



## ORIGINAL RESEARCH

### Cinacalcet adherence in dialysis patients with secondary hyperparathyroidism in Lombardy Region: clinical implications and costs

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#### Abstract

**Background:** Patients on dialysis often have secondary hyperparathyroidism (SHPT), a disorder associated with renal osteodystrophy, progressive vascular calcification, cardiovascular disease, and death. The objective of this retrospective observational study was to evaluate, in dialysis patients with SHPT, the impact of different levels of adherence to cinacalcet therapy on hospitalisations and direct healthcare costs charged to the Lombardy Regional Health Service (Italy).

**Methods:** Data recorded in the administrative databases on all citizens undergoing dialysis between 1 January 2011 and 31 December 2011 were selected. For the aim of this study, patients with SHPT already on dialysis in the first 6 months of 2009 who had been treated with cinacalcet for at least 365 days were selected and retrospectively analysed through to end of 2012. Healthcare resource utilisation, cinacalcet adherence, and costs for medication, hospitalisations, and diagnostic/therapeutic procedures were estimated.

**Results:** A total of 994 patients were identified (mean age 63.0 years, females 43.5%). The first patient tertile had an

adherence to cinacalcet of <64.1%, whereas the third had an adherence of over 91.5%. Patients in the third adherence tertile experienced fewer all-causes hospitalisations than those in the first tertile (−19.2%;  $p=0.01423$ ), fractures (−37.1%;  $p=0.59422$ ), cardiovascular disease (−23.8%;  $p=0.04025$ ), and sepsis (−32.3%;  $p=0.01386$ ). The increase in costs for cinacalcet-adherent patients is almost completely offset by the reduction in costs for hospitalisations.

**Conclusions:** The results of the analysis suggest that there may be some correlation between a high level of cinacalcet adherence and a decrease in hospitalisations.

**Keywords:** cinacalcet, costs, dialysis, SHPT, therapeutic adherence.

#### Citation

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## Introduction

Parathyroid hormone (PTH) plays a key role in the regulation of calcium-phosphorus metabolism, by maintaining normal bone processes along with the action of vitamin D. When kidney function is absent or impaired, this regulatory activity is compromised, resulting in high serum phosphorus and low serum calcium levels, and an increase in circulating PTH due to the repeated stimulation of the parathyroid glands, leading to the onset of secondary hyperparathyroidism (SHPT).<sup>1</sup> SHPT, which is characterised by high serum PTH levels, parathyroid gland hyperplasia, and mineral metabolism disorders, primarily causes renal osteodystrophy and is associated with progressive vascular calcification (VC), and ultimately, cardiovascular (CV) disease and death, especially in patients with chronic kidney

disease (CKD) receiving haemodialysis (HD). In the literature, this spectrum of disorders is jointly referred to as CKD-mineral and bone disease (CKD-MBD).<sup>2,3</sup> Given their key roles in the pathogenesis of SHPT, calcium-sensing receptors (CaSR) and vitamin D receptors (VDR) are biologically plausible targets for emerging therapies for the treatment of this condition.<sup>4</sup>

Initially, classical therapy for SHPT in dialysed patients usually consists of calcium salts, intestinal phosphate binders, and active vitamin D metabolites. As this therapeutic approach is very rarely able to prevent PTH elevation and a worsening of SHPT, in recent decades, the use of calcimimetics has been introduced.<sup>5</sup>

Calcimimetics bind with and activate the CaSRs, thereby increasing the response to serum calcium of the receptors on

the parathyroid glands that regulate parathyroid hormone secretion. Cinacalcet, therefore, acts by reducing PTH production by the parathyroid glands. In both placebo-controlled and single-arm studies, the most commonly reported adverse reactions were nausea and vomiting, which were experienced by approximately 30% of patients<sup>6</sup> conditioning treatment discontinuation associated with the use of calcimimetics. Thus, as with most medicinal products, the efficacy of cinacalcet is poorer in patients who are not adherent with the prescribed treatment schedule.

