An economic comparison of surgical and medical therapy in patients with secondary hyperparathyroidism—the German perspective

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Background. Treatment options for secondary hyperparathyroidism were significantly amended with the introduction of cinacalcet and paricalcitol. Limitations of resources in public health systems demand detailed analyses of accruing costs. The aim of this study was to compare the costs of these new treatment modalities to surgery.

Methods. Patients who underwent initial parathyroidectomy (n = 91) and patients treated with cinacalcet or paricalcitol (n = 100) at an ambulatory dialysis center between 01/2003 and 12/2006 were analyzed. The revenues of both therapies for the funding agencies were calculated by a cost-cost analysis. The real arising costs of the supplier were analyzed and compared to the revenues.

Results. Treatment costs for cinacalcet (60 mg/day/year) were 5828.40 € and 4485.20 € for paricalcitol (15 μg/week/year). Revenues for inpatient surgical treatment according to the German DRG system were 3755.38 €/case. Additionally, costs for postoperative ambulatory therapies were 545.05 € for the first year and 384.97 € for the following.

Conclusion. Due to linearly increases, expenses of medical treatment with cinacalcet for more than 9 months or paricalcitol for more than 12 months exceeded the costs of surgical therapy. The indication of these new medical therapies should be restricted to patients as an interim solution ahead of surgery or in patients considered unfit for surgery. (Surgery 2010;148:1091-9.)

SECONDARY HYPERPARATHYROIDISM (sHPT) is a common sequel of chronic kidney disease (CKD) developing in response to high phosphate, low calcium and low 1,25-dihydroxyvitamin D₃ (calcitriol) levels. High levels of parathyroid hormone (PTH) accelerate bone turnover, with efflux of calcium and phosphate leading to vascular calcifications and renal osteopathy.1 Until the beginning of this century, the medical treatment of sHPT comprised the application of calcitriol and calcium-based phosphate binders. A successful kidney transplantation is the only causal treatment available to correct the abnormalities in mineral metabolism.2 However, limited availability of kidney transplants or high comorbidities preventing transplantation led to a high percentage of patients requiring operative intervention with total parathyroidectomy (PTX) with autotransplantation or subtotal PTX, both worldwide accepted equivalent standard procedures in the surgical treatment of sHPT.3

The introduction of vitamin D analogs and calcimimetics in 2004 and 2005 was considered as a “breakthrough” in the medical treatment of sHPT.4 Vitamin D analogs such as paricalcitol (Zemplar®) inhibit PTH gene transcription and parathyroid hyperplasia and have the advantage of a reduced calcemic activity when compared to vitamin D. Several such analogs are now in use, and analogs with even greater selectivity than those currently available are in development.5 However, the role of vitamin D analogs and PTX needs to be re-evaluated in the calcimimetic era.6

Cinacalcet (Sensipar®/Mimpara®) is the first of the new class of calcimimetic drugs approved for the treatment of sHPT. Calcimimetics suppress the
secretion of PTH by sensitizing the parathyroid calcium receptor to extracellular calcium. Combined with higher doses of calcium-based oral phosphate binders, it is mostly well tolerated and already considered as an effective alternative to standard medical treatments such as vitamin D derivatives together with non-calcium-based oral phosphate binders. Clinical trials demonstrated cinacalcet to be effective in suppressing PTH secretion in uremic patients with severe sHPT in whom formerly PTX might have been considered. Therefore, calcimimetics were claimed to be an alternative to PTX. However, evidence for an impact on clinical events such as mortality, cardiovascular events or fractures is based on short-term post hoc analyses and most of the trials with cinacalcet are supported by the industry merchandising this drug. Whether the application of cinacalcet will translate in improved outcomes remains to be demonstrated and adequately powered prospective controlled randomized studies independently performed from industrial influence are needed. Reports about PTX rates before and after the introduction of either one of these new drugs are unavailable and the rate of patients requiring PTX after unsuccessful treatment with either calcimimetics or vitamin D analogs needs to be evaluated. At present, the rising costs of vitamin D analogs and cinacalcet are refunded without any restrictions in Germany, and consecutively decision-making between medical or surgical therapy often depends on personal interests and experiences of both patients and nephrologists.

