Secondary hyperparathyroidism and adverse health outcomes in adults with chronic kidney disease

Yang Xu¹, Marie Evans¹, Marco Soro², Peter Barany³, Juan Jesus Carrero¹

¹ Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden;
² Global HEOR, GPMA, Vifor Pharma;
³ Division of Renal Medicine, CLINTEC, Karolinska Institutet, Sweden.

Short title: sHPT in non-dialysis dependent CKD

Correspondence to: Yang Xu and Juan Jesus Carrero;
E-mail: yang.xu@ki.se and juan.jesus.carrero@ki.se

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ABSTRACT

Background. Secondary hyperparathyroidism (sHPT) develops frequently in patients with chronic kidney disease (CKD). However, the burden and long-term impact of sHPT on the risk of adverse health outcomes is not well studied.

Methods. We evaluated all adults receiving nephrologist care in Stockholm during 2006-2011 who were not undergoing kidney replacement therapy and had not developed sHPT. Incident sHPT was identified by using clinical diagnoses, initiated medications or two consecutive parathyroid hormone measurements ≥130 pg/mL. We characterized sHPT incidence by eGFR strata, evaluated clinical predictors and quantified the association between incident sHPT (time-varying exposure) and the risk of fractures, CKD progression, major adverse cardiovascular events (MACE), and death.

Results. We identified 2556 adults with CKD stages 1-5 (mean age 66 years, 38% women), of whom 784 developed sHPT during follow-up. The incidence of sHPT increased with advancing CKD: from 57 cases/1000 person-years in CKD G3 to 230 cases/1000 person-years in G5. In multivariable analyses, low eGFR was the strongest sHPT predictor, followed by young age, male sex, and diabetes. Incident sHPT was associated with 1.3-fold (95% CI, 1.1-1.8) increased risk of death, 2.2-fold (1.42-3.28) higher risk of MACE, 5.0-fold (3.5-7.2) higher risk of CKD progression and 1.3-fold (1.5-2.2) higher risk of fractures. Results were consistent in stratified analyses and after excluding early events.

Conclusions. Our findings illustrate the burden of sHPT in advanced-CKD, and highlight the susceptibility for adverse outcomes of patients developing sHPT. This may inform clinical decisions regarding pre-sHPT risk stratification, PTH monitoring and risk-prevention strategies post-sHPT development.

Keywords: end-stage kidney disease, fracture, mortality, parathyroid hormone, SCREAM
INTRODUCTION

Secondary hyperparathyroidism (sHPT) is an important complication of chronic kidney disease (CKD), and is characterized by elevated blood parathyroid hormone (PTH) levels. sHPT develops in CKD as a consequence of abnormalities in several biochemical parameters, including increases in serum phosphorus and fibroblast growth factor 23, and reductions in serum calcium and vitamin D(1). The prevalence of sHPT in CKD is well described, with estimates ranging between 20 to 80%(2) depending on CKD severity stage(3-5). However, there is little information on the onset (i.e. incidence) of sHPT. Incidence is potentially more useful than prevalence in understanding disease etiology, as it allows measurement of disease burden, which is helpful for health service planning and identification of potentially modifiable risks factors.

Some(6-11) but not all(12, 13) observational studies in patients with non-dialysis dependent CKD suggest that the presence of sHPT associates with a heightened risk of CKD progression, cardiovascular diseases (CVD) and death. Moreover, because sHPT increases osteoclastic bone resorption, prolonged sHPT has been associated with the probability of fractures in populations undergoing chronic dialysis(14, 15). However, whether sHPT predicts the risk of fractures in patients with non-dialysis dependent CKD is not well known.(16) Evidence for this derives from cross-sectional cohorts comparing patients with and without sHPT, which may suffer from immortal time bias (i.e. only those who survived to the time of sampling can contribute to the analysis)(6, 7), as well as selection bias (i.e. there are clinical differences inherent to patients with and without sHPT that can explain the outcome associations)(9, 10), leaving uncertainties regarding unmeasured confounding, reverse causation, and the temporal relationship of these events.