Owing to the continuous stimulation of parathyroid glands, calcimimetic therapy must be continued over time, without interruption, adjusting the dose in line with PTH levels. The problem of treatment adherence, therefore, plays a crucial role in SHPT therapy.<sup>7</sup>

To evaluate different levels of therapeutic adherence to cinacalcet and their clinical and economic effects, we investigated the administrative database of the Regional Health Service of the Lombardy region (Italy) concerning CKD patients on renal replacement therapy (RRT). The main objective of this analysis was to describe the impact on hospitalisations and healthcare costs charged to the Italian National/Lombardy Regional Health Service (INHS/LRHS) of different treatment adherence to cinacalcet in SHPT patients on dialysis in the Lombardy region during 2011.

## Methods

### Data sources

For this retrospective observational study, data from the administrative database of the Lombardy region covering a total of 9.7 million residents were analysed. Healthcare services provided by the Italian National Health Service (specifically, drugs, hospitalisations, and diagnostic procedures) are systematically reported for each person in Local Health Services databases and subsequently pooled in regional databases for administrative assessments. The Italian National Health Service provides all citizens with free healthcare including hospital admissions, drugs, outpatient visits, and instrumental and biochemical tests and procedures through regional institutions. All citizens of Lombardy on dialysis in the period between 1 January 2011 and 31 December 2011 were selected. All data of this study regarding patients, in accordance with applicable Italian privacy regulations, were extracted already anonymised from the administrative databases of Lombardy Region and analysed anonymously so that the informed consent was not applicable. All data regarding healthcare resource utilisation and costs charged to the LRHS were extracted for the period from 1 January 2009 to 31 December 2012.

Each identified patient was included in the dataset with an anonymous code (an untraceable code generated automatically during data extrapolation), in accordance with applicable Italian privacy regulations;<sup>8</sup> this anonymous code is used to identify each patient in the individual section of the dataset.

All drugs charged to the INHS was recorded, including those dispensed by both INHS facilities and local pharmacies. Data on hospital admissions charged to the INHS were recorded (admission and discharge dates, diagnosis, procedures performed during hospitalisation, and costs). Diagnostic procedures (laboratory tests, instrumental procedures, and ambulatory care) were recorded in terms of type, date, and costs; results were not recorded as they are not present in the Regional database.

### Healthcare costs and perspective of the analysis

Unitary healthcare costs for hospitalisation and diagnostic procedures were extracted directly from the administrative database, and they coincide with the tariffs applied in the Lombardy region for the period considered; medication costs were also extrapolated directly from the database, and they represent the actual cost charged to the LRHS.

Indirect costs (not charged to the LRHS) and productivity losses were not considered, as they were outside the scope of this analysis. The analysis was conducted from the perspective of the LRHS.

### Patient selection and classification

Of the patients on dialysis during 2011 in the Lombardy Region (identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM)<sup>9</sup> codes 39.95 and 54.98), those already on dialysis in the first 6 months of 2009 who did not have acute kidney injury (ICD9-CM code 548) were selected.

In this population, SHPT patients were identified using the following criteria: hospitalisations with diagnosis of SHPT of renal origin (in or outside of the Lombardy Region, ICD9-CM code 588.81) and/or hospital admissions for parathyroidectomy (in or outside of the Lombardy Region, ICD9-CM code 06.81 and/or 06.89) and/or prescriptions for cinacalcet (ATC code H05BX01, all reimbursed dosages, 30, 60, and 90 mg) and/or paricalcitol (ATC code H05BX02 all reimbursed dosages and formulations 1 µg, 2 µg, and 5 µg/mL). The SHPT population was described in terms of demographic characteristics and the presence of major comorbidities (cardiovascular (CV) disease, diabetes, and cancer). These comorbidities were identified as follows: CV disease by diagnosis at hospitalisation (ICD9-CM codes between 390 and 459 (diseases of the circulatory system) in or outside of the Lombardy Region), diabetes through the prescription of drugs with ATC code A10 (drugs for diabetes), and cancer through the prescription of drugs with ATC code L01 (antineoplastic drugs) and/or hospitalisation (in or outside of the Lombardy Region) with ICD9-CM code between 140 and 239 (tumours). Other comorbidities used for the calculation for Mary Charlson index<sup>10</sup> were also identified using ICD9-CM codes and the prescription of specific classes of drugs.<sup>11</sup>

Hospitalisation for all causes, due to CV disease, fractures (femur, hip, pelvis, and vertebral column), and sepsis were

identified using the diagnosis reported in the hospital discharge records and analysed to identify possible differences amongst the cinacalcet adherence tertiles.

