Title	An Observational Study to Evaluate the Potential Association Between Cinacalcet and Gastrointestinal Bleeding
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Marketing Authorization Holder(s)	Amgen, Inc.
Research Question and Objectives	To assess the potential association between cinacalcet use and risk of gastrointestinal bleeding in patients receiving maintenance hemodialysis
Country(ies) of Study	United States
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1. ABSTRACT

- **Title**

An Observational Study to Evaluate the Potential Association Between Cinacalcet and Gastrointestinal Bleeding

- **Keywords**

Cinacalcet, gastrointestinal bleeding, maintenance dialysis, chronic kidney disease, secondary hyperparathyriodism

- **Rationale and Background**

Gastrointestinal (GI) bleeding is a frequent complication of chronic kidney disease (CKD) among dialysis patients. Gastrointestinal bleeding was estimated to be responsible for 1.4% of hospitalizations among United States (US) Medicare-insured hemodialysis patients in 2013, with an admission rate of 23 per 1000 patient-years. The death rate (per 1000 patient-years) from GI bleeding in US Medicare hemodialysis patients was estimated to be 0.9 in 2013, while the percentage of deaths due to GI bleeding was 0.5%. Patients with kidney disease are at elevated risk of GI bleeding due to the disease itself, its attendant comorbid conditions, and the many medications commonly used in this population. Additionally, dialysis patients who are ≥ 50 years old, female, or whose end-stage renal disease (ESRD) was caused by hypertension have an elevated risk of GI bleeding events. Previous episodes of GI bleeding have been strongly associated with a greater risk of a subsequent episode (hazard ratio [HR]: 3.93, 95% confidence interval [CI]: 3.82 to 4.05), and a prior episode of GI bleeding in long-term dialysis patients has been associated with an increased hazard of death (HR: 1.90, 95% CI: 1.86 to 1.93).

Amgen conducted this observational study to fulfill an Food and Drug Administration (FDA) postmarketing requirement.

- **Research Question and Objectives**

To assess the potential association between cinacalcet use and risk of gastrointestinal bleeding in secondary hyperparathyroidism (HPT) patients receiving maintenance hemodialysis.

- **Study Design**

A matched case-controlled study design was used; cases were nested within a cohort of hemodialysis patients with secondary HPT. A case was defined as a patient who experienced GI bleeding in the case assessment period.

The *case assessment period* for each patient was from the cohort entry date to the earliest date of GI bleeding, death, loss of Medicare coverage (any of Parts A, B, or D), parathyroidectomy,

change to peritoneal dialysis, kidney transplant, or end of 2010. The *cohort entry date* was when a patient met the inclusion/exclusion criteria during the designated study period (2007 to 2010). A *baseline period* of 1 year (365 days) with no exposure to cinacalcet or GI bleeding event was also applied for each patient to assess comorbidities.

Each case was matched to up to 4 controls based on age, race, sex, time on dialysis, and baseline PTH level (< 600 pg/mL and ≥ 600 pg/mL). The *index date* was designated as the date of the first recorded GI bleeding event (fatal or nonfatal). Incidence density sampling was used to match case and controls exactly on the time from cohort entry to index date (ie, exact number of days).**Error! Reference source not found.**

- **Setting**

This study included Medicare hemodialysis patients with secondary HPT who received dialysis in a DaVita, Inc. dialysis facility between 2007 and 2010 (the study period).

- **Subjects and Study Size, Including Dropouts**

Hemodialysis patients satisfying the following eligibility criteria were selected for the case and control study cohorts.

- age ≥ 18 years
- at least 91 days on hemodialysis
- covered by Medicare Parts A, B, and D for at least 1 year
- received hemodialysis for at least 91 days in a DaVita dialysis facility
- parathyroid hormone (PTH) > 300 pg/mL during the baseline period
- no cinacalcet use for 1 year (baseline period)
- no GI bleeding event for 1 year (baseline period)

Patients were excluded from the study for the following reasons:

- history of parathyroidectomy
- previous kidney transplant

A total of 52,393 patients were included in the study. Of these, 2,570 patients were cases (ie, patients with a GI bleeding event) and 49,823 were condidates for control. Out of them, 2,465 (96%) cases were matched to 9,400 controls (**Table 1 and 2**).

- **Variables and Data Sources**

DaVita electronic medical record (EMR) data linked to Medicare ESRD claims during the period 2006 to 2010 were used for this study (linked DaVita-USRDS database).

