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Original Article

Mortality in dialysis patients with cinacalcet use: A large observational registry study

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ABSTRACT

Background: Secondary hyperparathyroidism (sHPT) is associated with higher mortality in dialysis patients. The calcimimetic cinacalcet reduces intact parathyroid hormone (iPTH) in dialysis patients. The randomized controlled EVOLVE trial failed to unequivocally prove survival advantage of cinacalcet in dialysis patients. However, recent post hoc analyses suggested a benefit in subgroups of dialysis patients. Large observational cohort studies may represent an option to better determine such subgroups.
Methods: Data from the nationwide Austrian registry of dialysis patients between January 2004 and December 2009 were analyzed with follow-up until December 2010. All-cause and cardiovascular mortality analyses were performed using the Kaplan-Meier and Cox proportional hazards regression. To reduce confounding effects a propensity score (PS) based method (matching by stratification) was used for group comparison.
Results: The cohort included 7983 dialysis patients, 1572 (19.7%) were prescribed cinacalcet. During a median follow-up of 2.7 years, 3574 (44.8%) patients died, including 1342 (16.8%) deaths from cardiovascular causes. Survival analyses in the PS-matched study population (n = 6109) showed lower all-cause mortality for cinacalcet-treated as compared to untreated patients only in subsets characterized by younger age, low prevalence of diabetes, iPTH levels between 300 and 599 pg/mL, concomitant therapy with vitamin D and phosphate binders.
Conclusions: Our data suggest that a subgroup of dialysis patients, namely those with moderate sHPT, younger age and without diabetes benefit from cinacalcet with reduced overall and cardiovascular mortality. These findings may help to identify populations for further controlled trials and may allow a more individualized sHPT treatment using cinacalcet in specific patient subgroups.

1. Introduction

The risk of cardiovascular mortality is dramatically higher in dialysis patients as compared to the general population at any given age [1]. Traditional cardiovascular risk factors are highly prevalent in patients on dialysis (chronic kidney disease (CKD) stage 5D), but cannot fully explain their outrageous mortality rate. Abnormalities in mineral and bone metabolism, particularly high levels of parathyroid hormone (PTH), phosphate and calcium, are associated with morbidity and mortality in CKD5D [2]. Those three factors are linearly or in a J-shaped curve independently related to cardiovascular events and all-cause mortality in several observational studies in CKD5D [2–4]. Cinacalcet effectively reduces PTH without elevating phosphate and calcium levels in randomized controlled trials (RCTs) [5–9] as well as in observational "real world" studies [10,11]. Treatment with cinacalcet has also been found to be associated with reduced mortality in a large observational study conducted in >19,000 dialysis patients [12].

The randomized controlled EVOLVE-study with approximately 4000 participants followed for 3–5 years exhibited no significant benefit of cinacalcet over placebo on survival or major cardiovascular events in dialysis patients [13]. However, in the a priori defined adjusted intention to treat analysis (ITT), balancing the uneven age distribution in the cinacalcet and placebo groups, there was a benefit of cinacalcet [13]. Because of the limitations of the trial including an actual statistical power of only 54% to detect a 20% relative difference in primary outcome, an

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unexpectedly low event rate, frequent treatment crossover, and a high rate of discontinuation of the study drug, the results of EVOLVE were considered inconclusive and led to an ongoing discussion and controversy over how to translate the study findings into daily clinical practice [14,15]. A recent post hoc analysis of the EVOLVE trial identified a subgroup of patients who could benefit from cinacalcet based on the capability of cinacalcet to reduce fibroblast growth factor (FGF 23) levels [16]. Since further large cinacalcet-based RCTs after EVOLVE are unlikely to be conducted, large observational cohort studies may represent an alternative approach to detect subgroups of dialysis patients with secondary hyperparathyroidism (sHPT) likely to benefit from cinacalcet. Therefore, the present analysis using propensity score matching (PS) by stratification of a large national registry of dialysis patients aimed at identifying subgroups in which treatment with cinacalcet is associated with reduced all-cause and cardiovascular mortality.

2. Subjects and methods

2.1. Study design and patient selection criteria

This was an observational retrospective cohort study based on the Austrian Dialysis and Transplant Registry (OEDTR), a nationwide database holding records of patients receiving renal replacement therapy (RRT) including >95% of Austrian dialysis patients [17]. The database was established in 1965 and has almost complete annual follow up of patients on haemo- and peritoneal dialysis as well as patients who received a renal transplant. Data are obtained from dialysis centers on a voluntary basis, written informed consent from the patient is required. The registry provides information on demographics, primary renal disease, weight and height, biochemical laboratory readings, mode and changes of RRT, comorbidities, and date as well as organ/disease-specific cause of death. Biochemical parameters such as electrolytes, iPTH, C-reactive protein (CRP), and hemoglobin are obtained annually since 2004. Furthermore prescriptions of medications such as types of phosphate binders, vitamin D preparations and calcimimetics are recorded. Comprehensive annually reports can be obtained from the website www.nephro.at.

