Lower Risk of Cardiovascular Events in Adult Patients with Chronic Hypoparathyroidism Treated with rhPTH(1–84): A Retrospective Cohort Study

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ABSTRACT

Introduction: Patients with chronic hypoparathyroidism are at increased risk of cardiovascular disease. This study evaluated the risk of developing cardiovascular conditions over a period of 5 years in adult patients with chronic hypoparathyroidism treated with recombinant human parathyroid hormone (1–84), rhPTH(1–84), compared with a historical control cohort of patients not treated with rhPTH(1–84).

Methods: This retrospective cohort study comprised patients with chronic hypoparathyroidism treated with rhPTH(1–84) in the REPLACE (NCT00732615), RELAY (NCT01268098), and RACE (NCT01297309) clinical trials, and controls selected from the IBM® Explorys electronic medical record database (January 2007–August 2019) who did not receive parathyroid hormone but who had enrollment criteria similar to those for the clinical trials. Cardiovascular outcomes were the first diagnosis of cerebrovascular, coronary artery, peripheral vascular disease, or heart failure during the study period.

Results: We evaluated 113 adult patients with chronic hypoparathyroidism treated with rhPTH(1–84) and 618 control patients who did not receive rhPTH(1–84). Over the 5-year follow-up period, 3.5% of patients (n = 4) in the rhPTH(1–84) cohort had a cardiovascular event compared with 16.3% (n = 101) in the control cohort. Kaplan–Meier analysis demonstrated that patients in the rhPTH(1–84) cohort had lower risk of experiencing a cardiovascular event compared with patients in the control cohort (P = 0.005). Multivariable analyses adjusted for baseline variables showed that patients in the rhPTH(1–84) cohort had 75% lower risk for a cardiovascular event compared with patients in the control cohort (adjusted hazard ratio, 0.25 [95% CI 0.08–0.81]; P = 0.020).

Conclusion: Long-term treatment with rhPTH(1–84) was associated with a lower risk of incident cardiovascular conditions compared...
with conventional therapy in patients with chronic hypoparathyroidism. Previous studies demonstrated that mineral homeostasis was maintained with lower use of calcium and active vitamin D when rhPTH(1–84) was added to conventional therapy. Future studies are needed to understand whether improved regulation of mineral homeostasis conferred by rhPTH(1–84) may provide long-term cardiovascular benefits to patients with chronic hypoparathyroidism.

**Keywords:** Cardiovascular disease; Electronic health records; Hypoparathyroidism; Parathyroid hormone; Retrospective cohort study; rhPTH(1–84)

**Key Summary Points**

**Why carry out this study?**

Patients with chronic hypoparathyroidism treated with conventional therapy of calcium/active vitamin D who lack the calcium-conserving and phosphaturic effects of parathyroid hormone, remain symptomatic, and have an increased risk of developing cardiovascular disease.

Previous clinical trials demonstrated that long-term rhPTH(1–84) treatment leads to adequate control of calcium and phosphate homeostasis, while significantly reducing the serum phosphate, calcium-phosphate product, and the amount of oral calcium and active vitamin D supplementation required. Given the importance of mineral homeostasis in the pathophysiology of cardiovascular disease (CVD), we hypothesized that long-term treatment with rhPTH(1–84) may be associated with reduced CVD.

**What was learned from the study?**

After adjustment for confounders, patients with chronic hypoparathyroidism treated with rhPTH(1–84) had a lower risk for incident cardiovascular conditions compared with patients who were not treated with rhPTH(1–84).

The potential benefit of a lowered risk for CVD with rhPTH(1–84) treatment in patients with chronic hypoparathyroidism should be explored further.