An alternative approach to more comprehensibly quantify absolute and relative risks is to consider the development of sHPT as an intermediate event (or a time-dependent exposure), and evaluate the risk that incident sHPT confers over and above the background CKD risk. In this study, we focused on quantifying incidence rates of sHPT in patients with non-dialysis CKD routinely cared by nephrologists. We aimed at identifying characteristics that predict sHPT occurrence, and evaluated the adverse health outcomes associated with the development of sHPT, with special emphasis on the risk of CKD progression, major adverse cardiovascular events (MACEs), bone fractures and death.
MATERIALS AND METHODS

Data source
The study population derives from the Stockholm Creatinine Measurements (SCREAM) project, a healthcare utilization cohort from the region of Stockholm, Sweden, described in detail elsewhere(17). In brief, SCREAM is a repository of laboratory tests from any resident of Stockholm who had plasma or serum creatinine measured at least once during the years 2006–2011. These lab tests were linked, via each citizens’ unique personal identification number, to regional and national administrative databases with complete information on demographics, health care use, dispensed drugs, validated renal outcomes, diagnoses and vital status, with no loss to follow-up. The Regional Ethical Review Board in Stockholm approved the study; informed patient consent was not deemed necessary since all data were de-identified at the government’s offices.

Study population
For this study, we included adults (≥18 years) residing in Stockholm who receiving nephrologist care during July 1st 2006 to December 31st 2011, but not undergoing kidney replacement therapy (KRT, i.e. chronic dialysis or kidney transplantation, as ascertained via linkage with the nationwide Swedish Renal Registry). From those, we selected records with at least one PTH measurement documented, with the date of the first PTH measurement set as the index date, which was the initial state. We excluded patients with a history of primary or secondary hyperparathyroidism (ascertained by the presence of a relevant diagnosis prior to index date, Supplementary Table 2), parathyroidectomy, receiving calcimimetics or active vitamin D (defined by recorded dispensations within 6 months before index date, Supplementary Table 3. Note that the use of vitamin D analogues was not considered an exclusion criterion), and/or having an index PTH twice above the upper reference limit (≥130 pg/mL). Other exclusion criteria included missing information on age and sex, recent or ongoing cancer (diagnosis within 3 years with the exclusion of benign skin cancers), human immunodeficiency virus or hepatitis C virus infection. A flow chart of records selection is depicted in Supplementary Figure 1.

Exposures & Outcomes
This study contains two complementary designs: First, we analyzed the incidence of shHPT and evaluated baseline predictors. The outcome was thus incident shHPT, which was defined as: the date in which a diagnosis of shHPT (ICD-10 code: N258) was issued, calcimimetics or active vitamin D therapies were initiated, parathyroidectomy was performed, and/or two consecutive PTH tests (>3 months and less than 1 year apart) twice above the upper reference limit (≥130 pg/mL) were encountered, whatever happened first. The date of the diagnosis, the date of the first recorded pharmacy dispensation and the date of the second consecutive elevated PTH test were considered the event date.

Second, we studied adverse health outcomes associated with the development of shHPT. To this end, shHPT was considered an intermediate event, which can also be seen as a time-dependent exposure. The risks of death and major adverse cardiovascular events (MACEs) were our primary study outcomes. Deaths (by any cause) were ascertained by linkage with the Swedish population register, which is considered to have virtually no loss to follow-up. MACE was defined as the composite of death due to CVD and non-fatal MI, stroke or heart failure. The risks of fractures or CKD progression were considered secondary outcomes, progression of CKD was defined as the
composite of doubling of creatinine or initiation of KRT. Fractures were defined by relevant diagnoses, excluding fractures of the face and skull. Outcome definitions are detailed in Supplementary Table 1.

Covariates
Study covariates include age, sex, comorbidities, concomitant medications and laboratory values. Comorbidities included presence of diabetes mellitus, hypertension, cardiovascular disease, cancer history, dementia, liver disease, osteoporosis, and fracture history, all of them assessed using the International Classification of Disease-Tenth Edition (ICD-10). Medications included the use of angiotensin-converting enzyme inhibitors (ACEis)/angiotensin II receptor blockers (ARBs), beta blockers, thiazide diuretics and loop diuretics, etc. Information on drug dispensations was obtained from the Dispensed Drug Registry, a nationwide register with complete information on all prescribed drugs dispensed at Swedish pharmacies. Treatments were assumed ongoing if there was a pharmacy dispensation at the time of or within the previous 6 months from index date, with the exception of bisphosphonates, for which we did not impose a time limit. Covariate definitions are further detailed in Supplementary Table 2 and Supplementary Table 3.

Laboratory tests were those performed in connection with an outpatient healthcare encounter. PTH was measured by four different methods at three central laboratories in the region of Stockholm. All three laboratories used second generation assays which also measured the PTH fragments and reported the results in pg/mL. Two PTH methods specifically measured intact-PTH by chemoluminescence, with a reference interval of 1.5-7.6 pmol/L. A third one has a reference interval of 1.6-6.9 pmol/l, and we could not retrieve information in the fourth and last PTH method. All plasma creatinine measurements were standardized to isotope dilution mass spectrometry standards, and glomerular filtration rate was estimated by the CKD-EPI equation(18). Other laboratory tests included urinary albumin to creatinine ratio (UACR), serum albumin, calcium, phosphorus, hemoglobin and LDL-cholesterol, following standardized methods at the central laboratories. The closest measurements at time of or prior to the index date were selected as baseline.

