Incidence, predictors and therapeutic consequences of hypocalcemia in patients treated with cinacalcet in the EVOLVE trial

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The calcimimetic cinacalcet is used to treat secondary hyperparathyroidism in patients receiving dialysis, and asymptomatic hypocalcemia is often observed following its initiation. Here we investigated the incidence, predictors and therapeutic consequences of hypocalcemia by a post hoc analysis of the randomized, double-blind, placebo-controlled EValuation Of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events (EVOLVE) trial. Hypocalcemia was classified as mild (total serum calcium 8.0–8.39 mg/dL), moderate (7.5–7.99 mg/dL) or severe (under 7.5 mg/dL). At least one episode of hypocalcemia developed within 16 weeks after the first administered dose among 58.3% of 1938 patients randomized to cinacalcet versus 14.9% of 1923 patients randomized to placebo. Hypocalcemia in the cinacalcet group was severe in 18.4% of the patients versus 4.4% in the placebo group. Severe hypocalcemia following administration of cinacalcet was associated with higher baseline plasma parathyroid hormone, lower corrected total serum calcium, higher serum alkaline phosphatase, geographic region (patients from Latin America and Russia had a higher risk relative to the United States) and higher body mass index. The median cinacalcet dose immediately prior to the first hypocalcemic episode was 54-58 mg/day and similar in the three hypocalcemia categories. In the majority of patients, hypocalcemia resolved spontaneously within 14 days without modification of background therapy. Among patients who received an intervention, the most common was an increase in the active vitamin D sterol dose. Thus, the occurrence of hypocalcemia is frequent following initiation of cinacalcet and the likelihood of developing hypocalcemia was related to the severity of secondary hyperparathyroidism. Hypocalcemia was generally asymptomatic and self-limited.

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Cinacalcet is an allosteric activator of the calcium-sensing receptor and via this mechanism lowers parathyroid hormone (PTH) release from the parathyroid glands. Treatment with cinacalcet commonly results in a reduction in serum calcium, often accompanied by a reduction in serum phosphate—findings documented in numerous clinical trials and observational studies.[1–6] Qualitatively, these reductions resemble the so-called hungry bone syndrome,[7] frequently observed after parathyroidectomy in patients receiving dialysis with severe secondary hyperparathyroidism (sHPT). With hungry bone syndrome, the precipitous drop in serum PTH after surgery reflects the avid incorporation of calcium and phosphate by the bone, which allows it to remineralize. However, whereas hypocalcemia in hungry bone syndrome is typically pronounced and requires immediate attention and therapy, cinacalcet-induced hypocalcemia usually develops less rapidly and is less pronounced.[1–5]

Cinacalcet-induced hypocalcemia is rarely associated with clinical symptoms in clinical practice.[1–5] It is noteworthy that the revised 2017 Kidney Diseases Improving Global Outcomes (KDIGO) clinical practice guideline no longer advises maintaining serum calcium concentrations within the population reference range in patients receiving dialysis; rather, it recommends avoiding hypercalcemia and considers mild hypocalcemia acceptable, especially when associated with calcimimetic treatment.[8]

Against this background, we performed a *post hoc* analysis of the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) trial (www.ClinicalTrials.gov identifier: NCT00345839), in which patients receiving hemodialysis with moderate-to-severe sHPT were randomized to cinacalcet or placebo.[9,10] Examining data from patients randomized to cinacalcet in EVOLVE, we assessed the epidemiology, correlates, and consequences of mild, moderate, and severe hypocalcemia.

RESULTS

Occurrence of hypocalcemia episodes

Among 1938 patients randomized to cinacalcet and who received at least 1 dose of cinacalcet, 1130 (58.3%) developed at least 1 hypocalcemia episode during the first 16 weeks and 356 (18.4%) were categorized as severe hypocalcemia (Figure 1). In comparison, among 1923 patients randomized to placebo, 286 (14.9%) developed at least 1 hypocalcemia episode and 85 (4.4%) were categorized as severe (Figure 1). Within the cinacalcet group the majority of patients experienced a single episode of hypocalcemia (data not shown); among the 356 patients with severe hypocalcemia, 294 patients had a single episode, while 46 patients had 2 consecutive serum calcium values below the threshold and 16 subjects had 3 or more consecutive values below the threshold. Independent of the severity of hypocalcemia, the first hypocalcemia episode manifested at a median of day 56 to 58 after the initiation of cinacalcet (data not shown).

Analysis of baseline demographics of the 3 hypocalcemia category subjects (Table 1) was notable for more patients from Latin America and Russia and fewer patients from the United States clustering in the moderate and severe hypocalcemia categories, which was also reflected in the racial analysis. In comparison to patients with no or mild hypocalcemia, patients of the severe and moderate category tended to be younger and had a more frequent history of prior parathyroidectomy and kidney transplantation.

