

# Cinacalcet for secondary hyperparathyroidism: From improved mineral levels to improved mortality?

M.G. Vervloet<sup>1\*</sup>, P.W.G. du Buf-Vereijken<sup>2</sup>, B.-J. Potter van Loon<sup>3</sup>, N. Manamley<sup>4</sup>, L.J.M. Reichert<sup>5</sup>, P.J.H. Smak Gregoor<sup>6</sup>

<sup>1</sup>Department of Nephrology, VU University Medical Centre, Amsterdam, the Netherlands, <sup>2</sup>Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands, <sup>3</sup>Department of Internal Medicine, St Lucas Andreas Hospital, Amsterdam, the Netherlands, <sup>4</sup>Amgen Limited UK, Cambridge, United Kingdom, <sup>5</sup>Department of Internal Medicine, Rijnstate Hospital, Arnhem, the Netherlands, <sup>6</sup>Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, the Netherlands, \*corresponding author: tel.: +31 (0)20-4442673, fax: +31 (0)20-4442675; e-mail: m.vervloet@vumc.nl

## ABSTRACT

Secondary hyperparathyroidism is an almost inevitable complication of advanced kidney failure. The introduction of the calcimimetic cinacalcet for the treatment of secondary hyperparathyroidism in patients on dialysis was based on its ability to reduce elevated levels of parathyroid hormone (PTH). Subsequent clinical studies confirmed the beneficial effects of cinacalcet on biochemical parameters reflecting mineral disturbances and bone disease. In this review we summarise the impact of cinacalcet on biochemical, intermediate and clinical outcomes. We also present previously unpublished mineral metabolism data from 144 Dutch dialysis patients treated with cinacalcet who participated in the pan-European ECHO observational study. Although secondary hyperparathyroidism tended to be more severe in our Dutch cohort, compared with the entire ECHO cohort, cinacalcet was nevertheless effective in reducing PTH in these patients. Two recent clinical studies evaluated, respectively, the efficacy of cinacalcet in improving the intermediate endpoint of cardiovascular calcifications (ADVANCE trial), and its impact on clinical outcomes, including all-cause mortality and cardiovascular events (EVOLVE trial). The ADVANCE trial provided evidence that cinacalcet may indeed improve calcification in both large arteries and cardiac valves. The EVOLVE trial, however, did not meet its clinical primary endpoint (time to all-cause mortality, myocardial infarction, hospitalisation for unstable angina, heart failure or a peripheral vascular event), although secondary and sensitivity analysis suggested a beneficial effect. The clinical implications of these important studies are also addressed in this review.

## KEYWORDS

Cinacalcet, CKD-MBD, dialysis, secondary hyperparathyroidism, ECHO

## INTRODUCTION

Secondary hyperparathyroidism is a frequent complication of chronic kidney disease (CKD).<sup>1</sup> Levels of parathyroid hormone (PTH) increase as CKD progresses, thus there is a high prevalence of secondary hyperparathyroidism among patients with end-stage renal disease.<sup>2</sup> Hypocalcaemia, vitamin D deficiency, and hyperphosphataemia, all hallmarks of CKD, are physiological stimuli for PTH secretion.<sup>3</sup> Moreover, during CKD expression of the vitamin D receptor, the calcium-sensing receptor and Klotho on parathyroid glands declines, thereby abolishing the inhibitory effects of 1,25-dihydroxyvitamin D, calcium and fibroblast growth factor 23 (FGF-23) on PTH production and secretion.<sup>2,4-7</sup> All these factors lead to hyperplasia of the parathyroid glands, which, once established, is generally irreversible.<sup>8</sup> Originally, PTH was considered to be an indicator of renal bone disease, but it is a poor predictor of bone histology, especially in advanced CKD,<sup>9</sup> unless levels of alkaline phosphatase are also considered along with PTH.<sup>10</sup> In end-stage renal disease, PTH was found to be associated with mortality. This association, after multivariate adjustment, showed a U-shaped curve for studies using both cross-sectional data and evolution of values over time,<sup>11-14</sup> with increased mortality at both high and low PTH levels. Unfortunately,

