EVOLVE

Evaluation of Cinacalcet Hcl to Lower Cardiovascular Events

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Disclosures

- None to declare

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ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

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Background and Objectives

- CVD is common among patients with CKD, including those treated with HD
  - CVD ↑ 10 X in CKD patients compared to general population
  - Multiple CV risk factors including ↑phosphate, calcium, PTH, ALP, fibroblast growth factor-23
  - Mineral metabolism disorders cause arterial calcification, ↓vascular compliance and lead to myocardial ischemia, HF, sudden death
- Cinacalcet reduces PTH by activation of the calcium-sensing receptor in parathyroid tissue; levels of phosphate and calcium also reduced
  - results from pooled studies>6 months, showed reduced CV events, fracture and decreased PTHectomy rates

N Engl J Med 2012; 367: 2482-94

Background and Objectives

- Study Objective:
  - Treatment with Cinacalcet would reduce risk of death and non-fatal events among patients with secondary hyperparathyroidism undergoing dialysis
- Study sponsored by Amgen
  - Develop operational strategy
  - oversee global study execution
  - promote alignment among all regions
  - monitoring and site management in European Union and Australia

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Study Design

- Multicenter, prospective, randomized, PC trial
- Inclusion Criteria:
  - Adults ≥18 years treated with HD 3X weekly for ≥3 months
  - PTH ≥ 31.8 pmol/L; serum Ca ≥2.1 mmol/L; Ca X P ≥3.64 $mmol^2/L^2$
- Exclusion Criteria:
  - Unstable medical condition
  - PTHectomy within 12 weeks of informed consent or 6 months after randomization
  - Severe (Life-threatening) concomitant disease (e.g. cancer)
  - Hospitalization within 12 weeks of randomization with MI, USA, HF, PVD, Stroke
  - History of seizure
  - Scheduled Kidney Transplant with living donor

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Study Design

- Study Intervention
  - Cinacalcet 30 mg po daily starting dose, with potential dose escalation once every 4 weeks during a 20 week titration phase (60,90,120, 180 mg/d) or every 8 weeks during follow-up
  - Dose escalation dependent on PTH and serum calcium
  - Dialysis, phosphate binders, vitamin D sterols, calcium supplements and other medications prescribed at discretion of treating physician
  - Biochemical measurements: PTH, calcium, phosphate every 2 weeks during titration phase and every 8 weeks in follow-up phase
  - Allocation concealment: not stated
  - randomization method: not stated

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Study Design

- Primary Endpoint:
  - Time to death (CV or non-CV) or first non-fatal CV event (MI, hospitalization for USA, HF, PVD)
- Secondary Endpoints:
  - Individual components of primary composite endpoint
- All primary and secondary endpoints adjudicated by an independent clinical-events group
- Sample size based on the following assumptions:
  - Annual rate of primary composite endpoint-23.2% in placebo group and 20% treatment effect, a 1.5 year enrollment period and 4 year study duration with 1% annual loss to follow-up; 10% dropout rate
- Data analyzed in accordance with ITT principle

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Study Design

- Lag censoring
  - data were censored for 6 months after patient stopped using study drug (thought to be duration of effect of altered mineral metabolism or extraskeletal calcification)
  - Reasons for discontinuing drug before endpoint anticipated to be:
    - Kidney transplant
    - PTHectomy
    - initiation of commercially available cinacalcet

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Results

- From August 22, 2006 to January 31, 2008, 3883 patients underwent randomization:
  - 1430 in USA
  - 1188 in Europe
  - 687 in Latin America
  - 283 in Russia
  - 149 in Australia
  - **146 in Canada**
- Median duration of drug exposure:
  - placebo: 21.2 months
  - Cinacalcet 17.5 months
- Median dose: 55 mg

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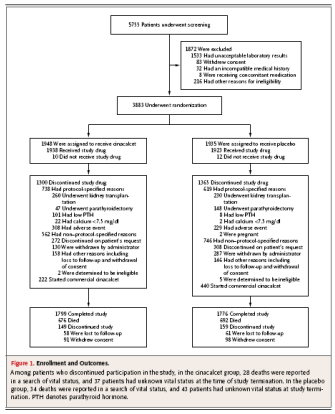

Figure 1. Enrollment and Outcomes.
Among patients who discontinued participation in the study, in the cinacalcet group, 28 deaths were reported in a search of vital status, and 37 patients had unknown vital status at the time of study termination. In the placebo group, 14 deaths were reported in a search of vital status, and 43 patients had unknown vital status at study termination. PTH denotes parathyroid hormone.

