Clinical and Practical Use of Calcimimetics in Dialysis Patients With Secondary Hyperparathyroidism

Jordi Bover,* Pablo Ureña,** César Ruiz-García,** Iara daSilva,** Patricia Lescano,** Jacqueline del Carpio,** José Ballarín,** and Mario Cozzolino†

Abstract
CKD and CKD-related mineral and bone disorders (CKD-MBDs) are associated with high cardiovascular and mortality risks. In randomized clinical trials (RCTs), no single drug intervention has been shown to reduce the high mortality risk in dialysis patients, but several robust secondary analyses point toward important potential beneficial effects of controlling CKD-MBD–related factors and secondary hyperparathyroidism. The advent of cinacalcet, which has a unique mode of action at the calcium-sensing receptor, represented an important step forward in controlling CKD-MBD. In addition, new RCTs have conclusively shown that cinacalcet improves achievement of target levels for all of the metabolic abnormalities associated with CKD-MBD and may also attenuate the progression of vascular and valvular calcifications in dialysis patients. However, a final conclusion on the effect of cinacalcet on hard outcomes remains elusive. Tolerance of cinacalcet is limited by frequent secondary side effects such as nausea, vomiting, hypocalcemia and oversuppression of parathyroid hormone, which may cause some management difficulties, especially for those lacking experience with the drug. Against this background, this review aims to summarize the results of studies on cinacalcet, up to and including the publication of the recent ADVANCE and EVOLVE RCTs, as well as recent post hoc analyses, and to offer practical guidance on how to improve the clinical management of the most frequent adverse events associated with cinacalcet, based on both currently available information and personal experience. In addition, attention is drawn to less common secondary effects of cinacalcet treatment and advisable precautions.


Introduction
CKD is currently accepted as an independent cardiovascular (CV) and mortality risk factor (1). Multiple CKD-related derangements may account for the extremely high mortality observed in these patients (1) and, among these disturbances, CKD-related mineral and bone disorders (CKD-MBDs) seem to play an important role (1–3). Classic biochemical alterations of calcium (Ca), phosphate (P), Ca × P product, parathyroid hormone (PTH), and other bone-related biomarkers have been increasingly associated, although not uniformly, with prediction of bone disease and also with CV events and survival (2–5). On the other hand, it has been suggested that patients with CKD stages 3–5D, with known vascular or valvular calcifications, should be considered at the highest CV risk; therefore, it seems reasonable to use this information to guide the management of CKD-MBD (3,6–8). Nevertheless, the evidence from randomized clinical trials (RCTs) in dialysis patients is limited and contradictory results have been obtained on whether treatment of laboratory abnormalities or attenuation of the progression of calcifications actually affects mortality (3,9–14).

Drug interventions in RCTs aiming to correct anemia or dyslipidemia have not been proven to increase survival in this population, and controversial or only nominally significant secondary end points have been described with P binders such as sevelamer or lanthanum (9,15). A recent meta-analysis promoted debate on this issue, overriding the negative results of previous meta-analyses (15,16). Significant and robust but questionable associations with improved survival have been described with both vitamin D derivatives and calcimimetics in retrospective cohort studies in dialysis patients (17–21).

Against this background, this review aims to summarize the results of studies on cinacalcet in the context of the complex CKD-MBD up until the publication of the recent ADVANCE (A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low-Dose Vitamin D on Vascular Calcification in Subjects with CKD Receiving Haemodialysis) and EVOLVE (Evaluation of Cinacalcet Therapy to Lower CV Events) trials and to offer practical guidance on potential ways to improve the clinical management of most frequent secondary effects associated with cinacalcet, based on both the currently available information as well as our own personal experience.

CKD-MBDs
Although there may be debate over whether CKD-MBD is really a syndrome (22), CKD-MBD has been defined as a trinity of laboratory and bone abnormalities and vascular (or other soft tissue) calcification,
all of which are linked to hard outcomes such as fractures, CV morbidity, and mortality (3,23). This concept has been accepted by various national and international societies striving to improve outcomes (3,6,7).

Laboratory Abnormalities
In CKD, the failing kidneys disrupt the complex pathophysiologic regulation of Ca, P, vitamin D metabolism, fibroblast growth factor 23 (FGF23), and other as-yet-unidentified molecules, leading to secondary hyperparathyroidism (SHPT) (24). From the early CKD stages, FGF23 production is increased in response to several stimuli, including P retention and klotho reduction. The hyperphosphaturic effects of PTH and FGF23 are compromised by reduced PTH receptor and klotho expression, at least partially explaining the presence of resistance to PTH and FGF23 in CKD (24). Chronic overstimulation of PTH causes a progressive polyclonal parathyroid gland hyperplasia, which may later transform into a benign, tumor-like monoclonal growth (24).

Bone Abnormalities
The excessive production of PTH increases bone resorption and leads to classic osteitis fibrosa (25). However, in other situations, the initial increase in PTH and bone remodeling may be excessively slowed by a multitude of factors leading to low bone turnover or adynamic bone disease (ABD) (5). Both high and low bone turnover bone diseases are associated with a high risk of skeletal fractures and poor clinical outcomes (3,25).

Vascular Calcification
The increase in circulating Ca × P product, as well as the active transformation of vascular smooth muscle cells into osteoblast-like cells, favors the development of CV calcification, arterial stiffness, and CV diseases (3,8,22). Thus, the old well known relationship between kidney disease and bone (“renal osteodystrophy”) is now extended to a new bone–vascular axis (23,26), and bone has even been recently considered as a new endocrine organ at the heart of CKD-MBD (27).