**INTRODUCTION**

Hypoparathyroidism is a condition in which parathyroid hormone (PTH) levels are insufficient to modulate bone turnover and control circulating levels of calcium and phosphate. Patients with hypoparathyroidism present with symptoms caused by hypocalcemia [1, 2]. It is estimated that 58,625 persons in the USA [3] and approximately 3.2 per 10,000 people in the European Union are affected by this condition [4], which is associated with a considerable human and economic burden. Studies have demonstrated that patients with hypoparathyroidism have a lower health-related quality of life compared with the general population [5, 6], and the complications of hypoparathyroidism result in frequent utilization of healthcare resources [6].

Management of patients with hypoparathyroidism is centered on controlling serum calcium levels and calcium-phosphate product while avoiding hypercalcuria and extraskeletal calcification [7, 8]. To that end, conventional treatment is based on oral calcium supplements
and activated vitamin D \[7, 9\]. Conventional therapy, however, may not adequately control hypoparathyroidism. Consequently, some patients remain symptomatic because they lack the calcium-conserving and phosphaturic effect of PTH and can develop associated complications \[7, 10–15\]. Several retrospective studies have reported that patients with chronic hypoparathyroidism receiving conventional therapy have an increased risk for developing cardiovascular disease \[11, 16–20\]. Abnormal calcium homeostasis in patients with hypoparathyroidism, manifested by hypocalcemia or episodic hypercalcemia, has been associated with poor cardiovascular outcomes \[11, 21, 22\]. Increased serum phosphate is associated with vascular stiffness \[23\] and calcification \[24–26\], which are independent predictors of cardiovascular disease in the general population \[27–29\]. Patients with chronic hypoparathyroidism are at higher risk of developing chronic kidney disease (CKD) \[30\], an established risk factor for the development of cardiovascular events \[31\].

Recombinant human parathyroid hormone (1–84), rhPTH(1–84), is approved as adjunctive treatment to calcium and active vitamin D supplements for adults with hypoparathyroidism \[32, 33\]. In the USA rhPTH(1–84) is indicated to control hypocalcemia, and in Europe it is indicated to control hypoparathyroidism that cannot be adequately controlled with conventional therapy. In two single-arm clinical trials, treatment with rhPTH(1–84) reduced serum phosphate and calcium-phosphate product to below baseline levels over the long term, along with a significant reduction in the use of oral calcium and active vitamin D supplements \[34, 35\]. Furthermore, in those trials, estimated glomerular filtration rate (eGFR) levels in patients treated with rhPTH(1–84) remained stable. In a retrospective study, treatment with rhPTH(1–84) over a 5-year period was associated with stabilization of eGFR, in contrast to a decline in eGFR among patients not treated with rhPTH(1–84) \[36\]. The improved biochemical parameters and stabilization of kidney function associated with rhPTH(1–84) treatment led us to hypothesize that this treatment may reduce the risk of developing cardiovascular complications for patients with chronic hypoparathyroidism, including those with CKD. This retrospective study evaluated cardiovascular outcomes over a period of up to 5 years in adult patients with chronic hypoparathyroidism treated with rhPTH(1–84) in clinical trials compared with a historical control cohort of patients who did not receive rhPTH(1–84).

**METHODS**

**Patient Selection and Study Cohorts**

This study consisted of two cohorts of adult patients with chronic hypoparathyroidism (Fig. 1). The cohort treated with rhPTH(1–84) included a subset of the patients enrolled in the REPLACE (NCT00732615) \[37\], RELAY (NCT01268098) \[38\], or RACE (NCT01297309) \[34\] studies. Patients enrolled in RACE had previously been enrolled in RELAY or REPLACE (key eligibility criteria for REPLACE and RELAY are shown in Table S1 in the supplementary material) \[37, 38\]. For inclusion in the rhPTH(1–84) cohort for this study, patients were also required to have at least one study visit during the 5-year period on or after the index date (i.e., the day after treatment initiation in the clinical trials) and no diagnosis of cerebrovascular disease, coronary artery disease, heart failure, or peripheral vascular disease before the index date.

