) | 52.0 (15.7) | 50.6 (16.8) |
| Male                                        | 56%             | 57%     | 61%     | 57%     | 58%          |
| Years on dialysis                           | 1.7 [0.7, 4.3]  | 1.5 [0.5, 4.1] | 1.9 [0.5, 4.4] | 2.2 [0.5, 4.9] | 3.5 [1.3, 6.7] |
| Urine output > 200 mL/day                   | 29%             | 30%     | 35%     | 30%     | 24%          |
| Current smoker                              | 7%              | 7%      | 5%      | 10%     | 6%           |
| Body mass index, kg/m²                      | 25.9 (6.1)      | 26.9 (6.8) | 26.7 (6.5) | 27.5 (7.5) | 26.6 (6.7)  |
| **Dialysis Treatment**                      |                  |        |        |        |              |
| Catheter use                                | 44%             | 42%     | 41%     | 43%     | 35%          |
| SBP, mmHg                                    | 144 (22)        | 147 (22) | 146 (21) | 147 (21) | 146 (21)    |
| Treatment time, minutes                      | 217 (26)        | 223 (24) | 224 (24) | 224 (26) | 220 (25)    |
| Blood flow rate (mL/min)                    | 285 (45)        | 295 (47) | 297 (45) | 302 (55) | 300 (48)    |
| Single pool Kt/V                            | 1.4 (0.4)       | 1.4 (0.4) | 1.3 (0.4) | 1.3 (0.4) | 1.4 (0.4)  |
| Dialysate calcium, mEq/L                    |                  |        |        |        |              |
| < 2.5 mEq/L                                 | 1%              | 0%      | 1%      | 0%      | 0%           |
| 2.5 mEq/L                                   | 13%             | 21%     | 25%     | 28%     | 26%          |
| 3.0 mEq/L                                   | 54%             | 48%     | 50%     | 47%     | 56%          |
| 3.5 mEq/L                                   | 32%             | 30%     | 25%     | 25%     | 18%          |
| **Comorbidities**                           |                  |        |        |        |              |
| Coronary artery disease                     | 31%             | 31%     | 35%     | 27%     | 30%          |
| Cancer                                      | 2%              | 2%      | 1%      | 2%      | 1%           |
| Other cardiovascular disease                | 18%             | 16%     | 15%     | 14%     | 14%          |
| Cerebrovascular disease                     | 11%             | 9%      | 10%     | 10%     | 7%           |
| Congestive heart failure                    | 23%             | 19%     | 19%     | 19%     | 22%          |
| Diabetes                                    | 67%             | 63%     | 63%     | 62%     | 46%          |
| Gastrointestinal bleed in last year         | 6%              | 4%      | 3%      | 2%      | 3%           |
| Hypertension                                | 92%             | 95%     | 94%     | 93%     | 87%          |
| Lung Disease                                | 7%              | 6%      | 6%      | 5%      | 4%           |
| Neurologic disorder                         | 9%              | 8%      | 5%      | 5%      | 9%           |
| Psychologic disorder                        | 11%             | 8%      | 9%      | 8%      | 12%          |
| Peripheral vascular disease                 | 17%             | 17%     | 19%     | 20%     | 15%          |
| Recurrent cellulitis                        | 9%              | 7%      | 10%     | 8%      | 9%           |
| Parathyroidectomy<sup>b</sup>               | 4%              | 2%      | 0%      | 1%      | 3%           |
| **Labs**                                    |                  |        |        |        |              |
| Total calcium, mg/dL                        | 8.9 (0.9)       | 8.7 (0.8) | 8.7 (0.9) | 8.7 (0.9) | 8.7 (0.9)  |
| Characteristic          | < 150     | 150-300   | 301-450   | 451-700   | > 700     |
|------------------------|-----------|-----------|-----------|-----------|-----------|
| Phosphorus, mg/dL      | 4.7(1.9)  | 5.0(1.8)  | 5.2(1.9)  | 5.2(1.9)  | 5.7(1.9)  |
| Creatinine, mg/dL      | 8.4(3.2)  | 8.9(2.9)  | 9.1(3.2)  | 9.4(3.3)  | 10.1(3.0) |
| Albumin, g/dL          | 3.4(0.6)  | 3.5(0.5)  | 3.6(0.5)  | 3.5(0.6)  | 3.5(0.5)  |
| Hemoglobin, g/dL       | 10.8(1.5) | 10.9(1.5) | 10.9(1.5) | 10.8(1.6) | 10.9(1.4) |
| S. magnesium, mg/dL    | 2.2(0.5)  | 2.2(0.5)  | 2.2(0.6)  | 2.2(0.4)  | 2.3(0.8)  |
| WBC count              | 7.1(2.6)  | 6.9(2.2)  | 6.9(2.3)  | 6.7(2.2)  | 6.4(2.1)  |
| S. Bicarbonate, mEq/L  | 22.0(3.6) | 21.3(3.4) | 21.8(3.3) | 22.0(3.7) | 21.4(3.2) |
| PTH, pg/mL             | 82.9(39.4)| 220(41)   | 376(44)   | 563(72)   | 1293(620) |
| PTH, pg/mL median [IQR]| 84.6[50.4,115.0] | 223[184,252] | 373[336,416] | 560[504,621] | 1067[842,1560] |
| HbA1c, %c              | 6.7(1.8)  | 7.2(1.6)  | 7.1(1.6)  | 6.9(1.6)  | 7.3(2.6)  |