## Evaluation of adherence to cinacalcet therapy

To evaluate adherence to cinacalcet treatment, SHPT patients treated in the observational period for at least 1 year were selected.

Adherence to treatment was calculated, on a patient-by-patient basis, as the percentage of treatable days (equal to the total number of dispensed tablets) out of the total number of days of treatment with the drug (calculated as the difference between the first and last date of cinacalcet treatment plus 28 days, coinciding with the number of days covered by the last pack). The population was split into tertiles according to adherence. The selected population was observed, for the aims of adherence evaluation and cost analysis, over the period from 1 January 2009 to 31 December 2012.

## Statistical analysis

Proportions as the descriptive statistic for categorical variables and mean  $\pm$  standard deviation (SD) or median, for continuous variables, were used. Kruskal–Wallis rank sum test was used to compare the distribution of the number of hospitalisations and costs between the three adherence tertiles. Differences in the demographic and clinical characteristics in patients amongst different tertiles were assessed through the Pearson Chi-squared or the Fisher exact test for categorical variables and the Kruskal–Wallis rank sum test for continuous ones. *R* (version 3.2.5) was used to perform data analysis.<sup>12</sup>

## Results

In Lombardy Region, 8316 patients were on dialysis in 2011 and 4791 were already on dialysis in the first 6 months of 2009 (38.8% females; 86.3% treated with haemodialysis alone, 5.8% with peritoneal dialysis alone, and 7.8% with both).

According to the selection criteria, 1793 patients (37.4% of the population on stable dialysis) had SHPT; the average age of this population was  $63.3 \pm 14.4$  years (median age 65.9), and 42.9%

were females. In the population without SHPT, the average age was  $70.2 \pm 13.2$  years (median age 72.9) and 36.3% were females. The total annual healthcare cost covered by the LRS in the SHPT population was €41,555 per patient, of which 68.7% for dialysis, 12.3% for hospitalisations, 8.9% for other diagnostic procedures and laboratory tests and 10.1% for drugs.

Of the SHPT population, 1373 patients were treated with cinacalcet and 994 (mean age  $63.0 \pm 65.3$  years, females 43.5%) received at least 12 months of treatment during the observation period. Median adherence to cinacalcet in the analysed population was 78.06% (48.5% of patients had an adherence greater than 80%). The first tertile of patients ( $n=333$  patients, mean age  $62.5 \pm 64.3$  years, females 46.0%) had an adherence to cinacalcet treatment of  $<64.1\%$ , the second ( $n=330$  patients, mean age  $63.3 \pm 66.1$  years, females 41.8%) had an adherence of between 64.1% and 91.5% and the third ( $n=331$  patients, mean age  $63.0 \pm 64.2$  years, females 42.6%) had an adherence of  $>91.5\%$ .

The average number of per patient hospitalisations for all causes, hospitalisations due to fractures, CV hospitalisations, and hospitalisations for sepsis in the various tertiles are reported in Table 1.