To the best of our knowledge, no analysis is available comparing the costs of the surgical treatment and the costs of these new medical treatments with either cinacalcet or paricalcitol.

The aim of this study was to obtain objective information allowing a transparent estimation of costs associated with cinacalcet or paricalcitol medication as well as with surgical therapy to find out which therapy is more cost effective. Consequently, the results should facilitate the decision-making process in reference to resources, regulations, and developmental processes.

**MATERIALS AND METHODS**

Data of the present study refer to a retrospective analysis of a prospective database regarding the patients who underwent surgery and to a retrospective review of outpatient files of patients who received a medical therapy with either cinacalcet or paricalcitol in 2 dialysis centers.

The inpatient surgical sector taken for economic evaluation comprised all patients with advanced sHPT who underwent initial PTX between January 2003 and January 2006 at a tertiary referral surgical center (n = 91). The standard surgical procedure was a total PTX with a parathyroid autotransplantation into the forearm.

The costs of surgical therapy comprised inpatient costs, as well as costs for special postoperative ambulatory measures including blood examinations and calcium and calcitriol supplementation. The revenues were calculated on the basis of the German diagnosis related grouping (DRG) calculation system, where base-case values are multiplied with a relative weight. To find out if the inpatient surgical therapy can be performed cost-effectively, the real arising costs for the supplier (hospital) were analyzed and compared to the revenues. An activity-based costing approach based on clinical pathways, which allocated the individual and overhead costs to processes, was chosen for an appropriate real cost accounting. Therefore, primary, secondary, and tertiary processes were defined.

Primary processes comprised main activities including personal and material costs, which were directly related to the treatment. The nursing related activity was calculated summarizing the daily allocation of each patient with correlated working minutes. Nursing related activities comprised admission examinations, transport of patients (x-ray, electrocardiogram, operation theater), preoperative preparation of patients as well as documentation and other nursing activities on the ward. Nursing efforts in the operation theater were defined in a special “operation pathway” including the efforts of 1 anesthetic and 2 surgical nurses. The personnel costs of the nurses were calculated on the basis of the salaries and the working minutes at 0.50€ per minute. The physician related activity was calculated on the working minutes for every process per patient on the ward (interviews, examinations, ward rounds, documentations). In the operation theater, the efforts of 2 surgeons and 1 anesthetist were taken into consideration. The calculated minutes were multiplied with personnel costs on the basis of the mean salaries of 2 residents (1 surgeon and 1 anesthetist) and 1 consultant of 1.05€ per minute. Material costs were calculated considering wound dressing materials, surgical drapes, anesthetic materials, and drugs and disposable items like clips and sutures, as well as costs for sterilization of surgical instruments. The working minutes of physicians and nurses on the ward were extrapolated from estimates based on interviews to all nurses and physicians involved in the care of patients with...
sHPT. The working minutes in the operation theater were extrapolated as the mean of the precise data provided by both the surgical and anesthetic protocols of all 91 patients who underwent a PTX.

Secondary processes comprised personal and material costs provided by other departments of the hospital. The costs of medical functional services such as laboratory, radiology, pathology, nuclear medicine, and others were calculated according to a catalog listing the equivalence-numeral-calculations of the German Hospital Society (DKG-NT-table), where a point system of inpatient and outpatient services for hospitals is depicted. Every department is given a score which is calculated on the total costs for the department divided by the sum of all scores provided over a period of 1 year. Afterwards this score is multiplied with the points of the DKG-NT-table. The files of all patients who underwent surgery were screened for these services, and the costs for every service in each patient were calculated. The mean costs were used for the final calculation.

Tertiary processes were defined as activities of the hospital infrastructure without direct relation to the treatment (technical service, kitchen, cleaning service, energy costs). These estimates refer to the costs which arise for any patient admitted to the hospital per treatment day independently from the reason of admission. The sum of all overhead costs of 2006 was divided by the sum of all treatment days of 2006 and multiplied by the individual hospital stay of each of the 91 patients who underwent surgery. The mean costs were used for the final calculation.