Cinacalcet as a Treatment for SHPT
Traditional therapies for SHPT have entailed correction of hypocalcemia and excessive synthesis and secretion of PTH by administration of Ca salts and vitamin D derivatives, as well as prevention of hyperphosphatemia by means of Ca- or aluminum-containing P binders or, only recently, nonmetal-containing P binders (24). However, these therapies are limited by the occurrence of hyperphosphatemia and hypercalcemia, by a lack of specificity, and by limited long-term efficacy. On the other hand, surgical parathyroidectomy is not exempt from important, sometimes neglected, risks, as recently reported (5,28). Fortunately, with the advent of calcimimetics, enormous progress has been made in extending the armamentarium against SHPT, although we acknowledge that there is insufficient high-grade evidence on whether any treatment or a combination thereof should be preferred to control SHPT in dialysis patients (29,30).

Calcimimetic and Cinacalcet Generalities
Cloning of the calcium-sensing receptor (CaR) led to the discovery of several compounds capable of modulating its function in different organ tissues (31,32). Type I calcimimetics mimic the effects of extracellular calcium (Ca\(^{2+}\)) and type II calcimimetics act as allosteric activators of the CaR, changing its structural conformation and stereoselectively increasing sensitivity to Ca\(^{2+}\). Cinacalcet hydrochloride (AMG-073) belongs to the second generation and is the only approved calcimimetic. By increasing the sensitivity of the CaR to Ca\(^{2+}\), cinacalcet shifts the Ca-PTH concentration-response curves to the left and reduces the “set point” for Ca-regulated PTH secretion (31–33). Cinacalcet decreases the secretion of PTH in a dose-dependent manner and diminishes serum Ca concentration by mechanisms that are discussed below. Consequently, cinacalcet is currently indicated for the treatment of SHPT in dialysis patients and is shown to reduce hypercalcemia in patients with parathyroid carcinoma and in selected cases of primary hyperparathyroidism (34,35). AMG-416 is currently in development and represents a novel, third-generation intravenous long-acting selective peptide agonist of the CaR (36,37).

Cinacalcet Use in Patients with CKD Who Are Not on Dialysis
Cinacalcet is not indicated in patients with CKD who are not on dialysis. Investigational studies have shown that cinacalcet increases the risk for hypocalcemia, which may be attributable in part to lower baseline Ca levels, the presence of residual renal function, and the use of an inappropriate high dose of cinacalcet for often mild SHPT (34,35,38,39). In these patients, increased levels of P associated with decreased P urinary excretion have also been described (38,39). Preliminary studies have shown that cinacalcet has been successfully used to control hypercalcemia in patients with CKD and autonomous hyperparathyroidism (40,41).

In renal transplant patients, several reports and a recent RCT showed that cinacalcet effectively corrected the hypercalcemia and hypophosphatemia associated with persistent hyperparathyroidism (42,43), although no beneficial effect was observed in the percent change in bone mineral density (43).

Cinacalcet Use in Patients with CKD Treated by Dialysis
Phase 1 and phase 2 studies in dialysis patients with SHPT demonstrated the efficacy of cinacalcet in reducing circulating levels of laboratory abnormalities such as PTH, Ca, P, and the Ca × P product. The combined results of RCTs and phase 4 studies confirmed these results (11,13,21,44–58) (Table1), among other benefits, including a substantial reduction of the elevated bone formation rate/tissue area, generally improving bone disease (57,58). Importantly, two recent prospective RCTs evaluated both the efficacy of cinacalcet in preventing the progression of CV calcifications (ADVANCE) (11), and its effect on clinical outcomes, including all-cause mortality and CV events (EOLVE) (13).