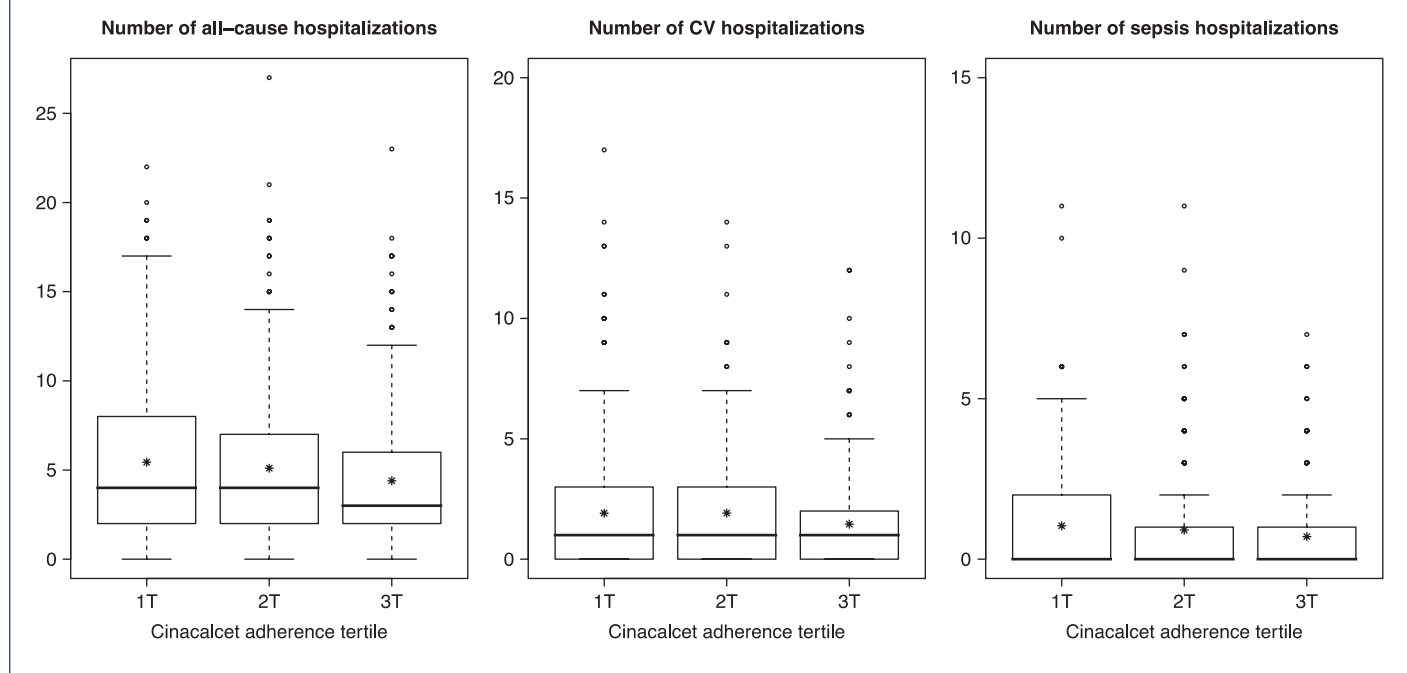
Between the third and first tertiles of adherence, there was a 19.2% decrease in all-cause hospitalisations, a 37.1% decrease in hospitalisations for fractures, a 23.8% decrease in CV hospitalisations, and a 32.3% decrease in hospitalisations for sepsis. The difference amongst the tertiles was statistically significant for all-cause hospitalisations ( $p=0.01423$ ), for CV hospitalisations ( $p=0.04025$ ), and for hospitalisations for sepsis ( $p=0.01386$ ) but was not significant for fractures ( $p=0.59422$ ) (Figure 1), suggesting that there may be some correlation between a high level of cinacalcet adherence and the lower number of all-cause, CV, and sepsis hospitalisations.

We investigated the presence of differences in the demographic and clinical characteristics of patients amongst tertiles that could explain the decrease in the number of hospital admissions (other than adherence to cinacalcet) (Table 2).

As shown in Table 2, the characteristics of the populations in the three tertiles were similar except the percentage of patients treated with calcium-based phosphate binders, which significantly decreased with the increase in adherence to cinacalcet treatment (Pearson's Chi-squared test,  $p=0.0417$ ).