The ***outcome variable*** was the composite of nonfatal (hospitalization) and fatal events of GI bleeding. A fatal event was defined as death with GI bleeding as a cause and a nonfatal event was defined as a hospitalization with GI bleeding as the primary diagnosis. Cinacalcet use was the ***exposure variable***; use was determined from Medicare Part D claims using National Drug Codes (NDC). The exposure definition period was from the cohort entry date to the index date. Cinacalcet exposure was defined as no use, any use, current use (within 61 days of the index date) and past use (use between cohort entry date and 61 days prior to the index date). Cumulative exposure time and cumulative dose were also assessed. ***Other variables*** included the matching variables of age, race, sex, time on dialysis, and PTH level (< 600 pg/mL and ≥ 600 pg/mL). Other confounders included ESRD cause (diabetes, hypertension, glomerulonephritis, and other), geographic region (10 Medicare regions), comorbid conditions, and medication use. Both comorbid conditions and medication use were assessed during the baseline period.

- **Results**

The adjusted odds ratio (cinacalcet use vs no use) of GI bleeding was 1.04 with 95% CI: (0.91,1.19). The upper limit of 95% CI is less than 1.3, the non-inferiority margin, which supports us to reject the null hypothesis: cinacalcet is associated with a higher risk of GI bleeding events The estimates were similar when exposure was categorized by current cinacalcet use (within 61 days of the GI bleeding event; adjusted OR: 0.97, 95% CI: 0.83, 1.13) or past cinacalcet use (more than 61 days before the GI bleeding event; adjusted OR: 1.22, 95% CI 0.99,1.50) (**Table 3**). A subgroup analysis of patients < 65 years of age and ≥ 65 years of age showed no difference in the relative risk of GI bleeding events with cinacalcet use versus no use (adjusted OR: 1.05, 95% CI: 0.86,1.28 and 1.05, 0.88,1.25, respectively) (**Table 4**). Results from all other subgroups evaluated, including race, sex, time on dialysis, and PTH level at baseline, were generally consistent with the primary results (**Table 4**).

Sensitivity analyses supported the primary results. Estimated risk was similar when evaluated by differing windows of cinacalcet exposure, including periods of cinacalcet discontinuation (**Table 5**).

In an analysis using death as a competing risk in the control group, the adjusted ORs were marginally elevated compared with the primary analysis (adjusted OR: 1.25, 95% CI: 1.10,1.43) (**Table 6**). A higher estimate was anticipated since the cases were matched with patients who died without events of GI bleeding.

- **Discussion**

Cinacalcet use was not associated with an increased risk of GI bleeding in US hemodialysis patients with secondary HPT. The benefit-risk profile for cinacalcet remains favorable.

Table 1. Patient Characteristics for Matched Cases and Controls (Primary Analysis)

Variable	Cases N = 2465	Controls N = 9400
Age (mean [SD])	65.99 (13.37)	66.09 (13.07)
Age, n (%)		
18 to 44	195 (7.91)	694 (7.38)
45 to 64	818 (33.18)	3143 (33.44)
65 to 74	769 (31.20)	3001 (31.93)
75 to 84	553 (22.43)	2102 (22.36)
≥ 85	130 (5.27)	460 (4.89)
Gender, n (%)		
Male	1282 (52.01)	4900 (52.13)
Female	1183 (47.99)	4500 (47.87)
Race, n (%)		
White	1331 (54.00)	5193 (55.24)
Black	1020 (41.38)	3886 (41.34)
Asian	80 (3.25)	234 (2.49)
Other	34 (1.38)	87 (0.93)
ESRD duration, n (%)		
Mean – years (SD)	2.50 (2.39)	2.31 (2.17)
91 days to < 1 year	731 (29.66)	2846 (30.28)
1 to < 3 years	942 (38.22)	3715 (39.52)
3 to < 5 years	456 (18.50)	1701 (18.10)
> 5 years	336 (13.63)	1138 (12.11)

Footnotes are defined on the last page of the table.