These primary, secondary, and tertiary processes were summarized for every individual patient in order to optimally display the clinical pathways and then to calculate the real costs for the inpatient therapy.

Costs for reoperations due to postoperative complications or recurrent/persistent disease were added into the calculation. A reoperation rate of 5% was chosen as a result of a follow-up study not yet published concerning 479 patients who underwent surgery at our department between the years 1976 and 2003. This study revealed a rate of persistent sHPT of 0.6% and a rate of recurrent sHPT of 4.6% after a mean follow-up of 57.6 months.

Patients who underwent initial PTX for sHPT in the following years (2007–2009) were counted to achieve information about the trend in the numbers of PTX performed in the era after the initiation of vitamin D analogs and calcimimetics.

The ambulatory medical sector comprised all patients who were treated with cinacalcet or paricalcitol in 2 dialysis centers (n = 100) between January 2003 and January 2006. The costs of both medical therapies for the funding agencies were calculated depending on their dosage and on costs for laboratory measures. Considering a typical discount of 5% for funding agencies, the costs were correspondingly reduced. The dosages per patient were analyzed, leading to a mean dosage of 60 mg/day for cinacalcet and of 3 ml/week for paricalcitol. The costs were summarized per month over a time period of 2 years. Physical or other examinations which were necessary due to dialysis were not taken into consideration.

An analysis comparing the costs for surgical and the costs for medical therapies was then performed (cost-cost analysis).

RESULTS

Ninety-one patients with sHPT who underwent initial PTX between January 2003 and January 2006 were analyzed. Of these 91 patients, 29 had a failed treatment attempt with cinacalcet or paricalcitol prior to surgery. The number of patients who underwent initial parathyroid surgery for sHPT decreased from 37 in 2003 to 28 in 2004, 21 in 2005, and 5 in 2006. The number of initial PTX for sHPT increased thereafter with 12, 13, and 20 patients in the years 2007, 2008 and 2009, respectively (Fig 1). The mean duration of hospital stay of the patients considered for economic evaluation was 7.3 ± 4.31 days. One patient had to undergo a cervical revision for persistent sHPT due to a missed fifth gland within the carotid sheath. Within a follow-up period of 3 years after surgery, 2 patients
developed recurrent sHPT at the parathyroid autograft and had to undergo an autograft reduction. The ambulatory medical sector comprised 50 patients who were treated with cinacalcet and 50 patients who were treated with paricalcitol in 2 dialysis centers \((n = 100)\) between 01/2003 and 01/2006. An interview with the nephrologists in charge addressing the outcome of these 100 patients revealed a high lost to follow-up rate of 18%, another 13% underwent PTX after a mean medical treatment duration of 25.6 months with either cinacalcet or paricalcitol, 38% achieved a significant (>50%) reduction in PTH levels, and 31% patients exhibited minor or no response regarding PTH. The latter are considered unfit for surgery, refuse surgical intervention, or are already scheduled for PTX in the meantime.

The calculation of the mean annual inpatient revenues is shown in Table I. The mean revenues per case for the whole period, calculated from the mean annual revenues and the number of patients treated per year, were 3559.79€ ± 484.22€. Considering a reoperation rate of 5% due to postoperative complications or recurrent/persistent disease the revenues increased to 3755.38€ for Germany. Additional costs for postoperative ambulatory therapies were 545.05€ for the first and maximum 384.97€ for the following year. The sensitivity analyses considering the different base-case values estimated a “worst-case” revenue of 3589.77€ and a “best-case” revenue of 3983.96€.

Costs of primary processes arising from nursing related activities were 571.50€ per case assuming 663 working minutes per patient on the ward and 480 minutes per surgery in the operation theater. Time for physician related work was 243 minutes per patient on the ward and 541 minutes in the operation theater resulting in a total amount of 823.20€ per case (Fig 2). Material costs were 643.66€ per case. Costs of 1118.27€ ± 650.40€ per case were calculated for secondary processes and of 685.89€ ± 407.45€ per case for tertiary processes. The summation of the costs for primary, secondary and tertiary processes revealed 3842.52€ per case as the real arising costs for the inpatient surgical treatment.