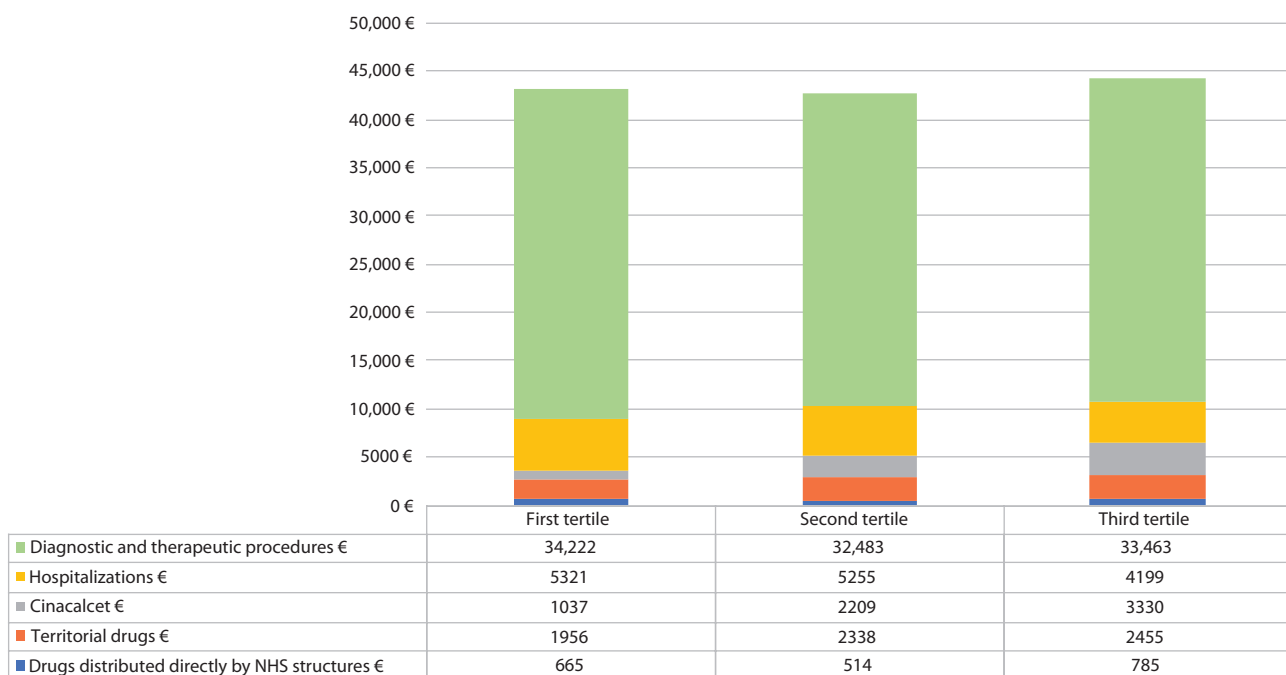
**Table 1. Average per-patient hospitalisations (4 years) by cinacalcet adherence tertile.**

Cinacalcet adherence tertile	Average number of all-cause hospitalisations per patient (4 years)	Average number of hospitalisations due to fractures per patient (4 years)	Average number of cardiovascular hospitalisations per patient (4 years)	Average number of hospitalisations for sepsis per patient (4 years)
First	5.438	0.07207	1.910	1.039
Second	5.103	0.06667	1.915	0.9091
Third	4.396	0.04532	1.456	0.7039

**Figure 1. Box plot of difference between tertiles in the per-patient number of hospitalisations.****Table 2. Demographic characteristics.**

Variables	First tertile (n=333)	Second tertile (n=330)	Third tertile (n=331)	p-value	Type of test
Age (mean, years)	62.53	63.33	63.03	0.9801	Kruskal–Wallis rank sum test
Gender (% females)	45.95	41.82	42.60	0.5244	Fisher's exact test for count data
MCI (mean)	1.56	1.52	1.46	0.526	Kruskal–Wallis rank sum test
Type of dialysis (%)					
HD only	87.99	86.36	86.71	0.6183	Pearson's Chi-squared test
PD only	5.41	5.45	3.93		
HD+PD	6.61	8.18	9.37		
Treatment with vitamin D (%)	28.23	30.91	31.72	0.591	Pearson's Chi-squared test
Paricalcitol treatment (%)	38.74	36.36	42.30	0.2902	Pearson's Chi-squared test
Non-calcium-based phosphate binders (%)	84.68	87.27	83.69	0.4071	Pearson's Chi-squared test
Calcium-based phosphate binders (%)	36.94	32.12	27.79	0.04174	Pearson's Chi-squared test
RAS inhibitors (%)	79.88	84.55	82.48	0.2883	Pearson's Chi-squared test
ESA (%)	22.82	21.82	23.26	0.9017	Pearson's Chi-squared test

ESA, erythropoietic stimulating agents; HD, haemodialysis, MCI, Mary Charlson index; PD, peritoneal dialysis; RAAS, renin–angiotensin–aldosterone system.

**Figure 2. Distribution of annual per-patient cost by tertile.****Table 3. Average per-patient hospitalisation costs (4 years) by cinacalcet adherence tertile.**

Cinacalcet adherence tertile	Per-patient cost of all-cause hospitalisations (4 years)	Per-patient cost of hospitalisations for fractures (4 years)	Per-patient cost of cardiovascular hospitalisations (4 years)	Per-patient cost of hospitalisations for sepsis (4 years)
First	€21,283	€476	€9005	€5383
Second	€21,020	€442	€9591	€4133
Third	€16,797	€249	€7264	€3121

Although it is not statistically significant, a higher percentage of use of VDRs activators (vitamin D and paricalcitol) in the third tertile than in the first can be observed. The average annual per-patient cost was €43,201 in the first tertile, €42,800 in the second, and €44,232 in the third (Figure 2).