Statistical analysis
Values are expressed as mean and SD for continuous variables with normal distribution, median (interquartile range) for non-normal distribution variables, and percentage of total for categorical variables. The course of patients after index date was described by four illness-death multistate models (Supplementary Figure 2), with sHPT as the intermediate event and the four adverse health outcomes that we evaluate in relation to incident sHPT. All covariates were complete for all patients, with the exception of laboratory tests. Serum albumin, calcium, phosphorus, hemoglobin were missing in <20% of patients. Levels UACR and LDL-cholesterol were missing in 36.0% and 37.8% of patients, respectively. Missing data were handled using chained equations by classification and regression trees, and 5 imputed datasets were generated.

We first evaluated the transition from baseline to incident sHPT. We evaluated baseline predictors of sHPT through Cox proportional hazard regression models. Predictors considered included demographic characteristics, comorbidities, use of medications, and laboratory tests, as detailed in Supplementary Table 4. Continuous variables were standardized as per standard deviation increase, and the relative importance for each predictor were evaluated by the estimated explained
relative risk ($R^2$) and overall explainable log-likelihood ($\chi^2$) attributable to each predictor in ANOVA. Finally, we reported incidence rates of shPT by baseline CKD stage and employed natural cubic splines to graphically illustrate the association between eGFR (as a continuous variable) and the risk of developing shPT, with truncated power series as basis functions and knots at 10%, 50% and 90% quantiles of eGFR distribution. For these analyses, patients were followed until the occurrence of shPT, death, emigration from Stockholm or end of follow-up (December 31st, 2012)). End of follow-up was an administrative censoring, and the remaining censoring events were treated as non-informative censoring.

Next, we considered intermediate shPT as a time-dependent exposure. Hence, a patient developing shPT during observation contributed with time to the non-shPT group before the event, and thereafter to the shPT “exposed” group. All study covariates were time-updated at the time of incident shPT. For the outcomes of death, MACE and CKD progression, we evaluated their association with incident shPT via time-dependent Cox proportional hazard regression. For the outcome of fractures, we considered the possibility of the event to be recurrent, and thus evaluated the association between incident shPT and (recurrent) fractures via Poisson regression. Death was considered as non-informative censoring event when evaluating other study outcomes, and follow-up ended otherwise at event occurrence, emigration outside the region of Stockholm, and end of follow-up (December 31st, 2011). On the basis of biological confounders, we considered different covariates for each of the study outcomes, and these are detailed in Supplementary Table 4.

Several analyses were performed to test the robustness of our data. First, we excluded events within the first 90 days after shPT to assess the impact of reverse causation bias (e.g. suspicion for an adverse event is the reason for clinical exploration that may have resulted in the detection of shPT). Second, stratified analyses were performed to test the consistency of our results by age strata (<65 and ≥65 years), sex (men and women), and presence/absence of CVD or diabetes. Third, we evaluated the risk of unmeasured confounding by the E-value methodology, which identifies the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome, conditional on the measured covariates, to fully explain the observed association. This estimates what the relative risk would have to be for any unmeasured confounder to overcome the observed association of incident shPT with the risk of adverse events.

**RESULTS**

**Baseline characteristics**

After applying inclusion and exclusion criteria, a total of 2556 CKD patients without shPT at baseline were included in our analysis. Mean age was 66±15 years, and 38% were women. Baseline characteristics are depicted in Table 1. The most common comorbidity was hypertension (73%), followed by cardiovascular disease (43%). The use of ACEis, ARBs and beta blockers was frequent, counting for 68% and 51% of patients respectively. The majority had CKD stage 3 (62%), followed by CKD stage 1-2 (28%), The median PTH value was 69 (interquartile range (IQR), 48-93) pg/mL, higher than the upper reference limit of PTH (65 pg/ml).

**Predictors of incident shPT**

During a median follow-up of 2.4 (IQR 1.2-4.1) years, 784 subjects (31%) developed shPT, with an overall shPT incidence of 114.9/1000 person-years (95% confidence interval (CI) 107.0-123.2). The majority of shPT cases (n=572, 73%) were identified by the initiation of specific shPT
medications, and the remaining by persistently elevated PTH values (n=287, 26%) or ICD diagnoses (n=5, 1%). No event was identified from performed parathyroidectomies. The incidence of sHPT increased with worse CKD stages (Supplementary Table 5): from 57 cases/1000 person-years in CKD stage 3 to 230 cases/1000 person-years in CKD stage 5. Consequently, cubic splines illustrate a strong inverse association between eGFR and the risk of sHPT (Figure 1), with risks becoming apparent at eGFR values below 45 ml/min/1.73 m².