there is no consistency across these studies regarding the optimal level of PTH in end-stage renal disease, and for this reason, the recently published Kidney Disease Improving Global Outcomes (KDIGO) guidelines could only suggest preventing PTH levels from moving outside extreme ranges (2 to 9 times the upper limit of normal range).<sup>15</sup> Apart from the epidemiological association that exists between levels of PTH and mortality in patients with secondary hyperparathyroidism, two additional lines of evidence suggest a contributory role for elevated PTH levels in the causal pathway to adverse clinical events. Firstly, patients with primary hyperparathyroidism (who do not have uraemia), have increased mortality, mainly due to cardiovascular complications,<sup>16</sup> including left ventricular hypertrophy.<sup>17</sup> Secondly, as the PTH receptor is present on cardiomyocytes and vascular smooth muscle cells,<sup>18</sup> elevated PTH levels may lead to changes in the functioning of these cells, including disturbances in calcium channels and energy handling.

Treatment options for secondary hyperparathyroidism aim to prevent hyperphosphataemia and hypocalcaemia, while correcting 1,25-hydroxyvitamin D deficiency.<sup>19,20</sup> These include active vitamin D sterols,<sup>21-24</sup> the calcimimetic cinacalcet,<sup>25-27</sup> (in dialysis patients), combinations of both,<sup>28,29</sup> phosphate binders<sup>15,30</sup> and surgery.<sup>31</sup> Although parathyroidectomy can effectively lower PTH, it is associated with postoperative hypocalcaemia,<sup>32</sup> and can induce prolonged irreversible hypoparathyroidism.<sup>33</sup> The latter is associated with increased mortality.<sup>34</sup> The use of parathyroidectomy is declining,<sup>35</sup> and a detailed discussion is beyond the scope of this review paper.

The present review summarises the subsequent effects of cinacalcet on biochemical endpoints, intermediate endpoints including bone mineral density (BMD) and arterial calcification, and finally on hard clinical endpoints. We also present previously unpublished mineral metabolism data from 144 Dutch dialysis patients treated with cinacalcet who participated in a pan-European observational study. We conclude with a discussion on the implications of these new data for clinical practice.

## CINACALCET

The calcimimetic agent cinacalcet hydrochloride (Mimpara®, Amgen Inc, Thousand Oaks, CA, USA) was approved in the Netherlands in 2005 for the treatment of secondary hyperparathyroidism in patients with stage 5 CKD on dialysis. This class of drugs acts by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium ions, inhibiting the release of PTH.<sup>36,37</sup> In phase III clinical trials, cinacalcet improved achievement of target levels for the metabolic abnormalities associated with chronic kidney disease-mineral and bone disorders

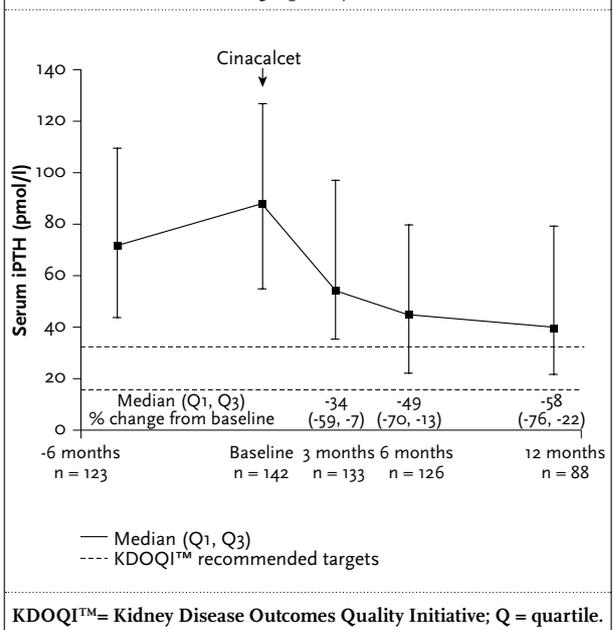
(CKD-MBD).<sup>25,26,38</sup> As the controlled setting of prospective clinical trials can differ substantially from everyday clinical practice, it was encouraging that similar levels of improvement in calcium, phosphorus, and especially PTH, were achieved in the ECHO observational study (Evaluation of the Clinical Use of Mimpara® in Haemodialysis and Peritoneal Dialysis Patients, an Observational Study).<sup>27,39</sup>

## DUTCH EXPERIENCE: THE ECHO STUDY

The ECHO study was a one-year observational study among European dialysis patients receiving cinacalcet (n=1865). Detailed descriptions of the methodology used have been published previously.<sup>27</sup> In short, all dialysis patients at participating centres who were prescribed cinacalcet at the decision of their treating physician were eligible for inclusion in the analysis. They were followed from six months prior to initiation of cinacalcet, until 12 months afterwards. There was no treatment algorithm provided. The main outcome parameter was the proportion of patients who attained target levels for PTH, phosphate, and calcium.