The mean revenues from the agencies for our hospital were 3912.99€ per case, leading to a cost-covering situation with a mean benefit of 70.47€ per case over all years analyzed (Table II). Neither the costs of the operative treatment nor the costs of the medical therapy varied over the years.
analyzed. However, the revenues decreased over the years mainly attributed to a reduction of the base-case values. The cost-revenue relation per case for every year analyzed is depicted in Table II. However, the cost-revenue analysis per year observed revealed an increasing unprofitable relation between these measures, leading to resumed negotiations between the hospital, the funding agencies, and the nephrologists in charge to compile a treatment plan in the aim to regain a cost-covering situation.

The costs of the ambulatory medical therapies mainly depended on the dosages of the drugs. Cinacalcet (28 tablets/package) was offered with 30, 60, and 90 mg at 232.72€, 421.47€, and 627.39€, respectively. Paricalcitol was offered in packages containing 5 × 1-ml (5 μg/ml) at 130.47€ and 5 × 2 ml (5 μg/ml) at 251.29€. Monthly and yearly costs for cinacalcet and paricalcitol are displayed in Tables III and IV.

Cost-intensive inpatient hospital stay caused higher expenses for the surgical therapy within the first months. Due to linearly rising costs and lifelong application of the drugs the surgical expenses were exceeded by cinacalcet after 9 months and by paricalcitol after 12 months (Fig 3). The postoperative costs remained almost constant within the outpatient period. These costs were depended on the dosages of calcium and vitamin D supplementation and the numbers of laboratory measures needed to control calcium and PTH levels and are displayed in Tables V and VI. We additionally performed a sensitivity analysis considering different dosages of the drugs to differentiate between best and worst-case scenarios. In the worst case scenarios all patients were treated with the highest dosage of each drug (cinacalcet 180 mg, paricalcitol 3 × 2 ml). In contrast, the best case scenario was based on the lowest dosages of each drug (cinacalcet 30 mg, paricalcitol 1 × 1-ml). The costs of surgical therapy were exceeded by the costs for cinacalcet in the worst case scenario after 3 months (Fig 4, A) and for paricalcitol after 6 months (Fig 4, B). Based on the best case scenario surgical therapy has to be preferred from an economic point of view after 16 months (C) treatment with cinacalcet and after 31 months (D) treatment with paricalcitol.

**DISCUSSION**

According to the third National Health and Nutrition Examination Survey, CKD affected as many as 19 million adults in the U.S. in 2003, with 20 million more at risk. The economic burden associated with CKD was recently analyzed in an observational study of 13,796 predialytic patients, the determined costs to treat CKD related comorbidities were almost twice of those treating CKD alone ($14,000 vs $8,000) and the cumulative costs of CKD plus comorbidities were greater than their simple sum ($26,000 vs $22,000). However, these findings underscored the importance of an active treatment of underlying risk factors for comorbidities.

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**Fig 2.** Timeline of primary processes to physician and nurse related activities to estimate the real arising costs.