The multivariable-adjusted risk of sHPT associated to baseline predictors is shown in Figure 2: factors associated with the risk of sHPT were: younger age, male sex, lower eGFR, higher UACR, higher serum calcium, lower serum albumin, presence of diabetes and use of loop diuretics. Their relative contribution depicted graphically in Supplementary Figure 3: eGFR emerged as the largest contributor to the prediction of sHPT risk, followed by serum albumin levels and diabetes comorbidity.

Outcomes associated to incident sHPT
At time of sHPT development, participants had lower eGFR and a higher prevalence of hypertension and CVD compared to baseline characteristics (Table 1). There was also a higher proportion of patients using ACEI & ARB and beta blockers. The median PTH at time of sHPT identification was 130 (95-168) pg/ml, but PTH levels were dependent on how sHPT was identified in our study: for events identified by persistently elevated PTH values, the median PTH was 166 pg/ml. For events identified by the initiation of treatments, the median PTH was 112 pg/ml; of these, as many as 350 (61.2% of the total number of patients identified by initiation of medications) initiated treatment at PTH levels above 100 pg/mL, and 32.3% at PTH levels above 130 pg/mL.

A total of 495 deaths and 221 MACE were recorded during a median follow up of 2.4 (95%CI, 1.2-4.0) and 2.3 (95%CI, 1.1-3.9) years, respectively. Their incidence rates were higher after incident sHPT 87.9 (95%CI, 75.4-101.9) /1000 person-years for death and 42.4 (95%CI, 33.6-52.8)/1000 person-years for MACE) compared to non-sHPT periods 46.9 (95%CI, 41.9-52.3)/1000 person-years for death and 21.3 (95%CI, 17.9-25.1)/1000 person-years for MACE. After multivariable adjustment, the development of sHPT was associated with a 1.4-fold (HR 1.38, 95%CI 1.05-1.83) higher risk of death and a 2.2-fold (HR 2.16, 95%CI 1.42-3.28) higher risk of MACE (Table 2, panel A). Sensitivity analyses excluding early events (within 90 days) from incident sHPT still showed elevated hazards (Table 2, panel B). Subgroup analyses gave no suggestion of heterogeneity across our 4 pre-specified strata of age (<65 and ≥65 years), sex (men and women), and presence/absence of CVD or diabetes (Supplementary Table 6). E-values for the risk of all-cause mortality and MACE were 1.81 and 2.79 respectively, which given the range of HR observed, were interpreted as moderately robust to potential unmeasured confounders (Supplementary Table 7).

A total of 293 CKD progression and 1392 fractures events occurred. Again, the incidence of these events was higher after incident sHPT (89.9 (95%CI, 76.1-105.6) /1000 person-years for CKD progression and 0.23 (95%CI, 0.21-0.25) /1000 person-years for fracture) compared to non-sHPT periods (22.0 (95%CI, 18.5-25.9)/1000 person-years for CKD progression and 0.14 (95%CI, 0.13-0.15) /1000 person-years for fracture). After multivariable adjustment, developing sHPT was associated with a 5.0-fold (95%CI, 3.5-7.2) risk of CKD progression and a 1.8 (95%CI, 1.5-2.2) higher relative risk of fractures. Results remained robust after excluding early events (Table 2 and
we observed a suggestion of heterogeneity regarding a potentially higher risk of fracture associated to incident shPT among patients with diabetes compared to without (Supplementary Table 6). E-values for the risk of CKD progression and fracture were 5.35 and 3.06 respectively, which given the range of HR observed, were interpreted as robust to potential unmeasured confounders (Supplementary Table 7).

**DISCUSSION**

Our study illustrates the high rate of occurrence of sHPT in CKD, particularly in patients with advanced CKD where the highest sHPT incidence was observed. It also highlights the susceptibility for adverse outcomes of patients developing sHPT, who were at increased risk of fractures, MACE, CKD progression and death compared to patients not developing this condition.