As there were important differences across the 12 countries that participated in the ECHO study, we conducted a separate analysis of the 144 participants from the

**Figure 1.** Evolution of intact parathyroid hormone (iPTH) in Dutch patients treated with cinacalcet in the ECHO observational study. During the observation period KDOQI™ guidelines were followed, aiming at PTH levels between 16-32 pmol/l



Netherlands (80% on haemodialysis, the remainder on peritoneal dialysis). The Dutch participants generally had more severe secondary hyperparathyroidism, as evidenced by higher baseline levels of PTH, compared with the pan-European ECHO cohort as a whole (n=1865).<sup>40</sup> Because of this higher baseline level of PTH, differences in PTH response might have been expected in the Dutch patients. The median age of the Dutch dialysis patients was 59 years (range 19-90), and the median dialysis duration was 52 months. Median PTH was 88 pmol/l (interquartile range 55-127, c.f. normal values of <7-9 pmol/l, depending on the assay used in the Dutch participating centres), despite extensive use of phosphate binders and active vitamin D sterols. Median calcium level was 2.6 mmol/l (IQR 2.4-2.7). As shown in *figure 1*, a relevant decline in PTH was observed. Simultaneously a decline in calcium and a small decline in phosphate were also observed (data not shown), leading to an improved calcium-phosphorus product. Interestingly, baseline PTH levels did not predict responsiveness to cinacalcet (*figure 2*). These data indicate that in everyday practice, patients with severe secondary hyperparathyroidism generally respond well to cinacalcet, even though the majority (73%) were already treated with active vitamin D sterols.

## EFFECT ON INTERMEDIATE ENDPOINTS

Better control of PTH and calcium by cinacalcet does not necessarily imply improved clinical outcome. This improved laboratory profile after initiation of cinacalcet, however, is accompanied by alleviation of both bone disease and arterial calcifications, which are thought to be modifiable entities and are accepted as intermediate endpoints.

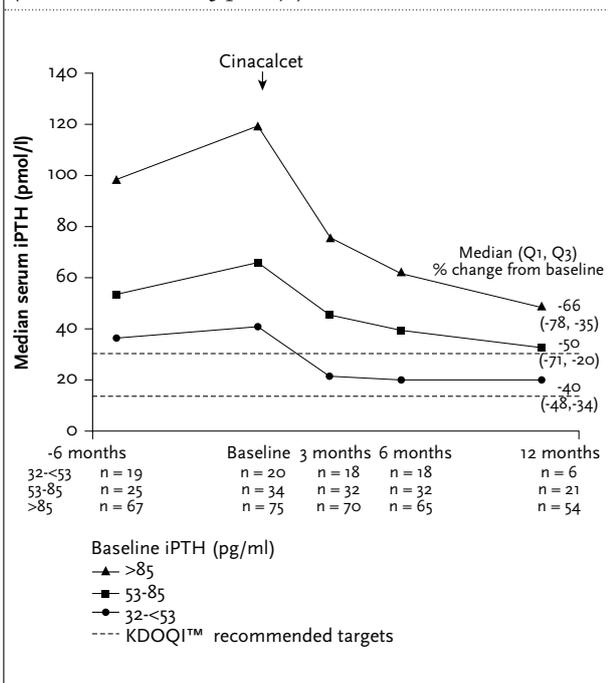
In a small subgroup of a placebo-controlled randomised trial,<sup>26</sup> the effects of 26 weeks of cinacalcet treatment on BMD included improvement in the proximal femur, but not in the lumbar spine.<sup>41</sup> After kidney transplantation this beneficial effect was confirmed for both the femoral neck and lumbar spine.<sup>42,43</sup> As BMD is considered a poor indicator of bone histology in advanced CKD, these results remain difficult to interpret. Ideally, detection of bone histology changes requires sequential bone biopsies. This indeed was performed in a placebo-controlled study in 32 dialysis patients and demonstrated that cinacalcet use for one year led to improved bone turnover, along with a decline in bone-specific alkaline phosphatase.<sup>44</sup> These results contrast somewhat with findings of a very recent pilot study that initiated cinacalcet only in haemodialysis patients with declining BMD and bone-biopsy proven osteitis fibrosa, the bone histological hallmark of hyperparathyroidism. Repeated bone biopsies were not conducted, but ongoing loss of BMD could not be halted in patients treated with cinacalcet.<sup>45</sup>