Diagnostic and therapeutic procedures (including dialysis) represented by far the major cost driver in all tertiles. Hospitalisation costs accounted for 12.3% of total costs in the first and second tertiles and decreased to 9.5% in the third. Conversely, drug costs (excluding cinacalcet) increased from 6.1% of total costs in the first tertile to 7.3% in the third. Cinacalcet costs accounted for 2.4% of total costs in the first tertile and increased to 7.5% in the third; whereas, in relation to total medication costs, cinacalcet accounted for 28% in the first tertile, 44% in the second tertile, and 51% in the third. We also analysed the differences amongst adherence tertiles in terms of the costs of hospitalisation for all causes, CV disease, fractures, and sepsis (Table 3).

Differences were statistically significant for all-cause hospitalisation costs ( $p=0.0127$ ) and for sepsis ( $p=0.01109$ ). The decrease in costs between the third and first adherence tertiles was 21.1% (–€4486) for all-cause hospitalisations, 47.7% for hospitalisations for fractures, 19.3% for CV hospitalisations, and 42.0% for hospitalisations for sepsis.

## Discussion and conclusions

In this retrospective study based on the data reported in the LRHS, amongst the 994 patients chronically treated with cinacalcet, the first tertile had an adherence to cinacalcet treatment lower than 64.1% and the third had an adherence of over 91.5%. Patients in the third adherence tertile experienced significantly fewer all causes and cardiovascular hospitalisations than those in the first tertile, fewer fractures, and sepsis. The reduction in hospitalisation cost almost completely offsets the increased cost of cinacalcet in this group.