In terms of baseline therapy, a higher proportion of the patients in the moderate and severe hypocalcemia categories received calcium-containing phosphate binders at baseline compared with subjects in the no or mild hypocalcemia categories (Table 1).

In comparison with patients with no or mild hypocalcemia, patients of the moderate and severe category had higher baseline plasma concentrations of PTH, serum bone alkaline phosphatase, and N-terminal telopeptide, as well as lower corrected serum calcium (Table 1). Other parameters including serum albumin and blood hemoglobin values (not shown) did not differ among the categories.

Comparison of the 16 patients with 3 or more consecutive severe hypocalcemia records (i.e., prolonged severe

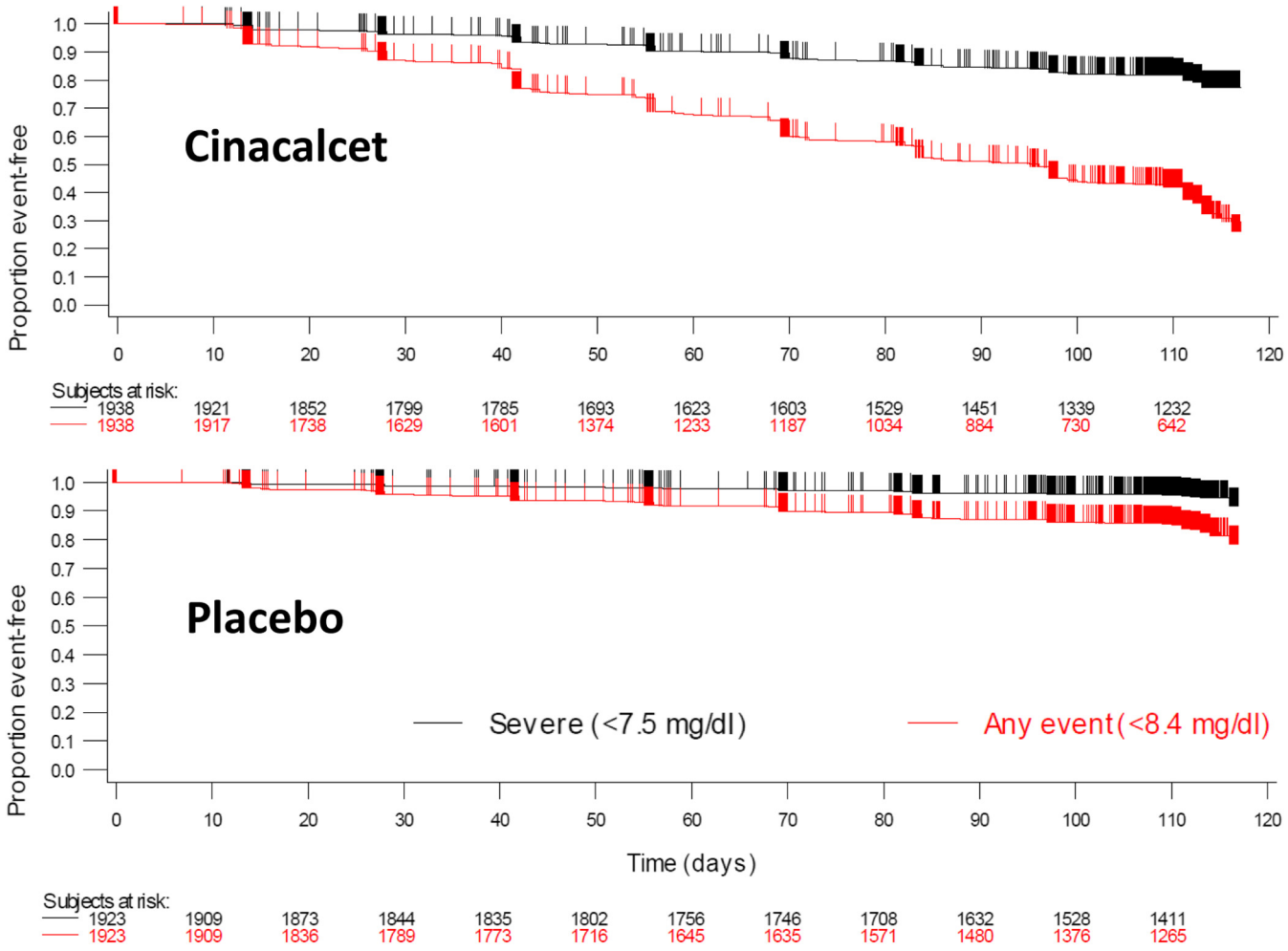

Figure 1 | Kaplan-Meier curve of time to first low–serum calcium (total albumin corrected calcium) episode in patients developing severe or any hypocalcemia following the initiation of cinacalcet or placebo in the EVOLVE (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) trial.