The diagnosis and management of sHPT is complex, but measuring and targeting of PTH constitutes the basis. There is currently no consensus on PTH targets for patients with non-dialysis CKD because (as opposed to patients on dialysis), there are no randomized controlled trials evaluating PTH thresholds in relation to risks. For this reason, the 2017 KDIGO guidelines for mineral bone disorders advise treatment of sHPT on the basis of the individual patient’s temporal PTH trends, with an emphasis on increasing or persistently elevated PTH values. The majority of patients with CKD 3-5 (20, 21) already have PTH values above the upper reference limit of 65 pg/ml and thus, we chose to define our study outcome with complementary composite events. One of them was the detection of persistently elevated PTH levels twice the upper PTH range, which is consistent with KDIGO recommendations. While our threshold (>130 pg/ml) has been used often in previous studies, we acknowledge that it is a conservative one, and that treatments may be initiated at lower PTH levels. Indeed, most sHPT cases in our study were instead identified by the initiation of sHPT-related medications, which occurred in most cases at PTH values>100 pg/ml. Collectively, we believe that we have a robust and prudent assessment of sPTH which also incorporates clinical judgement and the development of patient symptoms or other laboratory abnormalities beyond PTH levels that justify treatments. By doing so, we provide novel and credible estimates of sHPT incidence in routine care settings, which complement a wealth of research evaluating prevalence. Both estimates provide complementary information, because if individuals with sHPT die more often (7, 10), the prevalence will accordingly drop, and previous figures may signify an underestimation of true prevalence.

The development of sHPT is inherent to the impairment of kidney function (20, 21), and observational studies report a rise in PTH levels typically when eGFR drops below 45 ml/min/1.73 m², which is also supported by our study (Figure 1). It is thus perhaps not surprising that our analysis of factors associated with sHPT development identified eGFR as the main contributor. Interestingly, UACR also emerged as an independent predictor, possibly reflecting additional kidney damage over and above that of eGFR and expanding previous reports of albuminuria differences across PTH categories of patients with CKD stages 3-5 in cross-section. The use of loop diuretics also predicted sHPT strongly in our study. It has been reported that diuretics may indirectly stimulate PTH secretion by increasing calciuria (potentially inducing a negative calcium balance), which may cause chronic parathyroid stimulation. In our study, patients with diabetes were at increased risk of developing sHPT, which agrees with a study from the CRIC cohort showing that in patients with CKD stages 2–4, those with diabetes had higher levels of
serum phosphate, PTH, and FGF23 levels and lower vitamin D levels compared with those without diabetes. Also in that study, secondary hyperparathyroidism occurred earlier in the course of CKD in individuals with diabetes compared with those without(23). Underlying mechanisms are not well elucidated, but it is possible that this group possesses a greater number of characteristics predisposing them to sHPT (lower eGFR, higher BMI, greater proteinuria, and lower 25-hydroxyvitamin D levels - in part because of greater urinary loss of vitamin D–binding protein in proteinuria(24) This specific finding suggests that a closer surveillance of PTH may be needed in diabetes. Serum phosphate did not predict sHPT risk in our study, which is at odds with previous literature. We hypothesize that serum phosphate distribution in our cohort was narrow and that collinearity with the other covariates in our model (such as eGFR and calcium) abrogated the association.

Finally, the association of low serum albumin with sHPT risk reflects the complex interplay between nutritional status(25) and bone health. Classic studies unveiled a close relationship between sHPT and energy expenditure(26) as well as and subsequent weight loss(27). It has not been until recently, that underlying mechanisms have been characterized, implying the binding of PTH to receptors in both adipocytes and myocytes that lead to activation of thermogenesis genes resulting in increased resting energy expenditure with subsequent muscle mass and fat mass loss(28). Other identified predictors in our study, such as young age, male sex and low calcium are in line with previous reports and collectively, our results credibly illustrate the multiple factors that may have an effect on development of sHPT. As a clinical application, these findings may assist physicians in identifying populations at sHPT risk that deserve monitoring for CKD-MBD parameters and symptoms.

Our study describes an increased risk of fractures after sHPT development, a finding that expands a previous study in the general population(16) and agrees with observational evidence from populations undergoing maintenance dialysis(29-31). Potential mechanisms involve increased osteoclastic bone resorption due to excessive calcium release to circulation(1), and cross-sectional studies indeed associate sHPT with lower bone mineral density (BMD)(32). The causality behind these associations may be vindicated by the demonstration that correction of sHPT through parathyroidectomy(33) or calcimimetics(34) reduces the rate of clinical fractures, and increases BMD(35). Our stratified analyses suggested the possibility of a higher fracture risk associated to sHPT in patients with diabetes. This agrees with the generally higher fracture risk of adults with diabetes in the community(36) and attributed to multiple factors, including the effects of certain antidiabetic medications (rosiglitazone and pioglitazone) on osteoclastogenesis, predisposition to fractures due to diabetes complications (like neuropathy, impaired vision, or hypoglycemics), and poor glycemic control with subsequent accumulation of AGEs in bone collagen(37).