First, the ADVANCE trial suggested that cinacalcet plus low doses of vitamin D may attenuate the progression of
Table 1. Cinacalcet in the treatment of SHPT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Name</th>
<th>Population</th>
<th>N</th>
<th>Design</th>
<th>Treatment</th>
<th>Follow-Up</th>
<th>Patients in Range, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarles et al., 2003 (44)</td>
<td>HD and SHPT (PTH ≥300 pg/ml, Ca 8.8–11.0 mg/dl, P =2.5 mg/dl; and Ca × P &lt; 70 mg²/dl)</td>
<td>36</td>
<td>2 arms double-blind, random</td>
<td>Cinacalcet + standard treatment versus placebo + standard treatment</td>
<td>12 + 6 wk</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Lindberg et al., 2003 (45)</td>
<td>HD and SHPT (PTH ≥300 pg/ml, Ca 8.8–11.0 mg/dl, P =2.5 mg/dl; and Ca × P &lt; 70 mg²/dl)</td>
<td>38</td>
<td>2 arms double-blind, random</td>
<td>Cinacalcet + standard treatment versus placebo + standard treatment</td>
<td>12 + 6 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block et al., 2004 (46)</td>
<td>HD and SHPT (PTH &gt;300 pg/ml)</td>
<td>371</td>
<td>2 arms double-blind, random</td>
<td>Cinacalcet + standard treatment versus placebo + standard treatment</td>
<td>12 + 14 wk</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Lindberg et al., 2005 (47)</td>
<td>Dialysis and SHPT (PTH &gt;300 pg/ml)</td>
<td>294</td>
<td>2 arms double-blind, random</td>
<td>Cinacalcet + standard treatment versus placebo + standard treatment</td>
<td>16 + 10 wk</td>
<td>65%</td>
<td></td>
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<tr>
<td>Moe et al., 2005 (48)</td>
<td>Dialysis and PTH ≥300 pg/ml, and Ca ≥8.4 mg/dl</td>
<td>547</td>
<td>2 arms double-blind, random</td>
<td>Cinacalcet + standard treatment versus placebo + standard treatment</td>
<td>12–16 + 10–14 wk</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Cunningham et al., 2005 (49)</td>
<td>HD and SHPT (PTH ≥300 pg/ml)</td>
<td>697</td>
<td>Combined analysis of safety data from 4 previous random, double-blind, placebo-controlled clinical trials</td>
<td>Cinacalcet + standard treatment versus placebo + standard treatment</td>
<td>6–12 mo</td>
<td></td>
<td></td>
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<tr>
<td>Chertow et al., 2006 (50)</td>
<td>CONTROL</td>
<td></td>
<td>53</td>
<td>1 open arm</td>
<td>Cinacalcet + vitamin D (low dose)</td>
<td>8 + 8 wk</td>
<td>72%</td>
</tr>
<tr>
<td>Block et al., 2008 (51)</td>
<td>TARGET</td>
<td>HD and moderate to severe SHPT (PTH 300–800 pg/ml)</td>
<td>375</td>
<td>1 arm, open</td>
<td>Cinacalcet + standard treatment</td>
<td>8 + 8 wk</td>
<td>83%</td>
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<tr>
<td>Reference</td>
<td>Study Name</td>
<td>Population</td>
<td>N</td>
<td>Design</td>
<td>Treatment</td>
<td>Follow-Up</td>
<td>Patients in Range, %</td>
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<tr>
<td>Mesa et al., 2008 (52)</td>
<td>OPTIMA</td>
<td>HD and SHPT (iPTH 300–800 pg/ml and Ca =8.4 mg/dl)</td>
<td>368</td>
<td>2 arms random</td>
<td>Cinacalcet + standard treatment versus standard treatment</td>
<td>16 + 7 wk</td>
<td>71, 76, 63, 77</td>
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<tr>
<td>Fishbane et al., 2008 (53)</td>
<td>ACHIEVE</td>
<td>HD treatment with vitamin D</td>
<td>87</td>
<td>2 open arms, random</td>
<td>Cinacalcet + standard treatment versus standard treatment</td>
<td>16 + 11 wk</td>
<td>44, 63, 47, 73</td>
</tr>
<tr>
<td>Arenas et al., 2007 (54)</td>
<td></td>
<td>HD and SHPT (PTH ≥300 pg/ml with Ca &gt;10.2 mg/dl and/or P &gt;5.5 mg/dl)</td>
<td>28</td>
<td>1 arm, open</td>
<td>Cinacalcet + vitamin D (low dose)</td>
<td>9 mo</td>
<td>70, 94, 88, 94</td>
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<tr>
<td>Ureña et al., 2009 (55)</td>
<td>ECHO</td>
<td>Dialysis and SHPT</td>
<td>1865</td>
<td>Retrospective + prospective, 1 open arm</td>
<td>Cinacalcet + standard treatment</td>
<td>12 mo</td>
<td>26, 51, 48, 68</td>
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<tr>
<td>Bover et al., 2011 (56)</td>
<td>REHISET</td>
<td>Dialysis and SHPT</td>
<td>428</td>
<td>1 arm, retrospective</td>
<td>Cinacalcet + standard treatment</td>
<td>72 wk</td>
<td>47, 50, 58</td>
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<tr>
<td>Block et al., 2010 (21)</td>
<td></td>
<td>HD and SHPT treated with vitamin D</td>
<td>5976</td>
<td>Observational, 2 arms</td>
<td>Cinacalcet + standard treatment versus standard treatment</td>
<td>26 mo</td>
<td></td>
</tr>
<tr>
<td>Raggi et al., 2011 (11)</td>
<td>ADVANCE</td>
<td>HD [PTH &gt;300 pg/ml or 150–300 pg/ml with Ca × P &gt;50 (mg/dl)²] and treatment with vitamin D</td>
<td>180</td>
<td>2 open arms random</td>
<td>Cinacalcet + vitamin D (low dose ≤6 μg/wk of IV paricalcitol equivalent) versus flexible vitamin D</td>
<td>20 + 32 wk</td>
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<tr>
<td>Chertow et al., 2012 (13)</td>
<td>EVOLVE</td>
<td>HD and moderate-severe SHPT</td>
<td>1948</td>
<td>2 arms double-blind, random</td>
<td>Cinacalcet + standard treatment versus placebo + standard treatment</td>
<td>64 mo</td>
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Table 1. (Continued)

<table>
<thead>
<tr>
<th>Patients in Range, %</th>
<th>PTH (≤300 pg/ml)</th>
<th>Ca × P</th>
<th>P</th>
<th>P</th>
<th>P</th>
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<tr>
<td></td>
<td>(8.5–9.5 mg/dl)</td>
<td>(≤5.5 mg/dl)</td>
<td>(≤5 mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaP 3</td>
<td>24%</td>
<td>120%</td>
<td>20%</td>
<td>120%</td>
<td>20%</td>
</tr>
<tr>
<td>P</td>
<td>20%</td>
<td>120%</td>
<td>20%</td>
<td>120%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>20%</td>
<td>120%</td>
<td>20%</td>
<td>120%</td>
<td>20%</td>
</tr>
</tbody>
</table>

**Reference Study Name**

- Malluche et al., 2008 (57), HD and SHPT (PTH 300 pg/ml)
- Cinacalcet 2008 (57), blind, random standard treatment versus placebo 1 standard treatment versus placebo 1 standard treatment 1 open arm Cinacalcet 12 mo 19% cinacalcet monotherapy
- Behets et al., 2015 (58), $BONAFIDE Dialysis and PTH pg/ml, BALP ng/ml, and Ca $8.4 mg/dl and high bone remodeling (biopsy). 12 mo 19% cinacalcet monotherapy versus any vitamin D analogs
- Wetmore et al., 2015 (29), PARADIGM HD and moderate SHPT (PTH $450 pg/ml); Ca 8.4–10.1 mg/dl analogs
- Wetter et al., 2016 (60), Agatston score or surface of coronary artery calcification 1 open arms, randomized 20% cinacalcet monotherapy versus any vitamin D analogs 12 mo 19% cinacalcet monotherapy versus any vitamin D analogs