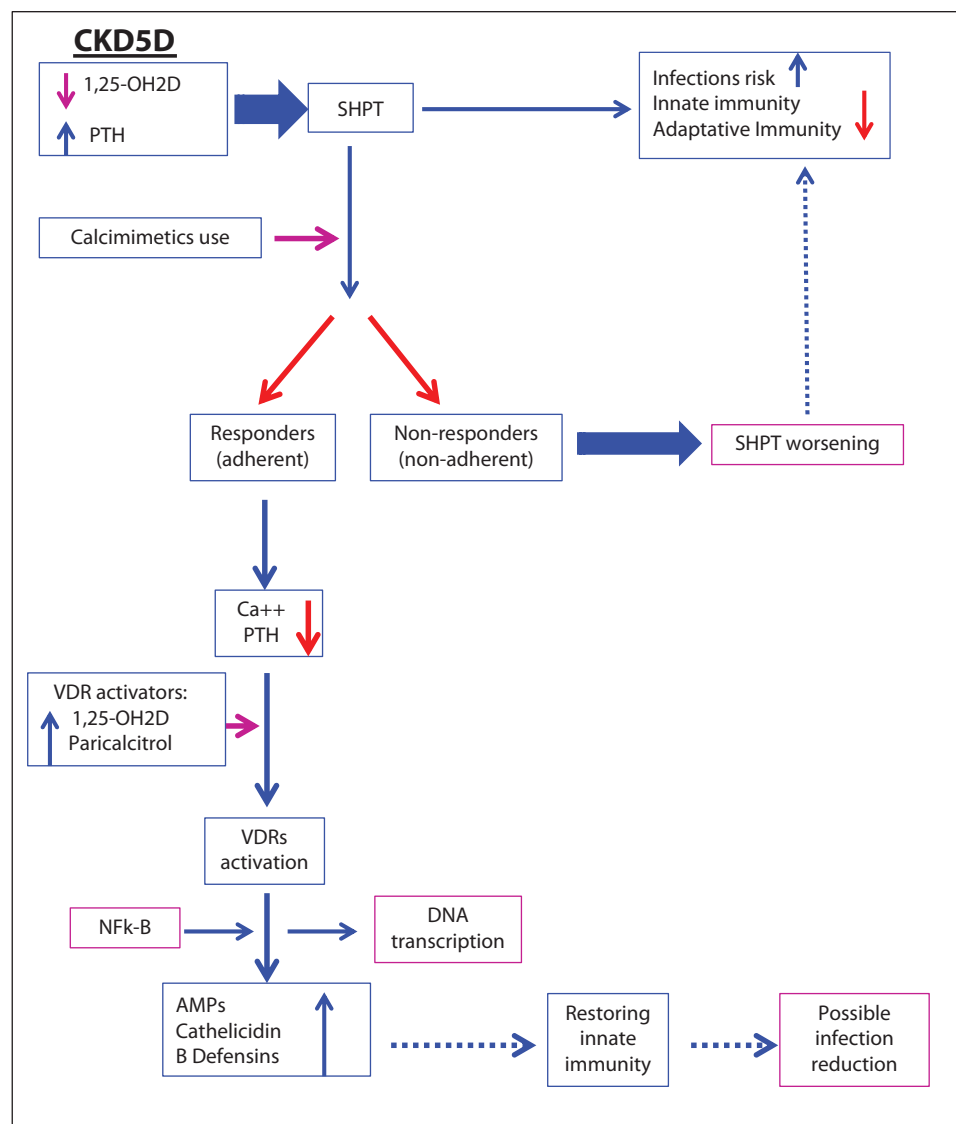
According to the selection criteria implemented on the database, 37.4% of patients had SHPT, a value that is not significantly different to that observed in the DOPPS data from Italian dialysis centres.<sup>13</sup> The use of calcimimetics (cinacalcet HCl) is particularly effective in reducing plasma PTH levels, and consequently Ca and P in patients with SHPT on dialysis.<sup>6,14</sup> Even in the approval phase, a number of gastrointestinal side effects emerged with a non-negligible frequency and they could be the cause of the high frequency of discontinuation of the treatment within 6–12 months from the start of therapy, and similar frequency of restart.<sup>15</sup> These side effects increase with the dose administered and could be associated with the specific activity exerted on the gastrointestinal CaSRs. Cinacalcet is nevertheless extensively used in CKD-5D patients due to both its efficacy and the high number of SHPT patients on dialysis and is likely to be considered the most effective treatment for SHPT, even though this statement was not uniformly shared by the working group of recent KDIGO due to the negative primary endpoints of the EVOLVE study.<sup>16,17</sup> In consideration of the influence of treatment adherence on the outcome also in RCTs, it is important to underline how the post hoc analysis of the EVOLVE study, made not on the basis of intention to treat (ITT) but on the real adherence to treatment, modify the significance of the results related to mortality and major cardiovascular events.<sup>18</sup>

The therapeutic adherence explored by comparing the time covered by medical prescription of the drug (also considering regimen changes) and the time elapsing between prescriptions showed that a large proportion of subjects had less than a reasonable level of therapeutic adherence, making it difficult to assess the impact of therapeutic adherence on expected outcomes. To investigate the role of therapeutic adherence in determining costs and clinical outcomes, the population was divided in tertiles: patients belonging to the first tertile had a low adherence (<64%), the second >64% but <91%, and the third had an adherence of >91%. Thirty-three percent of the patients considered achieved the highest level of adherence, in line with the findings of a study involving more than 4000 patients on dialysis that showed that 28% of patients had a high level of adherence 1 year after the start of the treatment.<sup>19</sup> This low cinacalcet adherence rate is not surprising, is supported by numerous other reports,<sup>20–22</sup> and may be explained by several factors including that CKD-MBD is not generally perceived by dialysis patients as a disease to be cured, as it produces little or no symptoms regardless of therapeutic adherence, until a late stage; whereas, the medicinal products prescribed have side effects (cinacalcet) or involve taking a large number of tablets (phosphate binders). Hospital admissions have been considered as the most reliable and safe clinical outcome, in absence in the administrative database of the recording of causes of death but only of their date. Frequency of hospitalisations for all causes, cardiovascular disease, sepsis, and fractures were analysed by tertiles. The data distribution and dispersion described in the box plot in Figure 1 showed a gradual decrease in the number of hospital admissions during the observation period for all the variables considered from the first to the third tertile of