We confirm previous observations of the adverse health consequences of sHPT on cardiovascular health, CKD progression and survival. By modelling sHPT as a time dependent exposure, we potentially offer less confounded estimates and minimize immortal time biases of cross-sectional studies. Our analysis excluding early events post-sHPT development suggests robustness against reverse causation bias. However, causality cannot be inferred by our study. Despite convincing experimental mechanistic research on the deleterious consequences of acute and chronic PTH loading on the CVD system, there is still no clear evidence on whether pharmacologically lowering PTH directly(38) or indirectly(39, 40) reduces the risk of death or MACE in patients on dialysis. However, it remains plausible that a combined medical approach targeting CKD-MBD homeostasis may be able to achieve this.
Strengths of our analysis include the complete regional capture of patients undergoing routine nephrologist care in a country with universal healthcare access. This allows improving patient selection and minimizing confounding indication bias associated with PTH monitoring by other medical specialties. The ascertainment of kidney function by eGFR is also a strength, as kidney dysfunction is one of the strongest risk factors for elevated PTH level, but this condition is generally affected by poor awareness and underutilization of ICD diagnoses in healthcare, which cannot reliably distinguish disease severity.(41, 42). Limitations in the interpretation of our study are its retrospective nature. Data reflects routine care in the region of Stockholm during 2006-2011 and findings may not necessarily extrapolate to other periods or settings. The use of vitamin D analogs and cinacalcet has increased in the recent years and it would be interesting to evaluate if increased shPT treatment rates have mitigated the adverse health outcomes associated to this condition. Finally, as any observational research, we are impacted by residual confounding due to unmeasured/undetected factors, for which we acknowledge the lack of information on body mass index and vitamin D levels. Our attempts to estimate the extent of residual confounding through the e-methodology or the exclusion of early events suggests, however, consistency in our findings.

To conclude, our findings illustrate the burden of shPT in CKD stages 3-5, and describe the range of adverse health events that associate with its onset. These findings may have clinical implications: previous reports have indicated that a low proportion of patients with non-dialysis dependent CKD are regularly monitored for their PTH levels in routine care and particularly in small/rural nephrology units(43-45) potentially leading to an underuse of shPT therapies in earlier CKD stages. Further, many persons with eGFR<45 ml/min/1.73 m² remain non-referred to nephrologists and PTH is less frequently monitored in primary care. Our estimates of shPT incidence by CKD stage and predictors of shPT risk may thus inform clinical decisions for health service planning regarding for whom and when to start monitoring PTH levels. Early identification of shPT in primary care may also allow treatment and/or represent a reason for nephrology referral. Our outcome analyses highlight the susceptibility for adverse outcomes of patients developing shPT, which may inform the need of risk prevention strategies post-shPT development, particularly in surveillance and monitoring for CVD risk and fractures.

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CONFLICT OF INTEREST STATEMENT
M.E. reports speaker or advisory board fees from AstraZeneca, Astellas Pharma and Vifor Pharma. J.J.C. reports funding from Astellas and AstraZeneca outside the submitted work and speaker or advisory board fees from Baxter, AstraZeneca and Astellas Pharma. M.S. is a Vifor Pharma employee. P.B. and Y.X. have no conflicts of interest to report.
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Table 1. Characteristics of patients with non-dialysis dependent CKD at study inclusion and at time of sHPT occurrence