![Image](image-url)
Prior to the development of newer drugs such as vitamin D analogs and calcimimetics, medical treatment results of sHPT as the most important sequela of CKD remained inadequate. Less than 30% of all patients achieved 3 and only 5% of all patients all 4 Kidney Disease Outcomes and Initiative (KDOQI) target ranges (phosphate, calcium, PTH, calcium-phosphate product) leading to a high rate of PTX over time. The introduction of cinacalcet and vitamin D analogs into clinical practice opened a novel pathway in the treatment of patients with sHPT.12,13 Cinacalcet acts as an allosteric activator of the calcium-sensing receptor of parathyroid cells and therefore represents an appealing molecular target for therapeutic agents designed to control sHPT.14 Paricalcitol as a new analog of vitamin D suppresses synthesis and secretion of PTH as effectively as calcitriol but has a lower tendency to raise serum calcium and phosphorus.15,16 Several retrospective studies reported a significant reduction in the need to undergo PTX in patients receiving either cinacalcet or vitamin D analogs or both.17 Although we experienced a decreasing frequency of surgical interventions for sHPT in the years 2003–2006, the numbers of surgeries increased thereafter. The decreasing number of surgeries within the study period at our hospital can be explained by the introduction of cinacalcet and paricalcitol into the armamentarium of the medical treatment options in patients with sHPT and the increased usage of these new drugs during that time. Due to the first studies published, which reported excellent results for both cinacalcet and paricalcitol, and to an aggressive advertisement of the pharmaceutical industry merchandising these drugs, many nephrologists considered the new medical treatments as alternatives to the surgical treatment of sHPT. The clinical courses and results of laboratory measures in the following years demonstrated a treatment failure in some of the patients who received either cinacalcet or paricalcitol or both which consecutively led to an increased assignment of patients for surgery. Almost all of the patients who underwent surgery at our hospital within the last 3 years had undergone an attempt to treat sHPT with cinacalcet, vitamin D analogs, or both for several years (unpublished data), and therefore, had undergone an unnecessary and costly medical therapy. Thus, drug resistances to cinacalcet or vitamin D analogs are possible, already described in the literature and usually attributed to either nodular hyperplasia or patient incompliance.18

Table II. The cost-revenue relation per case for every year analyzed

<table>
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<tr>
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<tbody>
<tr>
<td>Mean revenue per case</td>
<td>3912.99</td>
<td>4258.75</td>
<td>3681.57</td>
<td>3451.81</td>
</tr>
<tr>
<td>Mean cost per case</td>
<td>3842.52</td>
<td>3842.52</td>
<td>3842.52</td>
<td>3842.52</td>
</tr>
<tr>
<td>Mean cost-revenue relation per case</td>
<td>70.47</td>
<td>416.23</td>
<td>–160.95</td>
<td>–390.71</td>
</tr>
</tbody>
</table>

All costs are in Euros.

Table III. Dosage dependent costs of medical treatment with cinacalcet

<table>
<thead>
<tr>
<th>Dose/day cinacalcet</th>
<th>30 mg</th>
<th>60 mg</th>
<th>90 mg</th>
<th>180 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical/month</td>
<td>240.17</td>
<td>434.96</td>
<td>647.46</td>
<td>1 294.93</td>
</tr>
<tr>
<td>Laboratory/month</td>
<td>50.70</td>
<td>50.70</td>
<td>50.70</td>
<td>50.70</td>
</tr>
<tr>
<td>Total therapy/month</td>
<td>290.87</td>
<td>485.66</td>
<td>698.16</td>
<td>1 345.63</td>
</tr>
<tr>
<td>Total therapy/year</td>
<td>3 490.44</td>
<td>5 827.92</td>
<td>8 377.92</td>
<td>16 147.56</td>
</tr>
</tbody>
</table>

All costs are in Euros.

Table IV. Dosage dependent costs of medical treatment with paricalcitol

<table>
<thead>
<tr>
<th>Dose/week paricalcitol (5 μg/ml)</th>
<th>1 × 1 ml</th>
<th>3 × 1 ml</th>
<th>3 × 2 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical/month</td>
<td>107.42</td>
<td>322.26</td>
<td>620.69</td>
</tr>
<tr>
<td>Laboratory/month</td>
<td>50.70</td>
<td>50.70</td>
<td>50.70</td>
</tr>
<tr>
<td>Total therapy/month</td>
<td>158.12</td>
<td>372.96</td>
<td>671.39</td>
</tr>
<tr>
<td>Total therapy/year</td>
<td>1 897.44</td>
<td>4 475.52</td>
<td>8 056.68</td>
</tr>
</tbody>
</table>

All costs are in Euros.
reported to have a higher risk for cinacalcet resistance. Thus, the severity of sHPT and the degree of nodular transformation potentially induce the development of resistance to the new drugs.