Table 1. Patient Characteristics for Matched Cases and Controls (Primary Analysis)

Variable	Cases N = 2465	Controls N = 9400
PTH at cohort entry date, n (%)		
301 to < 600 pg/mL	1976 (80.16)	7627 (81.14)
≥ 600 pg/mL	489 (19.84)	1773 (18.86)
Primary Cause of ESRD, n (%)		
Diabetes	1262 (51.20)	4881 (51.93)
Hypertension	754 (30.59)	2828 (30.09)
Glomerulonephritis	178 (7.22)	625 (6.65)
Other/Unknown/Missing Cause	271 (10.99)	1066 (11.34)
Geographic region, n (%)		
Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont	84 (3.41)	294 (3.13)
New Jersey, New York, Puerto Rico, Virgin Islands	160 (6.49)	601 (6.39)
Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, West Virginia	318 (12.90)	1104 (11.74)
Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee	596 (24.18)	2374 (25.26)
Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin	407 (16.51)	1327 (14.12)
Arkansas, Louisiana, New Mexico, Oklahoma, Texas	306 (12.41)	1343 (14.29)
Iowa, Kansas, Missouri, Nebraska	111 (4.50)	376 (4.00)
Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming	31 (1.26)	124 (1.32)
Arizona, California, Hawaii, Nevada, Pacific Territories	414 (16.80)	1750 (18.62)
Alaska, Idaho, Oregon, Washington	38 (1.54)	107 (1.14)

ESRD = end-stage renal disease; PTH = parathyroid hormone..

Table 2. Comorbidities of Matched Cases and Controls

Comorbidity, n (%)	Cases N = 2465	Controls N = 9400
High density lipoprotein	1268 (51.44)	4645 (49.41)
Necrosis	-	16 (0.17)
Hepatitis	905 (36.71)	2860 (30.43)
cirrhosis	111 (4.50)	160 (1.70)
Asthma	218 (8.84)	620 (6.60)
COPD	659 (26.73)	1914 (20.36)
GI Cancer	31 (1.26)	82 (0.87)
Hematologic Cancer	39 (1.58)	142 (1.51)
Solid tumor Cancer	158 (6.41)	553 (5.88)
Systolic Heart Failure	179 (7.26)	656 (6.98)
Heart Failure	1260 (51.12)	4250 (45.21)
Diabetes Mellitus	1744 (70.75)	6646 (70.70)
Cardiovascular Disease	515 (20.89)	1635 (17.39)
Thrombocytopenia	134 (5.44)	373 (3.97)
Low Serum Albumin	29 (1.18)	96 (1.02)
Calciphylaxis	220 (8.92)	918 (9.77)
CAD	1225 (49.70)	3925 (41.76)
PVD	220 (8.92)	722 (7.68)
Inflammatory GI	65 (2.64)	159 (1.69)
Diverticula GI	104 (4.22)	232 (2.47)
Lower GI	710 (28.80)	1969 (20.95)
Upper GI	762 (30.91)	2100 (22.34)
Surgery GI	59 (2.39)	125 (1.33)
Alcohol Use	51 (2.07)	115 (1.22)
Tobacco Use	242 (9.82)	676 (7.19)

COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; GI = gastrointestinal; PVD = peripheral vascular disease.

Table 3. Odds Ratio of Gastrointestinal Bleeding Events by Cinacalcet Use

	All Matched Cases and Controls			
	Unadjusted Model		Fully Adjusted Model[a]	
Cinacalcet use	Odds ratio (95% CI)	Estimates	Odds ratio (95% CI)	Estimates
Any use				
No (ref)	1		1	
Yes	1.08 (0.95,1.22)	0.07	1.04 (0.91,1.19)	0.04
No use, current use or past use				
No use (ref)	1.00		1.00	
Current use	0.99 (0.85,1.15)	-0.01	0.97 (0.83,1.13)	-0.03
Past use	1.29 (1.06,1.58)	0.25	1.22 (0.99,1.50)	0.20
Cumulative exposure				
0 day (ref)	1.00		1.00	
< 80 days	1.26 (1.05,1.52)	0.23	1.23 (1.02,1.49)	0.21
80 to < 220 days	0.98 (0.79,1.20)	-0.03	0.95 (0.77,1.17)	-0.05
≥ 220 days	0.98 (0.79,1.21)	-0.02	0.93 (0.75,1.16)	-0.07
Cumulative dose				
0 mg (ref)	1.00		1.00	
< 2700 mg	1.26 (1.04,1.53)	0.23	1.23 (1.01,1.49)	0.20
2700 to < 7500 mg	0.94 (0.77,1.16)	-0.06	0.90 (0.73,1.11)	-0.10
≥ 7500 mg	1.02 (0.83,1.26)	0.02	1.00 (0.80,1.23)	0.00

ESRD = end-stage renal disease; ref = reference.