**Follow-Up**

- 24 + 28 wk
- 20 + 30 + 12 wk
- 12 mo

**Design**

- 2 arms double-blind, random
- 1 open arm
- 2 open arms, randomized

**N**

- 19
- 77
- 312

**Population**

- HD and SHPT (PTH >300 pg/ml)
- Dialysis and PTH ≥300 pg/ml, BALP ≥20.9 ng/ml, and Ca ≥8 mg/dl, bone remodeling
- HD and PTH >60 mg/dl; Ca 8.4–10.1 mg/dl

**Study Name**

- RENAIDE
- PARADIGM
- Wetter et al., 2016 (60)

Several important factors could have seriously hindered the interpretation of the primary end point of the EVOLVE study (63,64), especially the excessive rate of drop-ins (19.8% of patients [annual rate 7.4%] randomized to standard of care plus placebo finally received commercially available cinacalcet but were analyzed as having received placebo throughout the study according to the ITT principle) and drop-outs (62% of patients [annual rate 27.3%]). These problems render the EVOLVE study an inconclusive
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Reduction PTH ≥30%, %</th>
<th>Change % Mean or Median with Respect to Basal</th>
<th>Other Results</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>PTH</td>
<td>Ca</td>
</tr>
<tr>
<td>Quarles et al., 2003 (44)</td>
<td>53</td>
<td>−32</td>
<td>−5</td>
</tr>
<tr>
<td>Lindberg et al., 2003 (45)</td>
<td>38</td>
<td>−26</td>
<td>−5</td>
</tr>
<tr>
<td>Block et al., 2004 (46)</td>
<td>64</td>
<td>−43</td>
<td>−7</td>
</tr>
<tr>
<td>Lindberg et al., 2005 (47)</td>
<td>65</td>
<td>−40</td>
<td>−6</td>
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<tr>
<td>Moe et al., 2005 (48)</td>
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<tr>
<td>Chertow et al., 2006 (50)</td>
<td></td>
<td>−2</td>
<td>−10</td>
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<tr>
<td>Block et al., 2008 (51)</td>
<td></td>
<td>−35</td>
<td>−11</td>
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<tr>
<td>Messa et al., 2008 (52)</td>
<td></td>
<td>−46</td>
<td>−7</td>
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<tr>
<td>Fishbain et al., 2008 (53)</td>
<td>68</td>
<td>−47</td>
<td>−7</td>
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<tr>
<td>Arenas et al., 2007 (54)</td>
<td>70d</td>
<td>−13d</td>
<td>−13d</td>
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<td>Uneria et al., 2009 (55)</td>
<td>66</td>
<td>−50</td>
<td>−6</td>
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<tr>
<td>Bover et al., 2011 (56)</td>
<td>73</td>
<td>−62</td>
<td>−3</td>
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<td>Block et al., 2010 (21)</td>
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<tr>
<td>Raggi et al., 2011 (11)</td>
<td></td>
<td>−32</td>
<td>−5</td>
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<tr>
<td>Chertow et al., 2012 (13)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Malluche et al., 2008 (57)</td>
<td></td>
<td>−50</td>
<td>−7</td>
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<tr>
<td>Behets et al., 2015 (58)</td>
<td>42.6</td>
<td>−48</td>
<td>−7</td>
</tr>
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</table>

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Table 1. (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Other Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wetmore et al., 2015 (29)</td>
<td>43 cinacalcet and 0.9 vitamin D, 20.7 vitamin D and 0.2 vitamin D, and 0.2 vitamin D, vitamin D analog monotherapy. Effects varied by region. Hypocalcemia was more common in the cinacalcet arm. Hypercalcemia and hyperphosphatemia occurred more often in the vitamin D analog arm.</td>
</tr>
</tbody>
</table>

**Note:**
- **Ca**: Calcium
- **P**: Phosphate
- **iPTH**: Intact parathyroid hormone
- **SHPT**: Secondary hyperparathyroidism
- **CONTROL**: Cinacalcet hydrochloride in hemodialysis patients on active vitamin D derivatives with controlled PTH and elevated calcium and phosphate
- **TARGET**: Combined therapy with cinacalcet and low doses of vitamin D sterols in patients with moderate to severe secondary hyperparathyroidism
- **OPTIMA**: Open-label, randomized study using cinacalcet to improve achievement of KDOQI targets in patients with ESRD
- **ACHIEVE**: Cinacalcet HCl and concurrent low-dose vitamin D improves treatment of secondary hyperparathyroidism in dialysis patients compared with vitamin D alone
- **ECHO**: Evaluation of the clinical use of mimpara in hemodialysis and peritoneal dialysis patients, an observational study
- **REHISET**: Spanish Registry of Secondary Hyperparathyroidism and its Treatment with Cinacalcet
- **ADVANCE**: A randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients with ESRD
- **BONAFIDE**: Bone biopsy study for dialysis patients with secondary hyperparathyroidism in ESRD
- **PARADIGM**: A randomized trial of cinacalcet versus vitamin D analogs as monotherapy in secondary hyperparathyroidism
- **HD**: Hemodialysis
- **PTH**: Parathyroid hormone
- **Ca**: Calcium
- **P**: Phosphate
- **iPTH**: Intact parathyroid hormone
- **Bnpc**: Bone-specific alkaline phosphatase
- **IV**: Intravenous
- **PD**: Peritoneal dialysis
- **RR**: Relative risk
- **CI**: Confidence interval
- **CV**: Cardiovascular
- **HRQoL**: Health-related quality of life
- **SF-36**: Short Form 36
- **CAC**: Coronary artery calcification
- **MI**: Myocardial infarction
- **PVD**: Peripheral vascular disease
- **RR**: Relative risk
- **CI**: Confidence interval
- **HRQoL**: Health-related quality of life
- **SF-36**: Short Form 36
- **CAC**: Coronary artery calcification
- **MI**: Myocardial infarction
- **PVD**: Peripheral vascular disease

