A COST EFFECTIVENESS MODEL FOR SECONDARY HYPERPARATHYROIDISM IN NON-DIALYSIS CHRONIC KIDNEY DISEASE

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INTRODUCTION

- Secondary hyperparathyroidism (SHPT) is a serious complication in chronic kidney disease (CKD). SHPT is associated with an increased disease progression of CKD and mortality in both dialysis and non-dialysis CKD (ND-CKD) patients[1,2] and affects 40–82% of patients with CKD stage 3 or 4.[3]
- The duration of clinical trials within SHPT treatment is usually short (<6 months) and the measured outcomes are mostly limited to biomarkers, such as parathyroid hormone (PTH).
- This poses a methodological challenge as cost-effectiveness modelling requires linking disease biomarkers and treatment effect to outcomes and cost in a life-time horizon.[4]
- Therefore, for modelling the full value of SHPT treatment, relevant outcomes such as mortality need to be incorporated into the model by linkage to biomarker values.
- The literature on health-economic (HE) modelling for SHPT is scarce. A targeted literature review on HE models in SHPT treatment identified only two previously published studies[5,6] (using the same model with different country perspectives) for SHPT treatment in ND-CKD patients.

OBJECTIVE

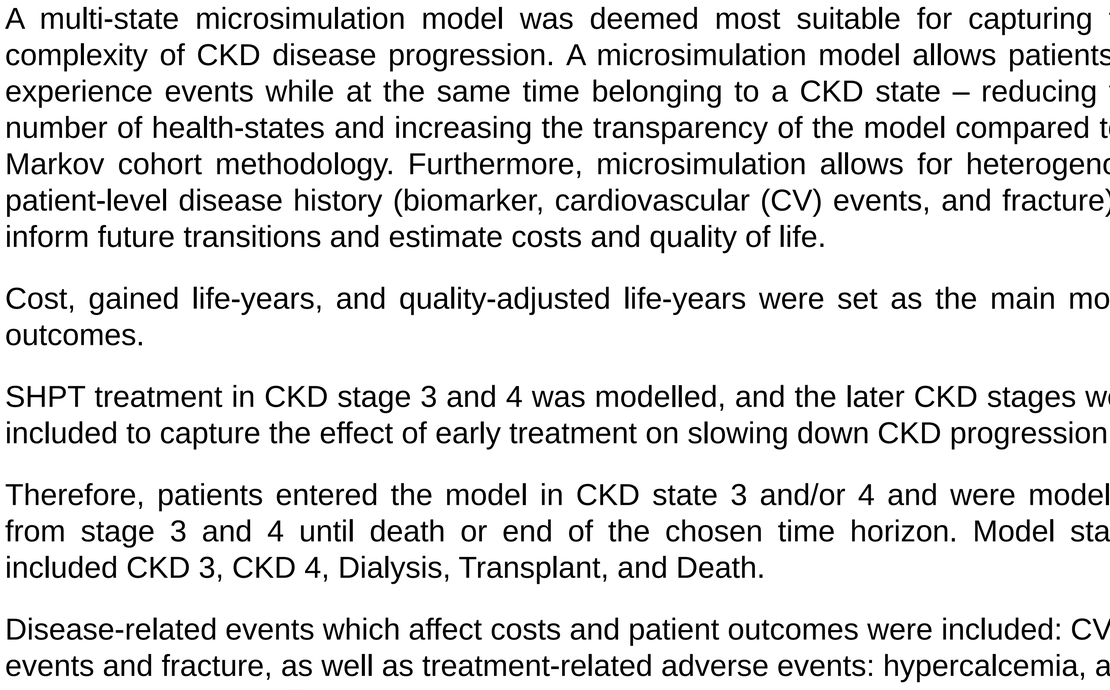
- The objective was to develop a cost-effectiveness model framework for assessing SHPT treatment in ND-CKD patients by linking clinical surrogate endpoints to hard outcomes.

METHODS

MODEL STRUCTURE

- A multi-state microsimulation model was deemed most suitable for capturing the complexity of CKD disease progression. A microsimulation model allows patients to experience events while at the same time belonging to a CKD state – reducing the number of health-states and increasing the transparency of the model compared to a Markov cohort methodology. Furthermore, microsimulation allows for heterogenous patient-level disease history (biomarker, cardiovascular (CV) events, and fracture) to inform future transitions and estimate costs and quality of life.
- Cost, gained life-years, and quality-adjusted life-years were set as the main model outcomes.
- SHPT treatment in CKD stage 3 and 4 was modelled, and the later CKD stages were included to capture the effect of early treatment on slowing down CKD progression.
- Therefore, patients entered the model in CKD state 3 and/or 4 and were modelled from stage 3 and 4 until death or end of the chosen time horizon. Model states included CKD 3, CKD 4, Dialysis, Transplant, and Death.
- Disease-related events which affect costs and patient outcomes were included: CV events and fracture, as well as treatment-related adverse events: hypercalcemia, and hyperphosphatemia. These were modelled as transitory event states as patients could experience them while existing in one of the model states (Figure 2).
- A one-year cycle length was deemed sufficiently short to capture changes in the disease status of CKD while maintaining computational speed and efficiency, in line with previous CE models within SHPT[5,6] and CKD[7,8,9] treatment.