[a] Conditional logistic regression analysis. Model adjusted by age, primary ESRD cause, geographic location, comorbid condition, and medication use.

Table 4. Odds Ratio of Gastrointestinal Bleeding Events by Cinacalcet Use by Subgroups

	All Matched Cases and Controls		
		Fully Adjusted Model[a]	
Subgroup	Any vs No Use OR (95% CI)	Current Use vs No OR (95% CI)	Past Use vs No OR (95% CI)
Age (years)			
< 65	1.05 (0.86,1.28)	1.00 (0.80,1.25)	1.19 (0.86,1.65)
≥ 65	1.05 (0.88,1.25)	0.95 (0.77,1.17)	1.27 (0.97,1.67)
Race			
White	1.13 (0.94,1.36)	0.99 (0.80,1.24)	1.48 (1.11,1.97)
Non-white	0.96 (0.80,1.16)	0.93 (0.75,1.15)	1.03 (0.76,1.40)
Sex			
Men	1.17 (0.98,1.41)	1.05 (0.85,1.31)	1.49 (1.11,2.01)
Women	0.90 (0.75,1.09)	0.87 (0.70,1.09)	0.97 (0.72, 1.31)
Time on dialysis			
91 days to < 1 year	1.02 (0.80,1.31)	1.00 (0.75,1.34)	1.06 (0.72,1.58)
1 year to < 3 years	1.08 (0.87,1.34)	0.94 (0.73, 1.22)	1.43 (1.02,2.02)
3 years to < 5 years	1.07 (0.79,1.46)	0.85 (0.59,1.22)	1.80 (1.11,2.92)
≥ 5 years	0.96 (0.67,1.36)	1.07 (0.71,1.59)	0.74 (0.41,1.33)
PTH level at baseline (pg/mL)			
< 600	1.07 (0.92,1.24)	0.97 (0.81,1.16)	1.27 (1.01,1.60)
≥ 600	1.00 (0.76,1.32)	1.00 (0.74,1.35)	1.00 (0.61,1.63)

PTH = parathyroid hormone.

[a] Conditional logistic regression analysis. Model adjusted by age, primary ESRD cause, geographic location, comorbid condition, and medication use.

Table 5. Odds Ratio of Gastrointestinal Bleeding Events by Cinacalcet Use Exposure Windows

	All Matched Cases and Controls	
	Fully Adjusted Model	
Cinacalcet use	Odds ratio (95% CI)	Estimates
Exposure windows, including periods of discontinuation[a]		
No use (ref)	1	
1 to 60 days use	0.97 (0.83,1.13)	-0.03
61 to 120 days se, no use 1 to 60 days	1.00 (0.67,1.50)	0.00
121 to 180 days use, no use 1 to 120 days	1.01 (0.63,1.62)	0.01
181 to 365 days use, no use 1 to 180 days	1.29 (0.91,1.83)	0.25
≥ 366 days Use, no use 1 to 365 days	1.55 (1.06,2.27)	0.44
Exposure during the 1-year (365 days) period before event[b]		
Any use		
No (ref)	1	
Yes	0.99 (0.87,1.14)	-0.01
No use, current use or past use[c]		
No use (ref)	1	
Current use	0.95 (0.82,1.11)	-0.05
Past use	1.12 (0.89,1.43)	0.12

ESRD = end-stage renal disease; PTH = parathyroid hormone; ref = reference.

[a] Conditional logistic regression analysis. Model adjusted by age, primary ESRD cause, geographic location, comorbid condition, and medication use.

[b] Conditional logistic regression analysis. Model adjusted by age, time on dialysis, PTH level, primary ESRD cause, geographic location, comorbid condition, and medication use.

[c] Current use and past use definitions were as defined for the primary analysis.

Table 6. Odds Ratio of Gastrointestinal Bleeding Events – Competing Risk Analysis

	All Matched Cases and Controls	
	Fully Adjusted Model[a]	
Cinacalcet use	Odds ratio (95% CI)	Estimates
Any use		
No (ref)	1	
Yes	1.25 (1.10,1.43)	0.23
No use, current use or past use		
No use (ref)	1	
Current use	1.15 (0.99,1.33)	0.14
Past use	1.52 (1.24,1.87)	0.42

ESRD = end-stage renal disease; ref = reference.

[a] Conditional logistic regression analysis. Model adjusted by age, primary ESRD cause, geographic location, comorbid condition, and medication use.