| Characteristic                              | At study inclusion (n=2556) | At time of sHPT occurrence (n=784) |
|--------------------------------------------|----------------------------|-----------------------------------|
| Age (mean (SD)), years                     | 65.4 (14.5)                | 65.5 (14.2)                       |
| Women, n (%)                               | 967 (38)                   | 277 (35)                          |
| eGFR (median [IQR]), ml/min/1.73m²         | 38.9 [28.8, 51.1]          | 27.3 [20.0, 35.8]                 |
| eGFR category, n (%)                       |                            |                                  |
| G1-2                                       | 264 (10)                   | 16 (2)                            |
| G3a                                        | 669 (26)                   | 64 (8)                            |
| G3b                                        | 920 (36)                   | 244 (31)                          |
| G4-5                                       | 703 (28)                   | 460 (59)                          |
| Diabetes mellitus, n (%)                   | 799 (31)                   | 329 (42)                          |
| Hypertension, n (%)                        | 1866 (73)                  | 668 (85)                          |
| Cardiovascular disease, n (%)              | 1101 (43)                  | 415 (53)                          |
| Myocardial infarction                      | 433 (17)                   | 179 (23)                          |
| Heart failure                              | 562 (22)                   | 242 (31)                          |
| Cerebrovascular disease                    | 369 (14)                   | 142 (18)                          |
| Peripheral vascular disease                | 343 (13)                   | 138 (18)                          |
| Atrial fibrillation                        | 361 (14)                   | 147 (19)                          |
| Dementia, n (%)                            | 36 (1)                     | 13 (2)                            |
| Liver disease, n (%)                       | 32 (1)                     | 8 (1)                             |
| Osteoporosis, n (%)                        | 149 (6)                    | 66 (8)                            |
| History of fractures, n (%)                | 785 (31)                   | 276 (35)                          |
| PTH (median [IQR]), pg/mL                  | 69 [48, 93]                | 130 [95-168]                      |
| Albumin (median [IQR]), g/L                | 37 [34, 40]                | 36 [33, 38]                       |
| Calcium (median [IQR]), mmol/L             | 2.3 [2.2, 2.4]             | 2.3 [2.2, 2.3]                    |
| Phosphate (median [IQR]), mmol/L           | 1.1 [1.0, 1.3]             | 1.2 [1.0, 1.4]                    |
| Hemoglobin (median [IQR]), g/L             | 128 [116, 141]             | 123.8 [113, 135]                  |
| LDL-cholesterol (median [IQR]), mmol/L     | 2.9 [2.2, 3.7]             | 2.8 [2.1, 3.6]                    |
| UACR (median [IQR]), mg/mmol               | 4.9 [1.0, 38.9]            | 12.6 [1.3, 92.1]                  |
| ACEI/ARB, n (%)                            | 1737 (68)                  | 636 (81)                          |
| Beta blocker, n (%)                        | 1300 (51)                  | 513 (65)                          |
| Thiazide diuretics, n (%)                  | 173 (7)                    | 42 (5)                            |
| Loop diuretics, n (%)                      | 999 (39)                   | 505 (64)                          |
| Corticosteroids, n (%)                     | 344 (13)                   | 102 (13)                          |
| Vitamin D, n (%)                           | 294 (12)                   | 587 (75)                          |
| ESA, n (%)                                 | 91 (4)                     | 156 (20)                          |
| Phosphate binder, n (%)                    | 353 (14)                   | 188 (24)                          |
| Statins, n (%)                             | 1004 (39)                  | 393 (50)                          |
| Aspirin, n (%)                             | 839 (33)                   | 322 (41)                          |
| Sodium bicarbonate, n (%)                  | 121 (5)                    | 235 (30)                          |
| Prednisolone, n (%)                        | 320 (13)                   | 99 (13)                           |
| Estrogen supplements, n (%)                | 139 (5)                    | 35 (4)                            |
| Bisphosphonates, n (%)                     | 143 (6)                    | 42 (5)                            |
| Calcium salts, n (%)                       | 348 (14)                   | 169 (22)                          |

Abbreviation: ACEI/ARB, angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; LDL-cholesterol, low-density lipoprotein cholesterol; PTH, parathyroid hormone; UACR, urinary albumin to creatinine ratio.
Table 2. Association between incident sHPT and risk of subsequent adverse health outcomes (Panel A) and sensitivity analysis excluding early events (within the 90 days) after sHPT development to assess the impact of reverse causation bias (Panel B)