Although a final conclusion on the effect of cinacalcet on hard relevant outcomes remains elusive (30,71), the use of cinacalcet may be fully justified at least as a component of a multifaceted intervention in dialysis patients with SHPT, including P binders and vitamin D (71). Furthermore, in experimental conditions, the possibility of a crossed positive, bidirectional and additive interaction between calcimimetics and vitamin D derivatives has been described (72,73). Such an interaction is probably mediated by the heterologous upregulation of the parathyroid vitamin D and Ca receptors (72,73). An ITT analysis is mandatory to establish the universal applicability of results observed in the studied population; however, from the perspective of the individual patient, it may be much more important to know whether cinacalcet can be taken without side effects and whether the benefits that it offers in terms of increased survival and other important clinical outcomes justify the associated risks (64). Therefore, practical guidance regarding potential improvements in management of the most frequent secondary effects is definitely needed.
Practical Management of Side Effects of Cinacalcet
Nausea and Vomiting

Gastrointestinal adverse events (mostly nausea and vomiting but also diarrhea, among others) are the secondary effects most frequently associated with cinacalcet. The vast majority of episodes of nausea and vomiting are mild to moderate in severity and transient in nature (34,35,46,47,74). Although such episodes are not usually a cause of treatment withdrawal and a dose reduction often proves sufficient, it is also the case that discontinuation of therapy as a result of undesirable effects is mainly attributable to nausea (1% placebo; 5% cinacalcet) and vomiting (<1% placebo; 4% cinacalcet). These gastrointestinal adverse events add to the common digestive secondary effects of other agents given for the control of CKD-MBD, such as P binders (3,9). In the Summary of Product Characteristics (SmPC) (34), the reported incidence of nausea is 31% in cinacalcet-treated patients versus 19% in placebo-treated patients, and the comparable rates for vomiting are 27% versus 15%, respectively (34).

The mechanisms by which cinacalcet induces nausea and vomiting are still not well identified. It has been suggested that cinacalcet may stimulate the CaR present in the hypothalamus and other brain regions controlling vomiting (75). It also seems that nausea and vomiting may be a consequence of a direct effect of cinacalcet on the gastrointestinal CaR; however, gastrointestinal and pancreatic enzymes do not appear to be uniformly modified by cinacalcet (76,77).

It cannot be forgotten that the availability of cinacalcet increases by approximately 50%–80% with food; consequently, it is recommended that cinacalcet be administered with food or shortly after a meal (34,35,74). With a view to reducing nausea and vomiting (74), in the study to investigate cinacalcet treatment in hemodialysis patients with secondary hyperparathyroidism (SENSOR) study, we investigated the effect of administration of cinacalcet with the first main meal after dialysis and found that this improved its efficacy and tolerance. In our study, the rate of treatment discontinuation due to nausea and vomiting was low (2.5% of patients overall), and only a 1% withdrawal rate was reported in the postdialysis meal group. For unclear reasons, the incidence of gastrointestinal adverse events in the SENSOR study also appeared to be lower when cinacalcet was administered in the evening; this was possibly related to distinct geographic dietary habits, chronobiology, or a potential timing effect rather than a food effect (74).

Although nausea and vomiting may appear after an initial 30-mg single dose, there is a clear dose dependence in the frequency of these symptoms. The mean dose in the SENSOR study was 67 mg/d in the postdialysis meal group, which is lower than the doses in phase 3 trials although patients had more severe disease (mean PTH 840±766 pg/ml). In the EVOLVE study, the median daily dose was 55 mg for a median PTH of 695 pg/ml for the same targets. It is necessary to remember that 180 mg/d is the maximum dose recommended in the SmPC (34,35). Taken together, these findings suggest that an earlier intervention with cinacalcet may allow lower doses and decrease the potential for secondary effects.

If only mild/moderate nausea and vomiting are present, cinacalcet should not be immediately withdrawn because symptoms may diminish with time. Obviously, when symptoms appear after increasing previous doses, a similar approach can be utilized and, if symptoms do not abate, reduction to the previous tolerated dose is often sufficient. Rapid escalations of cinacalcet doses should also be avoided, and intermediate doses (e.g., 15 mg/d, 30–60 mg/60–90 mg every other day) have also been successfully used for clinical control in both primary hyperparathyroidism and SHPT (33,40), although this practice is not specified in the SmPC (34,35). It is often forgotten that in primary hyperparathyroidism, cinacalcet is indicated twice a day (34,35,41).

Antiemetic drugs, mainly metoclopramide, have long been used but many antiemetic gastroprokinetic drugs, including domperidone, cisapride, or ondansetron can affect the electrocardiographic QT interval (http://www.QTdrugs.org or http://www.sads.org.uk/drugs_to_avoid.htm). In November 2014, metoclopramide was added to the combined list of drugs that can affect the QT interval. Although cinacalcet is not on this list, hypocalcemia can prolong the QT interval (see below).

A summary of the measures that may be taken to control nausea and vomiting is presented in Table 2.