Another intermediate endpoint that has been studied extensively is vascular and cardiac valve calcification. Based on encouraging results from animal models of uraemia<sup>46</sup> in which calcimimetics such as cinacalcet led to undisputable improvement, the ADVANCE trial was conducted.<sup>47</sup> This open-label randomised trial in 360 dialysis patients compared a treatment regimen of fixed low doses of active vitamin D plus cinacalcet with a regimen of flexible doses of active vitamin D (both known to lower PTH). After one year of treatment, the cinacalcet-treated group showed decreased calcification (using two scoring systems, based on electron beam CT scanning) in the coronary arteries, aorta, and mitral and aortic valves, although some of these changes, including the predefined primary endpoint, did not reach statistical significance (*figure 3*).

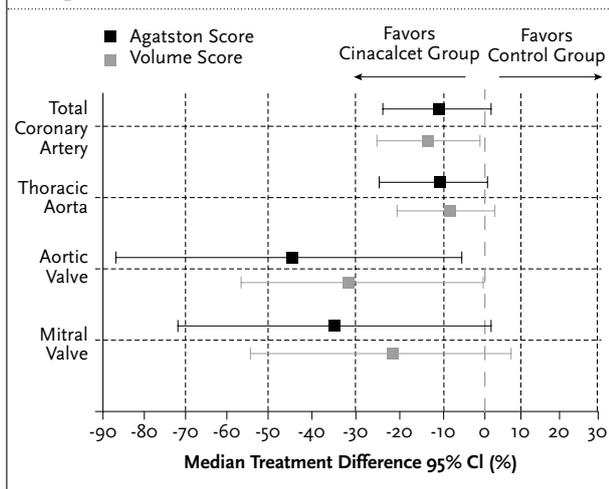
## EFFECTS ON CLINICALLY RELEVANT ENDPOINTS: THE EVOLVE TRIAL

It is well appreciated that a simple model of cause-effect in pathophysiology seldom explains observed complications in the clinical setting. Furthermore, the assumption that pharmacological intervention aimed at modifying the assumed cause can prevent complications is even

**Figure 2.** Magnitude of intact parathyroid hormone (iPTH) reduction according to baseline disease severity in Dutch patients treated with cinacalcet in the ECHO observational study: mild (baseline iPTH 32-53 pmol/l), moderate (baseline iPTH 53-85 pmol/l) and severe (baseline iPTH >85 pmol/l)



**Figure 3.** Percentage change from baseline to week 52 in calcification scores at four different anatomical sites in patients treated with cinacalcet (n=115) and a control group treated with flexible doses of vitamin D sterols (n=120) in the ADVANCE study. The box represents the median treatment differences; the line represents 95% confidence intervals. Raggi P, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant.* 2011, 26(4):1327-39. Reprinted by permission of the European Dialysis and Transplant Association - European Renal Association.<sup>47</sup>



more likely to be a misconception. A recent meta-analysis published while the EVOLVE trial was ongoing (see below) concluded that there is consistency among trial findings regarding the ability of cinacalcet to reduce PTH. This may subsequently reduce the progression rate of calcification, but existing literature does not support any impact of cinacalcet on mortality,<sup>39</sup> with the exception of some post-hoc analyses.<sup>48</sup> The randomised double-blind, placebo-controlled EVOLVE trial prospectively studied the impact of cinacalcet on a composite endpoint in haemodialysis patients. This comprised time to all-cause mortality, myocardial infarction, hospitalisation for unstable angina, heart failure or a peripheral vascular event.<sup>49</sup> After analysing according to the intention-to-treat principle, the study did not show a significant effect on its primary composite endpoint (hazard ratio [HR] 0.93, 95% confidence interval 0.85-1.02,  $p=0.11$ , figure 4). A prespecified secondary analysis adjusting for baseline covariates associated with the primary endpoint (including age: there was a one-year difference between treatment groups) revealed a nominally significant improvement in achievement of the primary endpoint in the cinacalcet group (HR 0.88, 95% confidence interval 0.79-0.97). The study was hampered by several problems. The two most important issues were the high dropout rate in both

