Title	Cinacalcet Use and the Risk of Gastrointestinal (GI) Bleeding Among Hemodialysis Patients with Secondary Hyperparathyroidism (SHPT) in the Dialysis Outcome and Practice Patterns Study (DOPPS)
Version Identifier of the Final Study Report	20170665, Version 1.0
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Active Substance	ATC Code H05BX01, Cinacalcet Hydrochloride
Medicinal Product	Cinacalcet (Sensipar®/Mimpara®)
Product Reference:	EU/1/04/292
Marketing Authorization Holder	Amgen, Inc.
Research Question and Objectives	1. Estimate (a) the rate of hospitalization from GI bleeding, (b) the rate of death from GI bleeding, and (c) the rate of hospitalization or death from GI bleeding, by region (US, Other) and overall. 2. Estimate the association between exposure to cinacalcet and (a) the risk of hospitalization from GI bleeding, (b) the risk of death from GI bleeding, and (c) the composite risk of hospitalization or death from GI bleeding, by region (US, Other) and overall.
Countries of Study	United States, France, Germany, Italy, Spain, United Kingdom, Belgium, Sweden, Australia, New Zealand, Canada, and Japan
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1. ABSTRACT

- **Title**

Cinacalcet Use and the Risk of Gastrointestinal (GI) Bleeding Among Hemodialysis Patients with Secondary Hyperparathyroidism (SHPT) in the Dialysis Outcome and Practice Patterns Study (DOPPS)

- **Keywords**

cinacalcet, gastrointestinal bleeding, chronic kidney disease, secondary hyperparathyroidism

- **Rationale and Background**

Gastrointestinal (GI) bleeding is a frequent complication among hemodialysis (HD) patients. It has been hypothesized that cinacalcet use increases GI bleeding risk in HD patients with secondary hyperparathyroidism (SHPT). We conducted an observational study to estimate the burden of GI bleeding in a population of hemodialysis patients with SHPT, and, in the same population, to address the potential association between cinacalcet and fatal and non-fatal GI bleeding.

- **Research Question and Objectives**

Objective 1: Estimate (a) the rate of hospitalization from GI bleeding, (b) the rate of death from GI bleeding, and (c) the rate of hospitalization or death from GI bleeding, by region (US, Other) and overall.

Objective 2: Estimate the association between exposure to cinacalcet and (a) the risk of hospitalization from GI bleeding, (b) the risk of death from GI bleeding, and (c) the composite risk of hospitalization or death from GI bleeding, by region (US, Other) and overall.

- **Study Design**

Among hemodialysis patients with SHPT, a retrospective cohort study design was used to estimate the rates of GI bleeding events. Nested within the cohort, we then conducted a matched case-control study to estimate the association between cinacalcet use and fatal and nonfatal GI bleeding events. Controls were sampled in a 1:4 matching ratio from the same SHPT population that gave rise to the cases (i.e., patients with GI bleeding events) and were matched on the following criteria: (1) duration of follow-up (exact match on number of days), (2) time on dialysis (≤ 1 year, > 1 year), (3) age (±1 year), (4) gender, and (5) race (U.S. only).

- **Setting**

The study population was comprised of individuals ≥ 18 years of age with ESRD from the Dialysis Outcome and Practice Patterns Study (DOPPS), an international prospective cohort study of a random sample of patients receiving center-based hemodialysis. All patients who survived at least four months after entry into DOPPS from the following countries were considered for inclusion: Australia, New Zealand, Belgium, Canada, France, Germany, Italy, Spain, Sweden, Japan, the United Kingdom, and the United States.

The enrollment date for the cohort study was the date at four months after first occurrence of a PTH lab > 300 pg/mL, and the baseline period was a period of 4 months prior to the enrollment date. Study participants were followed from the enrollment date until the date of the first occurrence of the following events: (1) hospitalization for GI bleeding or death from GI bleeding; (2) kidney transplantation; (3) parathyroidectomy, (4) death from causes other than GI bleeding, (5) termination of enrollment in DOPPS, and (6) administrative end of follow-up. The index date for the nested case-control study was the date of the first recorded GI bleeding event (fatal or nonfatal) during the follow-up period.