Hypocalcemia

As a consequence of its unique mode of action, cinacalcet may cause hypocalcemia instead of the hypercalcemia associated with vitamin D derivatives (3,17,24,29,68). The decreases in serum Ca levels mainly occur during the first 2 weeks of treatment and are significantly greater among patients with relatively higher baseline or pretreatment PTH values. By contrast, demographic factors do not materially influence the Ca-lowering effect of cinacalcet. The use of concurrent therapies such as Ca-containing medications, vitamin D sterols, and dialysate Ca content may modify the effect of cinacalcet in decreasing serum Ca levels (78).

The mechanism responsible for these reductions in serum Ca levels is not fully understood, but alterations

<table>
<thead>
<tr>
<th>Measure</th>
<th>Hypocalcemia</th>
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<tbody>
<tr>
<td>Tell the patient that cinacalcet is not an ulcer-inducing drug and explain the importance of the CKD-MBD treatment, including a potential beneficial cardiovascular effect</td>
<td>Give cinacalcet with the main meal after dialysis</td>
</tr>
<tr>
<td>Try cinacalcet in the evening</td>
<td>Earlier use will allow lower doses</td>
</tr>
<tr>
<td>Do not give up immediately if only mild/moderate symptoms are present</td>
<td>Decrease or fractionate the dose if symptoms appear after a dose escalation</td>
</tr>
<tr>
<td>Caution is advised with antiemetics, including metoclopramide (QT prolongation)</td>
<td>CKD-MBD, CKD-related mineral and bone disorder.</td>
</tr>
</tbody>
</table>
in the exchange of Ca between the extracellular fluid and a miscible pool of Ca in bone are probably responsible (31,79), especially in the absence of substantial residual kidney function. Ca levels will thus be affected significantly when plasma PTH levels are lowered abruptly by enhanced activation of the CaR and the secondary decrease of bone turnover by cinacalcet (58). Two other potential mechanisms may favor calcimimetic-induced hypocalcemia: (1) stimulation of the CaR in the thyroid C cells and the secretion of calcitonin and (2) inhibition of the intestinal Ca transporter protein TRPV6 (80,81).

Consequently, when using cinacalcet, it is recommended to pay attention to the rare appearance of symptomatic hypocalcemia (including paresthesias, numbness, tingling, myalgias, or cramping) and to monitor serum Ca levels frequently, especially soon after the initiation of treatment and whenever a dose increase is prescribed. According to the SmPC, serum Ca levels should be monitored within 1 week after initiation or dose adjustment of cinacalcet (34,35). Once the maintenance dose has been established, serum Ca is usually measured monthly. Initiation of cinacalcet is contraindicated when the corrected serum Ca is below the lower limit of the normal range (usually 8.4 mg/dl). However, during the maintenance phase, lower levels do not necessarily imply a need for modification of the cinacalcet dose. In fact, hypocalcemia, defined as a corrected Ca <8.4 mg/dl at two consecutive determinations, has been reported in up to 45% of patients, but it was almost always asymptomatic and caused treatment withdrawal in <1% of patients (51,74). In patients with CKD who were receiving dialysis and were administered cinacalcet, 4% of serum Ca values were undesirably lower than 7.5 mg/dl (34). Approximately 30% of patients have at least one serum Ca value <7.5 mg/dl (35). In patients with CKD receiving dialysis who were administered cinacalcet, 29% of those in the 6-month registration trials and 21% and 33% of those (within the first 6 months and overall, respectively) in the EVOLVE clinical trial had at least one serum Ca value <7.5 mg/dl (13). A continuous risk analysis showed a 10% increase in HR for mortality for a noncorrected serum Ca as low as <6.37 mg/dl but also for serum Ca >9.66 mg/dl (82).

Manifestations of severe hypocalcemia may include muscle spasms, tetany, and seizures. These life-threatening events and fatal outcomes have been reported in adult and pediatric patients treated with cinacalcet, and this information is currently included in the new package insert (35). Cinacalcet is not indicated for use in children and adolescents, because of a lack of data on safety and efficacy. A fatal outcome was reported in a pediatric clinical trial patient with severe hypocalcemia, and caution is advised in patients with other risk factors for QT prolongation (see below) (35). Other uncommon drug interactions (mostly with infrequently used drugs) should also be taken into account when using cinacalcet (Table 3).

It should be noted that although symptomatic hypocalcemia is extremely rare, caution is recommended to avoid severe hypocalcemia (i.e., <7.5 mg/dl); in those at risk, the administration of cinacalcet should therefore be withheld until serum Ca levels reach 8 mg/dl. Despite their inclusion in the SmPC (Table 4) (35), we do not recommend the use of “prophylactic” Ca-based P binders or an increment in the Ca content in the dialysate because these options are untested and in fact may be harmful, given that undesirable Ca deposition cannot be excluded.

**PTH Oversuppression**

It is important to consider that in order to properly evaluate PTH levels, PTH should be measured at least 12 hours after dosing with cinacalcet because a rapid nadir for PTH concentration occurs approximately 3 hours after dosing (34,35,83). PTH should be measured 1–4 weeks after initiation or dose adjustment of cinacalcet and every 1–3 months during maintenance (34,35). Treatment with cinacalcet apparently does not alter the relationship between intact and bioactive PTH (34,35), although this issue may need to be revisited in light of the recent description of a lower ratio of whole/intact PTH in cinacalcet users versus nonusers with comparable levels of serum Ca (84).