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Results: Enrollment and Outcomes

Reason for Discontinuation	Cinacalcet n=1300/1948	Placebo 1365/1935
Protocol-specified :		
-Kidney Transplant	268	230
-**PTHectomy**	**47**	**148**
-Low PTH	101	8
-Low Calcium	22	1
-AE	308	229
-Other	-	2
Non-Protocol:		
-Patient discontinuation	272	308
-Administrator withdrawn	130	287
-Loss to f/u; consent w/d	158	146
-Other	2	5
Started commercial cinacalcet	**222 (11%)**	**440/1935 (23%)**

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Results

- Baseline characteristics –similar
  - Cinacalcet n=1948
  - Placebo n=1935
- Primary Composite Endpoint (ITT)
  - Cinacalcet: 938/1948 (48.2%) vs. Placebo 952/1935 (49.2%) [95% CI 0.85-1.02; p=0.11)

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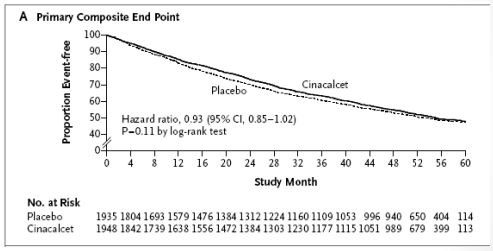
Primary Composite Endpoint



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Results

- Secondary Endpoints
  - Stroke: Cinacalcet 115 vs. placebo 102 [95% CI, 0.82-1.40 p=0.28]
  - Death CV causes: Cinacalcet 377 vs. Placebo 391 [95% CI, 0.80-1.07; p=0.28]
- Other Endpoints
  - PTHectomy: Cinacalcet 140 (7%) vs. Placebo 278 (14%) (relative hazard 0.44, 95% CI 0.36-0.54)
  - Fracture: Cinacalcet 238 (12%) vs. Placebo 255 (13%)(relative hazard 0.89, 95% CI 0.75-1.07)
  - Calcific Uremic Arteriolopathy (Calciphylaxis): Cinacalcet 6 (0.3%) vs. Placebo 18 (0.9%), corresponding to exposure-adjusted rates of 0.1 and 0.5/100 patient-years (p=0.009)
  - Multiple CV events: Cinacalcet 25.3 events vs. Placebo 27.3 events (P=0.02)

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Results

- Secondary Analyses:
  - After adjustment for baseline characteristics, relative hazard 0.88 [95% CI 0.79-0.97; p=0.008]= 12% RRR
    - This was done using multivariate regression (variants: region compared to US, age, Hx of CVD, DM, dialysis vintage, Ca x P, HDL, Albumin, tobacco use)
  - Lag-censoring analysis-censoring of data 6-months after study-drug discontinuation: relative hazard 0.85 [95% CI, 0.76-0.95; p=0.003]
  - After adjustment for kidney transplantation, PTHectomy or use of commercial cinacalcet, relative hazard 0.90 [95% CI, 0.76-0.93; p<0.001]

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Safety

- Adverse Events:
  - Led to discontinuation: Cinacalcet 18.1% vs. Placebo 13.0%
  - SAE: similar between groups (cinacalcet 69% vs. Placebo 70.3%)
  - Hypocalcemia developed in 7X and nausea 2X as many patients in the cinacalcet group vs. placebo
  - Neoplastic events: Cinacalcet 115 vs. Placebo 90 patients corresponding to 2.9 vs. 2.5 events/100 patient-years

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Discussion

- This R, PC, trial showed that cinacalcet vs. placebo resulted in no difference in the primary endpoint of time to death (CV or non-CV) or first non-fatal CV event (MI, hospitalization for USA, HF, PVD)
- Sub-group Analysis- resulted in nominally significant risk reductions in the primary endpoint (10-15%)
  - Multivariate Cox Regression: 12% risk reduction in primary composite endpoint
  - Censoring data for kidney transplant, PTHectomy or use of commercially-available cinacalcet: 10% risk reduction in primary composite endpoint
  - Lag-Censoring Endpoints:15% risk reduction in primary composite endpoint
- SAE- not remarkably different
- Other AE: Hypocalcemia 9X and nausea 2X higher with cinacalcet vs. placebo

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Discussion

- Study Limitations
  - Study drug discontinuation rate high (66.7%) – for e.g. AE, PTHectomy, transplantation
  - Commercial cinacalcet use in placebo group (23%)

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Conclusions

- Cinacalcet vs. placebo did not significantly reduce time to death or 1st non-fatal CV event in CKD patients undergoing chronic HD with secondary hyperPThism
- Limitations such as a high study-drug discontinuation rate and allowance of commercially available cinacalcet use may have affected the primary outcome
- Secondary analysis of the outcomes (baseline characteristics, lag-censoring and commercial cinacalcet /PTHectomy/transplantation) resulted in only nominally significant risk reduction in the primary outcome in the range of 10-15%

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