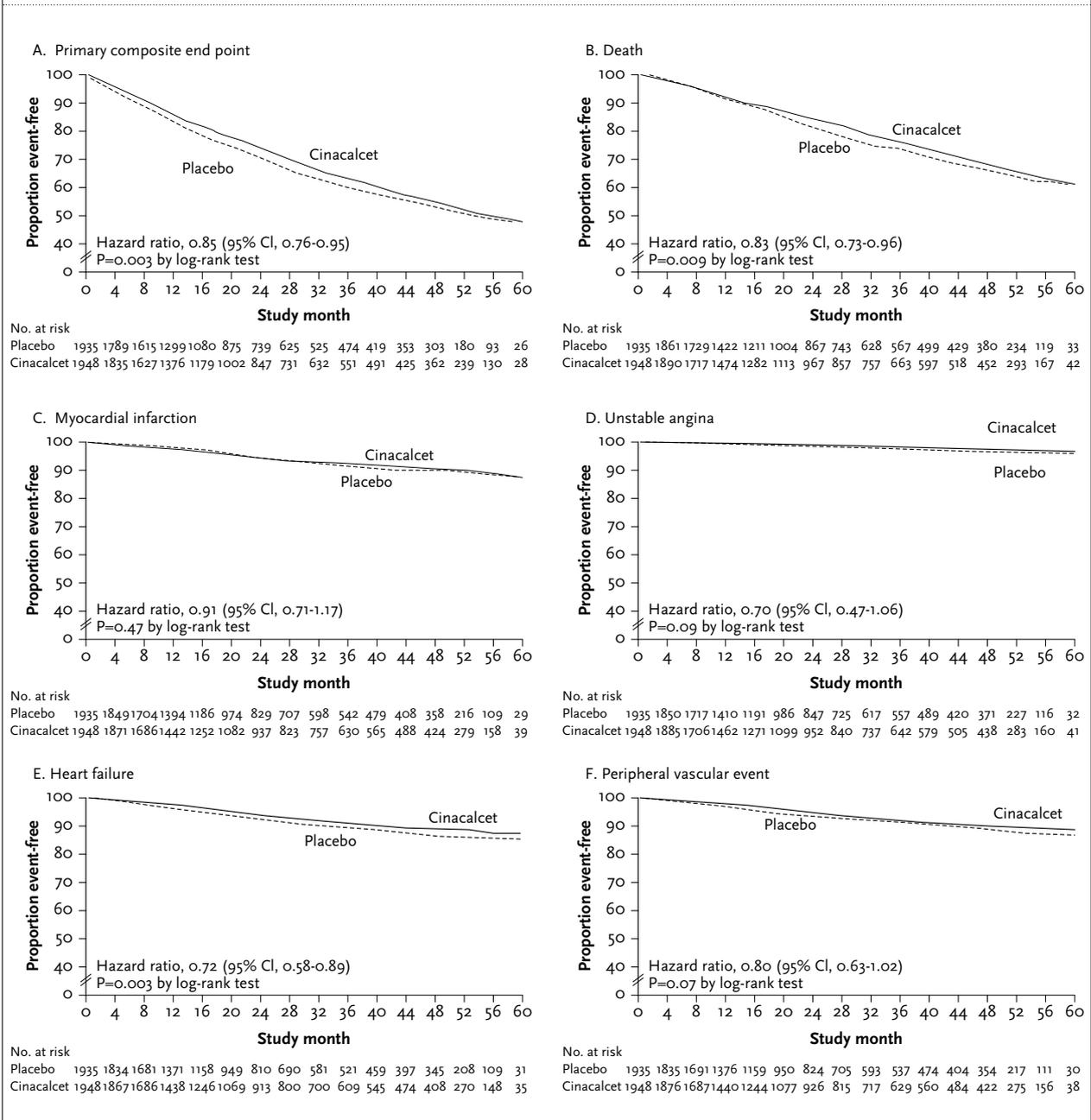
treatment groups and the number of patients who were prescribed cinacalcet as a component of their regular treatment. As expected, the latter event occurred mostly in the placebo group; in an attempt to correct for this issue, lag censoring was performed, with data being censored six months after discontinuation of the investigational product. (The period of six months was chosen as the anticipated duration of any effect of altered mineral metabolism on extraskeletal calcification.) This analysis also showed a nominally significant effect on the primary endpoint in favour of the cinacalcet group (HR 0.85, 95% CI 0.76-0.95).