The initial sample set for the historical control cohort who were not treated with rhPTH(1–84) was identified from the IBM® Explorys electronic medical record (EMR) database, which is an EMR database nationally representative of approximately 15% of the US population. This study used January 2007 to August 2019 records from close to 360 different hospitals and 330,000 different healthcare providers and physicians. The EMRs are sourced from ambulatory, inpatient, and post-acute settings and include laboratory measurements, diagnoses, procedures, medications, and demographics. Patients selected for the control cohort were required to meet criteria that aligned with enrollment criteria for patients in...
the clinical trials and the selection of the rhPTH(1–84) analysis cohort in this study: at least two diagnoses of hypoparathyroidism occurring 6 months or more apart, with at least one prescription for calcitriol after the first diagnosis of hypoparathyroidism; at least 18 years old at the index date (i.e., the day after the first calcitriol prescription received on or after the first hypoparathyroidism diagnosis); no diagnosis of thyroid cancer in the 5 years before the index date; no history of rhPTH(1–84) or teriparatide treatments; at least one serum creatinine value below 132.6 µmol/L (less than 1.5 mg/dL) and one serum calcium value of 2.65 mmol/L or below (10.6 mg/dL or less) in the 6 months before the index date; and
no cardiovascular disease at baseline (i.e., before the index date). Hypoparathyroidism was identified in the medical claims using International Classification of Diseases and Related Health Problems, 9th (ICD-9) or 10th (ICD-10) Revision, Clinical Modification diagnosis codes (see Table S2 in the supplementary material for details of codes).

A cardiovascular event was defined as cerebrovascular, coronary artery, or peripheral vascular disease, or heart failure, which was identified by (i) a reported treatment-emergent adverse event or medical history in the clinical trials for the rhPTH(1–84) cohort or (ii) a code in the EMR database for the control cohort (see Table S2 for details of codes).

Permission to access and use the trial data was granted by the data owner, Takeda. All patients enrolled in the clinical trials provided written informed consent. Permission to access and use the IBM® Explorys EMR database was granted by IBM. The Explorys database is a nationally representative EMR resource maintained by IBM. Institutional review board approval was not required as the Explorys database consists of pre-existing data that is de-identified in accordance with the Health Insurance Portability and Accountability Act.

**Study Outcome and Statistical Analyses**

The primary objective of this study was to evaluate the risk of cardiovascular outcomes in patients treated with rhPTH(1–84) compared with historical controls who did not receive rhPTH(1–84). A cardiovascular outcome was defined as the first occurrence of cerebrovascular, coronary artery, or peripheral vascular disease or heart failure on or after the index date up to 5 years after index. Cardiovascular events during the study period were identified as (i) a reported treatment-emergent adverse event in the clinical trials for the rhPTH(1–84) cohort or (ii) an ICD code in the EMR database for the historical control cohort.

Continuous variables were reported using means and standard deviations, and categorical variables were reported using frequencies and percentages. Patient demographics and clinical characteristics were compared between cohorts using the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. Risk of a cardiovascular event was compared between cohorts in a Kaplan–Meier analysis and adjusted Cox proportional hazards models. In the Kaplan–Meier analysis, patients who did not develop a cardiovascular event during the study period were censored at the date of last record available in the patient’s chart or at 5 years after the index date, whichever came first. The Cox model was adjusted for demographics (age, sex, race), baseline serum calcium and clinical conditions (hypercalcemia, hypertension, type 2 diabetes, acute hypoparathyroidism manifestations, CKD, hyperlipidemia), and statin use at index date. Acute hypoparathyroidism manifestations were defined as at least one ICD-9 or ICD-10 diagnosis code of cardiac dysrhythmia, hypercalcemia, hypocalcemia, laryngeal spasm, muscle spasm, other convulsions, palpitations, tachycardia, tetanic cataract, or tetany (see Table S2 for details of codes). Baseline CKD was defined as eGFR of less than 60 mL/min/1.73 m² at the closest eGFR measurement to the index date within 6 months before the index date. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [39]. The final analysis population included all eligible patients from the rhPTH(1–84) clinical trials and a control cohort constructed using the largest EMR database in the USA, to provide the maximum sample size possible.