–19% for all causes, –37% for fractures, –24% for cardiovascular diseases and –38% for sepsis with statistical significance for hospital admissions for all causes, CV disease and sepsis, suggesting a relationship between therapeutic adherence and hospitalisations; those decreases have a consequent effect on reduction of hospitalisation costs from the first to the third tertile. The majority of these data are supported by several observational and experimental studies that had reported a relationship between cinacalcet use and all-cause and cardiovascular-related hospitalisations.<sup>23–26</sup> The limited information available in the literature regarding the relationship between cinacalcet use and infection-related hospitalisations is largely controversial; the results of one meta-analysis<sup>27</sup> indicated that the cinacalcet use increased the upper respiratory tract infections, whereas in one more recent study<sup>28</sup> the authors did not observe any increase in infection-related hospitalisations, rather, in the patient group with the lowest PTH levels, there was a significant correlation with a lower incidence of infection-related hospitalisations. Although no clear explanation of the positive effect of better adherence to cinacalcet therapy and reductions in infection-related hospitalisation is given in any published paper, one explanation could be a more careful use of vitamin D receptor activator (VDRA) in compliant patients, as this seems to have occurred in third-tertile patients, most probably due to hypocalcaemia secondary to parathyroid inhibition (Figure 3). Although this hypothesis may be attractive, its demonstration based on the information contained in the analysed database is not possible as Ca, P, and PTH values are not included. From a clinical point of view, the fact that fewer infection-related hospitalisations were observed amongst cinacalcet-adherent patients is an important point that deserves further investigation, given the high risk of infection amongst dialysis patients. To exclude a well-known role of central venous catheters (cvc) in influencing infectious risk in dialysis patients,<sup>29</sup> we analysed the percentage distribution of cvc carriers in tertiles without finding any significant difference. The percentage decrease for hospital admissions for all causes and sepsis reached statistical significance ( $p=0.0127$  and  $p=0.01109$ , respectively). These results show a non-negligible relationship between therapeutic adherence, clinical outcomes, and costs.

The main strength of this analysis is the data integrity achieved by analysing administrative databases, because they automatically record all the events that take place for every citizen living in the region with the main purpose of an economic assessment, which makes them very detailed and precise. However, this characteristic can also be considered a weakness, as the data have no clinical or epidemiological purpose and lack certain important clinical and biological parameters. Furthermore, this reflects real-world practice at the population level.<sup>33</sup> Unfortunately, although they are able to provide accurate and reliable economic assessments, studies based on the analysis of this type of data are unable to provide solutions to clinical problems. Unlike prospective randomised clinical trials, the gold standard of medical evidence, the use of ‘real-world’ data may be particularly useful when considering

**Figure 3. Hypothesis for cinacalcet and decrease in infection-related hospitalisations.**<sup>28,30,31,32</sup>



According to Asada's hypothesis, SHPT patients with the highest adherence to cinacalcet therapy who achieve the objective of reducing PTH levels to almost normal values would also have a marked reduction in calcium levels. Hypocalcaemia leads to increased administration of VDR activators. Activated VDRs residing on immune cells increase the production of antimicrobial peptides, thus improving the level of innate depressed immunity. 1,25-OH2D: 1,25-dihydroxyvitamin D3; AMPs: antimicrobial peptides; Nfκ-B: protein complex-transcription factor; Dotted lines: hypothetical pathways.

the use of a drug and its level of therapeutic adherence in a specific group of subjects.

The major limitation of this study is linked to the structure of the administrative databases, in which the clinical and laboratory data are not collected; consequently, the effects of therapies should be evaluated through surrogate endpoints (in our case, the frequency of hospitalisations).

The other major limitation is that the data refer to years 2009–2013: this period still provides reliable data even if the national reimbursement tariffs for hospitalisations changed in 2013 but

with a very limited mean variation of  $-4.6\%$ .<sup>34</sup> Regarding the most relevant changes in drugs prices, the cinacalcet price did not change whilst the paricalcitol price decreased by 50% for the generic formulations with an impact on total per patient yearly cost of less than 2%. These variations do not affect significantly our results.

Finally, administrative databases do not contain information regarding the impact of the decrease in hospitalisations on the general expenses incurred for the organisation of Regional Health Services, or the direct and indirect benefits on patient well-being that were not part of the purpose of this study.

This study, despite limitations due to its retrospective approach, shows that an administrative data source, though lacking in clinical and biological parameters, can be used to assess the correct use

of medicinal products and patient adherence to therapy. The administrative accuracy also makes it possible to highlight the economic impact and, within certain limits, patient outcomes.

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