**Medications prescribed**

| Medication            | < 150 | 150-300 | 301-450 | 451-700 | > 700 |
|-----------------------|-------|---------|---------|---------|-------|
| Cinacalcet            | 12%   | 10%     | 17%     | 29%     | 51%   |
| Phosphate binder      | 75%   | 75%     | 74%     | 76%     | 80%   |
| IV vitamin D          | 14%   | 19%     | 28%     | 37%     | 40%   |
| Oral vitamin D        | 37%   | 43%     | 41%     | 31%     | 25%   |
| IV or oral vitamin D  | 50%   | 59%     | 67%     | 65%     | 62%   |
| Statin                | 48%   | 47%     | 57%     | 52%     | 43%   |
| ACE inhibitor or ARB  | 24%   | 19%     | 21%     | 21%     | 23%   |

**Medications details**

| Route                  | Oral vit D only | IV vit D only | IV+ oral vit D | Alphacalcidol only | Calcitriol only | Paricalcitol only | Other vitamin D or combination |
|------------------------|-----------------|---------------|----------------|-------------------|-----------------|-------------------|-------------------------------|
|                        | 72%             | 68%           | 59%            | 43%               | 37%             |                  |                               |
| Vitamin D route        |                 |               |                |                   |                 |                   |                               |
|                        | 26%             | 29%           | 39%            | 53%               | 60%             |                  |                               |
|                        | 2%              | 3%            | 2%             | 2%                | 4%              | 3%                |                               |
| Vitamin D (IV or oral) type |              |               |                |                   |                 |                   |                               |
|                        | 87%             | 84%           | 88%            | 74%               | 74%             |                   |                               |
|                        | 10%             | 13%           | 9%             | 18%               | 8%              |                   |                               |
|                        | 1%              | 2%            | 2%             | 2%                | 5%              | 17%               |                               |
|                        | 2%              | 2%            | 1%             | 3%                | 1%              |                   |                               |
| Phosphate binder type  |                 |               |                |                   |                 |                   |                               |
|                        | 70%             | 60%           | 54%            | 47%               | 41%             |                   |                               |
|                        | 13%             | 14%           | 22%            | 23%               | 28%             |                   |                               |
|                        | 14%             | 24%           | 20%            | 29%               | 29%             |                   |                               |
|                        | 3%              | 2%            | 3%             | 2%                | 2%              |                   |                               |

Values are shown as prevalence, mean (standard deviation), or median [interquartile range]

a. 25% of patients had PTH > 600 pg/mL
b. Parathyroid surgery or percutaneous ethanol injection therapy (PEIT) into the parathyroid gland
c. Restricted to diabetic patients
d. Prescription at DOPPS enrollment or in the month prior to DOPPS enrollment; vitamin D restricted to active vitamin D (calcitriol or one of its synthetic analogs)
e. Restricted to patients prescribed the drug class of interest
Figure 1: PTH distribution by country (GCC DOPPS, 2012-2018)

Footnote: Estimates weighted by sampling fraction in each facility. Based upon initial cross-sections in DOPPS 5 (2012-2015) and DOPPS 6 (2016-2018) in each country.
Figure 2: PTH categories and mortality, GCC DOPPS (2012-2018)

Footnote: N=1,422 patients and n=222 deaths; adjusted for age, sex, vintage, body mass index, comorbidities (diabetes, coronary artery disease, cerebrovascular disease, congestive heart failure, other cardiovascular disease), serum creatinine, and single pool Kt/V; stratified by GCC region and phase; placement of estimates along the x-axis determined by median PTH in each group (< 150, 150-300, 301-450, 451-700, > 700). Categories chosen to yield approximate similar sample sizes across categories. The PTH of 301-450 pg/mL category served as the reference group and the median PTH among the > 700 category was 1090 pg/mL.