Studies have found that approximately 19% of patients may show levels of intact PTH below the classic 150 pg/ml target (53,85), and cases of ABD have been confirmed after cinacalcet treatment and chronic low PTH levels (57,58). Low as well as high PTH levels have been associated with decreased survival in dialysis patients; consequently, both “extremes of risk” should be avoided. Thus, current KDIGO guidelines recommend maintaining intact PTH levels at 2–9 times the upper limit of normality for a particular PTH assay, although any tendency within these limits should also be taken into account (3). It must be emphasized that a significant proportion of patients with such intermediate PTH levels present quite different rates of bone remodeling, ranging from adynamic to normal to high turnover bone disease (25). Therefore, the clinical use of PTH (PTH monitoring and goals) is controversial (86,87). Nevertheless, because maintenance of appropriate PTH levels remains one of the main goals in contemporary nephrology practice, it probably should be monitored not only on a regular basis but also more frequently, at least until more specific new biomarkers and/or drugs with different targets demonstrate clinical superiority over current standard nephrology protocols (4,30).

It is also important to emphasize that classic US KDOQI limits between 150 and 300 pg/ml have been associated

<table>
<thead>
<tr>
<th>Table 3. Drug interactions</th>
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<tr>
<td><strong>Drugs and Interactions</strong></td>
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<tr>
<td><strong>Drugs that increase cinacalcet levels</strong></td>
</tr>
<tr>
<td>Ketoconazole, itraconazole, voriconazole, telithromycin, ritonavir</td>
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<tr>
<td><strong>Drugs which decrease cinacalcet levels</strong></td>
</tr>
<tr>
<td>Rifampicin</td>
</tr>
<tr>
<td><strong>Potential interactions</strong></td>
</tr>
<tr>
<td>Stopping or starting cigarette smoking, fluvoxamine, ciprofloxacin QT interval-affecting drugs (<a href="http://www.QTdrugs.org">http://www.QTdrugs.org</a>; <a href="http://www.sads.org.uk/drugs_to_avoid.htm">http://www.sads.org.uk/drugs_to_avoid.htm</a>) in high-risk patients</td>
</tr>
<tr>
<td><strong>Dose adjustment required (due to inhibition of cytochrome P450 by cinacalcet)</strong> for Flecaainide, propafenone, metoprolol, amitriptyline, desipramine, nortriptyline, clomipramine</td>
</tr>
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with improved survival in at least two different populations (88,89). Therefore, some authors and guidelines continue to recommend these “old” targets, or even lower ones (90), although a correction of PTH values for the kit utilized is currently advised in order to take into account the great variability in PTH assays (90), although a correction of PTH values for the kit utilized is currently advised in order to take into account the great variability in PTH assays (i.e., approximately 2–5 times the upper limit of normality for a particular PTH assay) (6,7,91–93). Consequently, the KDIGO target range for serum PTH in dialysis patients may be considered too broad, and a narrower range is still preferred by some (6,7,92,93). Recent changes in therapeutic approaches leading to increasing PTH levels have been documented in a recent analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS), where it was also shown that compared with PTH of 150–300 pg/ml, in adjusted models, all-cause mortality risk was higher for PTH of 301–450 pg/ml (HR, 1.09; 95% CI, 1.01 to 1.18) and >600 pg/ml (HR, 1.23; CI, 1.12 to 1.34) (94). In any case, general agreement seems to exist that oversuppression of PTH levels to below 2 times the upper limit of normality should be avoided, owing to the fear of inducing ABD and its potential detrimental consequences (5). Very low PTH (<50 pg/ml) was also associated with mortality in the recent DOPPS publication (94).

When PTH decreases below target levels, it is generally suggested that Ca-based P binders should be avoided and the doses of vitamin D and/or calcimimetics should be reduced (3,5–7). Treatment-induced low PTH is reversible and does not seem to represent an acute problem. The dose of Ca-based P binders can be decreased or substituted with non-Ca-based P binders in other to maintain control of serum P levels (5). The preferential adjustment of vitamin D doses should be considered when low PTH levels are associated with hypercalcemia and/or increased serum P. Some authors also prefer this approach if there is evidence of vascular/valvular calcification, in accordance with the results of the ADVANCE study (8,11). In fact, in the presence of low PTH levels or if active forms of vitamin D are withdrawn for any reason, supplementation with native vitamin D to correct vitamin D deficiency may be considered (5–7,17).

On the other hand, we consider reducing cinacalcet only if both Ca and PTH levels are low (see the section on hypocalcemia), and we do not abruptly discontinue cinacalcet unless symptomatic or significant hypocalcemia develops. Once PTH increases above the desired target, restarting cinacalcet at the next lowest dose is the usual approach, taking into account the other components of CKD-MBD (3).

Finally, it is also important to emphasize that cinacalcet therapy should not be discontinued when PTH target levels are reached (in the fear that a continuously decreasing PTH could lead to low PTH) because PTH levels will rebound after treatment withdrawal. There are obvious parallels with other conditions such as dyslipidemia, hypertension, and anemia, in which there would be no question that abrupt cessation of treatment when targets have been reached would be inappropriate. However, some fine adjustment may ultimately be required, and it has been suggested that cinacalcet doses may be decreased after long-term treatment in some circumstances perhaps due to regression of the parathyroid hyperplasia and/or apoptosis induction (95,96).

### QT Prolongation

Cinacalcet is not on the combined list of all drugs that can affect the electrocardiographic QT interval or the list of drugs to be avoided by patients with congenital long QT syndrome. Decreases in serum Ca concentration can prolong the QT interval, potentially resulting in ventricular arrhythmia, several cases of which have been reported in patients treated with cinacalcet during the postmarketing period (35); this information has been included in the most recent SmPC, although frequencies cannot be estimated from available data (34). Thus, although a QT evaluation is not mandatory, QT evaluation is advised in high-risk patients (e.g., those with a familial history, bradycardia, recent cardiac ablation, hypokalemia, hypomagnesemia, etc.).