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

The following inclusion criteria were applied to DOPPS participants on the enrollment date:

- Ages ≥18 years of age
- Received in-center hemodialysis at a DOPPS facility for a minimum of 4 months
- At least one measurement of a PTH lab > 300 pg/mL during the baseline period

Patients were excluded from the cohort study if there was evidence of any of the following events at any time prior to the enrollment date:

- Parathyroidectomy
- Kidney transplant
- Cinacalcet Use

For the case-control study, controls were selected from the SHPT cohort (the source population of dialysis patients that gave rise to the cases), and were selected independent of their exposure status. All controls were selected using risk-set sampling

using a 1:4 (cases:controls) matching ratio and matched on the following variables on the index date:

- Duration of follow-up (time at risk) in SHPT cohort (exact match on number of days)
- Time on dialysis (≤ 1 year, > 1 year)
- Age (± 1 year)
- Gender
- Race (black vs. other, U.S. only)

- **Variables and Data Sources**

The data source for this study was the Dialysis Outcomes and Practice Patterns Study (DOPPS), Phases IV & V. DOPPS is an international prospective cohort study of hemodialysis practices, based on observational longitudinal data from a random sample of patients from dialysis facilities in more than 20 countries.

The *primary outcome* was a composite of fatal and nonfatal GI bleeding events. Nonfatal GI bleeding events were those in which GI bleeding was the primary cause of hospitalization, while fatal GI bleeding events were those in which GI bleeding was entered as a cause of death. The *primary exposure* of interest in the nested case-control study was the use of cinacalcet occurring within 60 days prior to the index date. *Other variables* included age, gender, race, time on dialysis, as well as comorbid conditions and medication use. Confounding variables were identified prior to cohort entry, and included comorbid conditions (cirrhosis, chronic obstructive pulmonary disease, chronic heart failure, coronary artery disease), as well as medication usage (warfarin, tertiarytricyclics), and lifestyle factors (ever smoked, alcohol abuse in prior 12 months).

We estimated the crude incidence rates of GI bleeding events and associated 95% confidence intervals (CIs), using the Poisson distribution. Multivariable conditional logistic regression models were used to generate adjusted odds ratio (OR) and 95% CI for the effect of cinacalcet use on GI bleeding events.

- **Results**

A total of 9,349 hemodialysis patients satisfied the eligibility criteria for the cohort study, 4,399 patients from the United States and 4,950 patients from countries outside the United States. We estimated the rate of hospitalization or death due to GI bleeding (per

1,000 person-years [PYs]) in the U.S. as 10.2 (95% Confidence Interval [CI]: 7.9, 13.3); and 26.4 (95% CI: 23.5, 29.7) in countries outside the U.S.

For the main analysis, where we evaluated cinacalcet use in the 60 days prior to the index date, there was no association between cinacalcet exposure and GI bleeding (fatal or nonfatal events) in hemodialysis patients with SHPT (adjusted odds ratio [OR]: 0.68 [95% CI: 0.47, 1.00]). For the subset of cases and controls occurring outside the U.S., there was also no association between cinacalcet exposure and GI bleeding (adjusted O.R.: 0.75 [95% CI: 0.50, 1.12]).

In sensitivity analyses, when considering cinacalcet exposure in the 120 days prior to the index date, there was a lower risk for GI bleeding associated with cinacalcet exposure when considering all regions (adjusted O.R. 0.67 [95% CI: 0.46, 0.97], but no effect of cinacalcet exposure on GI bleeding events when considering only the ex-U.S. region (adjusted O.R.: 0.73 [95% CI: 0.49, 1.08]).

- **Discussion**

In this nested case control study using DOPPS data, cinacalcet use was not associated with an increased risk of GI bleeding events among U.S. and ex-U.S. adult hemodialysis patients with SHPT. The benefit-risk profile for cinacalcet remains favorable.

The study results are broadly generalizable to adult patients with ESRD receiving center-based hemodialysis in the U.S. and selected countries outside the U.S. Limitations of the analyses include the following: (1) relatively few GI bleeding events identified in U.S. DOPPS data; (2) less comprehensive capture of comorbid conditions in the U.S., relative to ex-U.S. countries, and (3) potential residual confounding due to unmeasured confounders.

- **Marketing Authorization Holder**

Amgen, Inc.

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