| Outcome                  | Non-sHPT periods | After incident sHPT | Crude HR/RR | Adjusted HR/RR |
|--------------------------|------------------|---------------------|-------------|----------------|
|                          | N                | Follow-up time, years | Incidence rate per 1000 person-years | N | Follow-up time, years | Incidence rate per 1000 person-years | Crude HR/RR | Adjusted HR/RR |
| **Panel A: Survival analysis with full follow up** |                  |                     |             |                |                                    |                     |             |                |
| All-cause death¹         | 320              | 2.4 [1.2-4.1]       | 46.9 (41.9-52.3) | 175           | 2.3 [1.2-3.8] | 87.9 (75.4-101.9) | 1.88 (1.55-2.28) | 1.38 (1.05-1.83) |
| MACE¹                    | 141              | 2.3 [1.2-4.0]       | 21.3 (17.9-25.1) | 80            | 2.1 [1.1-3.7] | 42.4 (33.6-52.8) | 2.04 (1.52-2.72) | 2.16 (1.42-3.28) |
| CKD progression¹         | 144              | 2.3 [1.1-3.9]       | 22.0 (18.5-25.9) | 149           | 1.8 [0.8-3.1] | 89.9 (76.1-105.6) | 5.26 (4.13-6.71) | 4.99 (3.47-7.17) |
| Fracture²                | 930              | 2.4 [1.2-4.1]       | 0.14 (0.13-0.15) | 462           | 2.3 [1.2-3.8] | 0.23 (0.21-0.25) | 1.70 (1.52-1.90) | 1.83 (1.55-2.15) |
| **Panel B: Survival analysis excluding events within the first 90 days after incident sHPT** |                  |                     |             |                |                                    |                     |             |                |
| All-cause death¹         | 320              | 2.4 [1.2-4.1]       | 46.9 (41.9-52.3) | 166           | 2.3 [1.2-3.8] | 83.4 (71.2-97.1) | 1.75 (1.44-2.13) | 1.26 (0.99-1.67) |
| MACE¹                    | 141              | 2.3 [1.2-4.0]       | 21.3 (17.9-25.1) | 74            | 2.1 [1.1-3.7] | 39.2 (30.8-49.2) | 1.85 (1.37-2.48) | 1.92 (1.25-2.94) |
| CKD progression¹         | 144              | 2.3 [1.1-3.9]       | 22.0 (18.5-25.9) | 122           | 1.8 [0.8-3.1] | 73.6 (61.1-87.9) | 4.04 (3.13-5.21) | 4.00 (2.73-5.86) |
| Fracture²                | 930              | 2.4 [1.2-4.1]       | 0.14 (0.13-0.15) | 460           | 2.3 [1.2-3.8] | 0.23 (0.21-0.25) | 1.70 (1.52-1.90) | 1.81 (1.53-2.13) |

1 Adjusted for age, sex, hypertension, CVD, dementia, liver disease, ACEis/ARBs, beta-blockers, diuretics, corticosteroid, vitamin D, ESA, phosphate binders, statin, sodium bicarbonate, prednisolone, aspirin, eGFR;
2 Adjusted for age, sex, diabetes, hypertension, CVD, dementia, liver disease, osteoporosis, fracture history, ACEis/ARBs, beta-blockers, diuretics, corticosteroid, vitamin D, ESA, phosphate binders, statin, sodium bicarbonate, prednisolone, aspirin, oestrogen supplements, bisphosphonates, calcium salts, eGFR.

Abbreviation: ACEis/ARBs, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers; CKD, chronic kidney disease; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; MACE, major adverse cardiovascular event; eGFR, estimated glomerular filtration rate; sHPT, secondary hyperparathyroidism; HR, hazard ratio; RR, rate ratio.
Figures and Figure legends

**FIGURE 1:** Multivariable-adjusted restricted cubic splines depicting the association between eGFR (continuous variable, per ml/min/1.73 m$^2$ lower) and the risk of developing sHPT in patients referred to Nephrologist care. Covariates used in the model are those listed in Figure 2. Abbreviation: eGFR, estimated glomerular filtration rate; sHPT, secondary hyperparathyroidism.

**FIGURE 2:** Forest plots depicting baseline factors associated with the risk of sHPT. Predictors are arranged from higher (on top) to lower (at the bottom) relative contribution to the full model. Abbreviations: ACEis/ARBs, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers; eGFR, estimated glomerular filtration rate; LDL-cholesterol, low-density lipoprotein cholesterol; PTH, parathyroid hormone; UACR, urinary albumin to creatinine ratio; SD, standard deviation.
| Covariates                                      | HR (95% CI)            |
|------------------------------------------------|------------------------|
| eGFR (per SD decrease), mL/min/1.73 m²          | 1.89 (1.72–2.08)       |
| Diabetes                                       | 1.38 (1.18–1.62)       |
| Albumin (per SD increase), g/L                 | 0.91 (0.85–0.99)       |
| Loop diuretic                                  | 1.29 (1.1–1.51)        |
| UACR (per SD increase), mg/mmol                | 1.16 (1.1–1.23)        |
| Calcium (per SD increase), mmol/L              | 0.83 (0.76–0.9)        |
| Cardiovascular disease                         | 1.12 (0.95–1.32)       |
| Hypertension                                   | 1.14 (0.94–1.38)       |
| Beta blocker                                   | 1.16 (0.99–1.35)       |
| Age (per SD increase), year                    | 0.83 (0.76–0.9)        |
| ACEis/ARBs                                     | 1.16 (0.97–1.38)       |
| Female                                         | 0.77 (0.66–0.9)        |
| Phosphate (per SD increase), mmol/L            | 1.06 (0.99–1.14)       |
| LDL–cholesterol (per SD increase), mmol/L      | 1.05 (0.98–1.13)       |
| Thiazide diuretic                              | 1.14 (0.87–1.49)       |
| Hemoglobin (per SD increase), g/L              | 0.96 (0.88–1.04)       |