### IMPLICATIONS FOR EVERYDAY PRACTICE

The failure of the EVOLVE trial to meet its primary endpoint requires reconsideration of the assumptions on which the study was based. Although the ability of cinacalcet to reduce PTH is undisputed,<sup>26,39</sup> its potential to slow or halt calcification, although likely, did not translate into a straightforward improved clinical outcome. An important consideration when trying to explain this finding is that in the ADVANCE study, the primary endpoint was a change in calcification scores.<sup>47</sup> However, calcification scores were extremely elevated in both groups at baseline, suggesting that considerable vascular damage may already have occurred, and calcification had therefore already become a non-modifiable risk factor by the time patients were enrolled in the EVOLVE study. Another possibility is that vascular calcification (as detected by electron beam CT or multi-slice CT) is just a marker of severe underlying vascular pathology.<sup>50,51</sup> If cinacalcet improves the marker (i.e. calcification), but not the underlying vascular disease (for instance atherosclerosis of the intima, elastin degradation or apoptosis of smooth muscle cells in the media), then it is not surprising that no clinical improvements were detected in EVOLVE, since the vascular processes that precede final calcification are the actual culprits for cardiovascular events. An additional factor that may explain the failure of the EVOLVE study to meet its primary endpoint is the fact that many aspects of clinical treatment were not predefined in a treatment algorithm, leading to important differences between the cinacalcet and placebo groups. For instance, the use of active vitamin D sterols, which have been associated with improved survival in dialysis patients,<sup>52</sup> was lower in patients randomised to cinacalcet.

It is important to realise that the minimal PTH level required for inclusion in the EVOLVE trial (31.8 pmol/l, based on the older KDOQI guideline) is within the range that can be considered acceptable according to

**Figure 4.** Kaplan-Meier curves comparing cinacalcet treatment and placebo for the primary composite endpoint (panel A) and the five components of the composite endpoint (panels B-F) in the EVOLVE trial. From *N Engl J Med*, Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis, Chertow GM, et al., 367:2482-94. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.<sup>49</sup>



the current KDIGO guideline.<sup>15</sup> However, the potential impact of this difference in upper PTH threshold is probably limited. The median baseline PTH for EVOLVE patients allocated to cinacalcet was 74 pmol/l (percentile 10-90: 39-182 pmol/l); therefore, the majority could also be considered candidates for treatment according to the current clinical guidelines. Moreover, additional analyses revealed that cinacalcet treatment postponed the first

clinical event by approximately five months. This potential gain in event-free time has to be weighed against potential adverse effects and costs of the intervention. Finally, sensitivity analysis showed a difference in effects of cinacalcet treatment on the primary endpoint based on age, suggesting that those above the age of 65 years derived the most benefit.

## CONCLUSION

For almost a decade cinacalcet has been considered to be an important addition to the pharmaceutical armamentarium for treating dialysis patients. It has proven to be valuable in improving laboratory markers, as seen in our Dutch cohort, with possible benefits on intermediate endpoints such as bone disease and vascular calcifications. However, a final verdict on the impact of cinacalcet on clinically relevant outcomes remains elusive and unfortunately there are no ongoing or planned studies that will elucidate this in the near future. The EVOLVE trial, which aimed to answer this question, did not meet its primary endpoint and could only suggest a benefit of cinacalcet. Nevertheless, the EVOLVE data may justify the use of cinacalcet as a component of future multi-targeted intervention trials in dialysis patients.

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## Conflicts of interest

M.V. has received research grants from Abbott and Genzyme, and participated in advisory boards for Abbott and Genzyme. N.M. is an employee of Amgen. Dr du Buf-Vereijken, Dr Potter van Loon, Dr Reichert, and Dr Smak Gregoor report no conflicts of interest.

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