### Other Undesirable Side Effects

Cinacalcet has also been associated with decreasing levels of P in dialysis patients, although this is not a uniform finding and is probably linked to the severity of SHPT (55,56,77,97). In a recent study, the P-lowering potential of cinacalcet was secondarily evaluated using data from a pan-European study (55,97). PTH was a key

<table>
<thead>
<tr>
<th>Serum Ca Value or Clinical Symptoms of Hypocalcemia</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>&lt;8.4 mg/dl (2.1 mmol/L) and &gt;7.5 mg/dl (1.9 mmol/L), or persistent symptoms of hypocalcemia despite attempts to increase serum Ca</td>
<td>Ca-containing P binders, vitamin D sterols, and/or adjustment of dialysis fluid Ca concentrations can be used to raise serum Ca according to clinical judgment</td>
</tr>
<tr>
<td>&lt;8.4 mg/dl (2.1 mmol/L) and &gt;7.5 mg/dl (1.9 mmol/L), or in the presence of clinical symptoms of hypocalcemia</td>
<td>Reduce or withhold the dose of cinacalcet</td>
</tr>
<tr>
<td>≤7.5 mg/dl (1.9 mmol/L) or persistent symptoms of hypocalcemia and vitamin D cannot be increased</td>
<td>Withhold administration of cinacalcet until serum Ca levels reach 8 mg/dl (2.0 mmol/L) and/or symptoms of hypocalcemia have resolved. Treatment should be reinitiated using the next lowest dose of cinacalcet</td>
</tr>
</tbody>
</table>

Ca, calcium; P, phosphate.

Table 4. Management of hypocalcemia according to the 2013 Summary of Product Characteristics
predictor of serum P reduction and regression analysis confirmed a significant 3% overall decrease in serum P for every 10% reduction in PTH. The authors concluded that serum P reduction appeared to result mainly from PTH reduction, rather than from changes in vitamin D or P binders (97). This subgroup probably represents those patients with the highest bone-derived P load. Decreasing levels of FGF23 have also been described with cinacalcet and AMG-416 (36,98). This possible mechanism for a beneficial effect of cinacalcet on vascular calcification and CV outcomes awaits further investigation, as well as other off-target effects of cinacalcet that cannot be just neglected (74).

Other common undesirable reported effects of cinacalcet include asthenia, anorexia, dizziness, headache, dyspepsia, constipation, diarrhea, abdominal pain, upper respiratory infection, dyspnea, cough, and hyperkalemia. Although most of these effects could not be directly attributable to cinacalcet treatment, the contribution of cinacalcet could not be excluded based on best-evidence assessment of causality (35).

Seizures (convulsions) were found to occur in 1.4% of cinacalcet-treated patients versus 0.7% of placebo-treated patients (35). Although the basis for the reported difference in seizure rate is not clear, it is known that the threshold for seizures is lowered by significant reductions in serum Ca. In the EVOLVE study a nonsignificant trend toward an increase in the crude incidence of seizures was observed in the cinacalcet-treated group (2.5% versus 1.6%) (13). In any case, cinacalcet must be used with caution in patients with seizures, and hypocalcemia should be avoided in these cases. Other nervous system disorders such as tingling, numbness, and paresthesias, which are frequent in dialysis patients, were observed to be significantly higher in the cinacalcet-treated group in the EVOLVE study (36.7% versus 30.5%; P<0.01) (13).

Testosterone levels are often below the normal range in patients with ESRD. In a clinical study, free testosterone levels decreased in cinacalcet-treated patients (34,35), but the clinical significance is unknown.

Clinical trial data showed that hypotension occurred in 7% of cinacalcet-treated patients versus 12% of placebo-treated patients, and heart failure occurred in 2% of patients receiving cinacalcet or placebo (35). In postmarketing safety surveillance, isolated, idiosyncratic cases of hypotension and/or worsening heart failure have been reported in patients with impaired cardiac function, but a causal relationship with cinacalcet could not be established. On the other hand, the HR of heart failure in the EVOLVE study was nominally significantly lower in the cinacalcet-treated group (0.72; 95% CI, 0.58 to 0.89; P=0.003) (13).

In the postmarketing experience, allergic reactions including rash, urticaria, angioedema, and leukocytoclastic vasculitis have been described (34,35). Cinacalcet should be used with caution in patients with moderate to severe hepatic impairment, because of the potential for 2- to 4-fold higher plasma levels of cinacalcet. No change in starting dose is necessary. Finally, patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take cinacalcet, in accordance with the SmPC (35).

In summary, CKD-MBD is associated with a high risk of mortality. No single drug intervention has been shown to decrease this risk and improve survival in dialysis patients in any RCT, but several robust secondary analyses point toward potential important beneficial effects of controlling SHPT with cinacalcet in addition to standard therapy, whenever it is tolerated. An improvement in the management of common cinacalcet-related secondary effects such as nausea and vomiting, hypocalcemia, and PTH over-suppression is absolutely plausible, while new drugs and studies on hard outcomes become available.

Acknowledgments


Disclosures

J.B. has received speaking honoraria from AbbVie, Amgen, Genzyme, and Shire; fees as a consultant for AbbVie, Amgen, Vifor, and Genzyme/Sanoﬁ; and a research grant from AbbVie. P.U. reports personal fees and grants from Amgen, AbbVie, Genzyme-Sanoﬁ, Hemotech, and Fresenius. M.C. reports lecture honoraria from AbbVie, Shire, Amgen Genzyme, and Roche and research grants from AbbVie and Shire.

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