Very few reports exist about the proposed length of treatment and dosage titration for cinacalcet or paricalcitol to achieve KDOQI targets. These articles report successful reductions in PTH already after 3 months of treatment. Accordingly, the National Institute for Health and Clinical Excellence of the United Kingdom recommended a continuation of medication only in patients who achieved a reduction in PTH levels of 30% or more within 4 months of treatment, including dose escalation if appropriate.

Our study demonstrated that the costs for surgical therapy were exceeded by the linearly rising costs for medical therapy already after a 9-month treatment with cinacalcet and after a 12-month treatment with paricalcitol. Our findings are in accordance to those of Narayan et al who found the surgical intervention to be more cost effective after 8 months when compared to a treatment with cinacalcet. In addition, Narayan showed that PTX was more cost effective after 16 to 19 months even after calculating a combination of maximum possible surgical costs and minimum cinacalcet costs. To the best of our knowledge, this is the first study which provides a detailed cost-cost analysis together with an estimate of the real arising costs concerning the treatment options in patients with sHPT. Based on our results one has to suggest that medical therapy may be optimal in patients with an anticipated short time on dialysis therapy (<12 months) and mild sHPT. This group includes patients with a high expected mortality due to co-morbid illness or poor general health, patients who expect to undergo transplantation in less than 1 year, dialysis patients with living donors, and those who do decline operative therapy, respectively. However, it is not known whether control of PTH will be sustained after cessation of cinacalcet or paricalcitol. It is possible that underlying disease progression still occurs or that effectiveness may not be sustained over the long-term. Moreover, cinacalcet is not approved in patients after kidney transplantation and it needs to be elucidated how many of those requiring pretransplant cinacalcet will have to undergo PTX or necessitate ongoing costly off-label administered cinacalcet therapy thereafter.

Because our study referred to 2 different medical treatment arms, the group of patients observed was unfortunately too small and heterogeneous to gain reliable data about the treatment successes. To evaluate the outcome of these treatments, prospective randomized multicenter trials with a structured follow-up protocol have to be conducted. However, the wise use of medical resources is paramount to delivering cost-effective care and our study adds a helpful piece of information to enable the development of a reasonable duration and dosage recommendation for the medical therapies.
therapies. A combination of our results and the results of future prospective trials comparing the success of medical and surgical treatments will help to facilitate the ever pressing challenge to surgeons in choosing the right patient to undergo surgery, choosing the right surgical technique, and then making the operative treatment more successful, less complicated, and less expensive.

In conclusion, shPT is an important sequela of CKD. The treatment options of shPT have expanded substantially in the last years, with vitamin D analogs and calcimimetics being the most recent addition. From an economic point of view surgical therapy should be preferred whenever possible. Especially in patients with only little effect on improving mineral balance by cinacalcet or vitamin D analogs, a prolongation of medical therapy over the recommended length of 4 months seems to be unjustifiable and should not be remunerated by the funding agencies. Randomized studies are needed to predict which patients will most likely gain benefit from early parathyroid surgery in order to avoid unnecessary, prolonged, and costly medical therapy.

Fig 4. Sensitivity analysis considering different dosages of the drugs compared to costs for surgical therapy over time.

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Calcium</th>
<th>PTH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs/laboratory measure (€)</td>
<td>2.76</td>
<td>33.12</td>
<td>35.88</td>
</tr>
<tr>
<td>Number of laboratory measures in the 1st year postsurgery</td>
<td>78</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>Total costs for laboratory measures in the 1st year postsurgery (€)</td>
<td>215.28</td>
<td>66.24</td>
<td>281.52</td>
</tr>
<tr>
<td>Number of laboratory measures in the 2nd year postsurgery</td>
<td>20</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Total costs for laboratory measures in the 2nd year postsurgery (€)</td>
<td>55.20</td>
<td>66.24</td>
<td>121.44</td>
</tr>
</tbody>
</table>

REFERENCES

without autotransplantation and without thymectomy versus total parathyroidectomy with autotransplantation and with thymectomy for secondary hyperparathyroidism: TO-PAR PILOT-Trial. Trials 2007;8:22.