Figure 2. Model structure

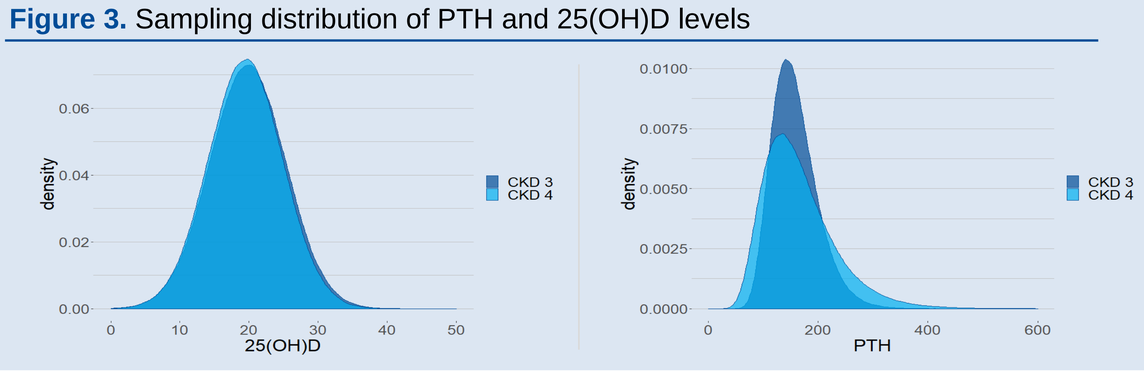


*Transition to this state is possible from all other states.
**Transition to this state is possible from CKD state 3 and 4 (while treated).

BIOMARKERS

- A systematic literature review[10] found that the biomarkers most commonly used in clinical trials for assessing treatment effects are PTH and 25-hydroxyvitamin D (25(OH)D) levels. Thus, these were included in the model and linked to hard outcomes such as CKD disease progression, CV events and mortality.
- Individual heterogeneity in biomarker levels (Figure 3) was introduced to allow the disease progression of ND-CKD to be modelled as a function of the proportion of patients reaching clinically significant thresholds.

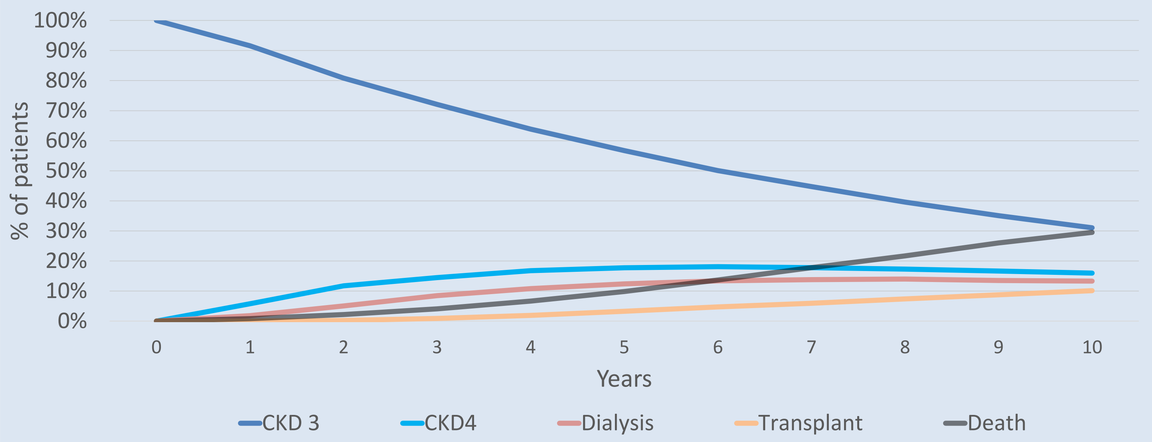
Figure 3. Sampling distribution of PTH and 25(OH)D levels



MODEL TRANSITION

- Underlying transition probabilities, so-called natural history of a CKD patient, were implemented in the model to simulate CKD progression unaffected by SHPT treatment (Figure 4). A targeted literature review was used to create an annual time-homogenous transition matrix[11,12] for the underlying model transition probabilities.
- Based on evidence from the literature, the underlying transition probabilities were then altered for each individual patient traversing the model, dependent on biomarker levels[2,13,14] (Table 1), and CV events[15].

Figure 4. Simulated state distributions of SHPT untreated patients in the CE model*



* Shown for the following population: CKD stage 3 patients, aged 65 years, 50% females, with mean (standard deviation) baseline PTH level of 126 (36) pg/ml, and mean 25(OH)D level of 20 (5) ng/ml.

Table 1. PTH and 25(OH)D association with hard outcomes

Biomarker		CKD progression	Mortality	CV event	Reference
PTH	↑	↑	↑	↑	2, 14
25(OH)D	↑	↓	↓	—	13

↑ = increases ↓ = decreases — = no direct association

CONCLUSIONS

- Modeling SHPT treatment in ND CKD patients poses methodological issues that previously published models did not fully tackle. The absence of hard endpoints in RCTs calls for a health economic model to link the clinical evidence available to tangible health outcomes.
- Our model framework proposes a method for estimating cost-effectiveness as a function of treatment effects, patient-level heterogeneity, and the intermediate link between surrogate biomarkers and hard endpoints.
- The value of the model is highly dependent on input data; further research effort is needed to provide robust data on natural history disease progression and the link between biomarkers and outcomes.

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