All patients registered between 01.01.2004 and 31.12.2009 (n = 8225) were evaluated. The starting date was chosen because cinacalcet became commercially available in Austria in 2004. Patients with no details of cinacalcet use, aged <18 years or with a documented survival time < 90 days were excluded (Fig. 1). The follow-up period ended on 31.12.2010.

Information about clinical characteristics was recorded in prevalent dialysis patients (n = 2657) as of study entry on 01.01.2004, and in incident patients (n = 5326) between 02.01.2004 and 31.12.2009 at initiation of dialysis. This information included history of diabetes mellitus, of cardiovascular disease (coronary artery disease, congestive heart failure and valvular heart diseases) and of hypertension, as well as primary kidney disease. Kidney transplant waiting list registration was defined as no or yes, no meaning never on waiting list, yes meaning at least one recorded registration. Treatment (at least one recorded prescription during the observation period) with cinacalcet, phosphate binders or vitamin D receptor activators (VDRA) was defined as a dichotomous

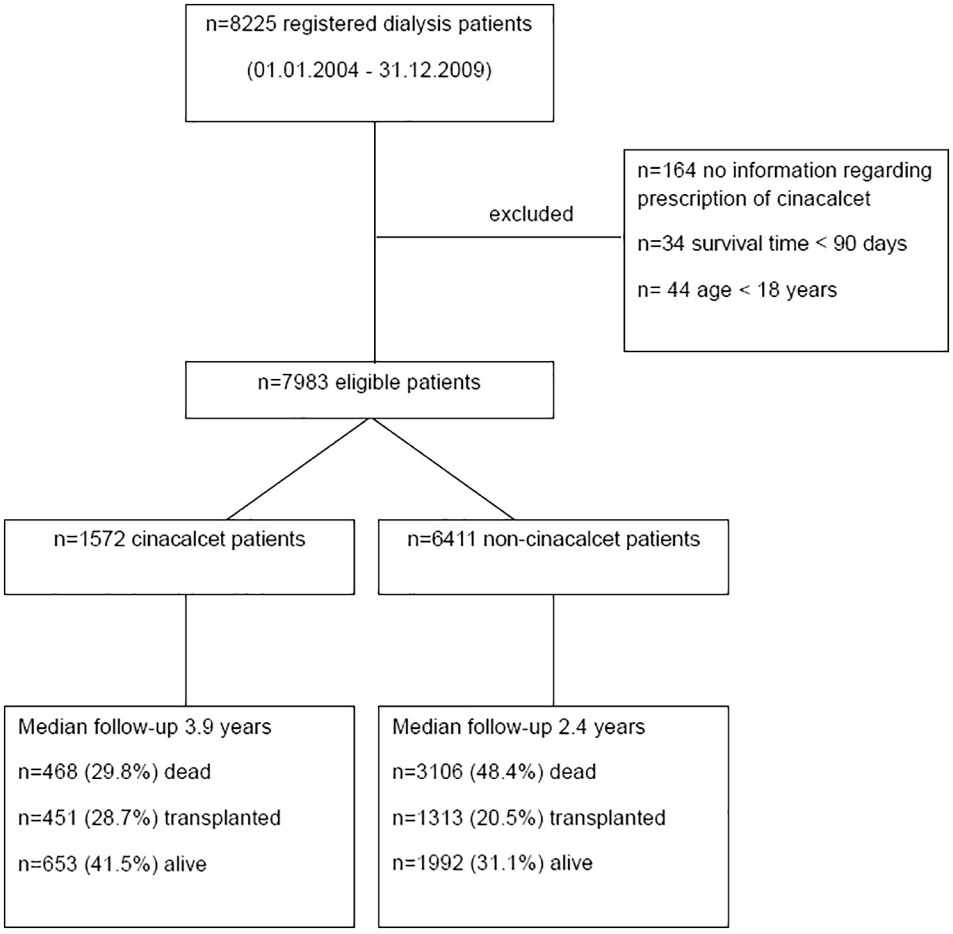

Fig. 1. Study flowchart Data from all prevalent and incident dialysis patients (n = 8225) included in the Austrian Dialysis and Transplant Registry between January 2004 and December 2009 were analyzed. Patients with no details of cinacalcet use, aged <18 years or with a documented survival time < 90 days were excluded. The final study cohort included 7983 patients (1572 cinacalcet, 6411 non-cinacalcet patients).

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