**RESULTS**

The analysis cohorts consisted of 113 patients treated with rhPTH(1–84) and 618 control patients (Fig. 1). Table 1 presents their baseline demographics, clinical characteristics, and biochemical parameters. A significantly lower proportion of patients in the rhPTH(1–84) cohort had hyperlipidemia ($P = 0.040$), type 2 diabetes ($P < 0.001$), any acute manifestations of hypoparathyroidism ($P < 0.001$), or statin use ($P = 0.021$) compared with patients in the control cohort.
Risk for Developing Cardiovascular Event

Over the 5-year follow-up period, 3.5% of patients \((n = 4)\) in the rhPTH(1–84) cohort had a cardiovascular event compared with 16.3% \((n = 101)\) in the control cohort \((P = 0.005)\). In some patients, multiple types of cardiovascular events were diagnosed at the same time during the follow-up period. Among patients in the rhPTH(1–84) cohort with a cardiovascular event \((n = 4)\), the distribution of the first diagnosis of events during the study period was as follows: cerebrovascular disease, 1 patient (25.0%); coronary artery disease, 2 patients (50.0%); heart failure, 1 patient (25.0%); and peripheral vascular disease, 1 patient (25.0%). Among patients in the control cohort with a cardiovascular event \((n = 101)\), the distribution of events was cerebrovascular disease, 32 patients (31.7%); coronary artery disease, 33 patients

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Kaplan–Meier analysis showed that patients in the rhPTH(1–84) cohort had a lower risk of a cardiovascular event compared with patients in the control cohort ($P = 0.005$, Fig. 2). In unadjusted analyses, treatment with rhPTH(1–84) significantly reduced the risk of incident cardiovascular events (HR 0.27 [95% CI 0.10–0.72]; $P = 0.010$) (Table 2). The adjustment for baseline variables, including age and type 2 diabetes, did not materially change the impact of rhPTH(1–84) treatment on the risk of cardiovascular events, which was associated with a 75% lower risk of cardiovascular events compared with no rhPTH(1–84) (adjusted HR 0.25 [95% CI 0.08–0.81]; $P = 0.020$) (Table 2).

**DISCUSSION**

This study set out to assess the impact of treatment with rhPTH(1–84) on cardiovascular outcomes in patients with chronic hypoparathyroidism. The results show that individuals treated with rhPTH(1–84) had a 75% lower risk of developing a cardiovascular event compared with a historical control group treated with conventional therapy without PTH replacement.

In several previous studies, patients with chronic hypoparathyroidism treated with conventional therapy were reported to have an increased risk for developing cardiovascular disease [11, 16–18]. In contrast, other studies reported mixed results. A study from China comparing patients with hypoparathyroidism ($n = 18$) with healthy age- and sex-matched controls reported differences in corrected QT interval and mild arrhythmias but no differences in cardiac structure, systolic function, or major cardiac events [40]. Two separate studies from Denmark reported that patients with postsurgical chronic hypoparathyroidism ($N = 688$) did not exhibit increased risk for cardiovascular disease [41], while cardiovascular disease risk was increased in nonsurgical hypoparathyroidism patients ($N = 180$) [41]. A retrospective study in the USA of patients from a managed care claims database of commercial and Medicare Advantage beneficiaries reported that, after adjustment for confounding factors, patients with chronic hypoparathyroidism ($n = 8097$) were at greater risk of eight incident cardiovascular outcomes: atrial fibrillation, cerebrovascular disease, coronary artery disease, heart failure, myocardial infarction, peripheral vascular disease, stroke, and tachyarrhythmia compared with patients without hypoparathyroidism [18]. To our knowledge, ours is the first large study evaluating the occurrence of cardiovascular events in patients with chronic hypoparathyroidism treated with conventional therapy alone or with rhPTH(1–84). The lower risk of new cardiovascular events in the rhPTH(1–84) cohort remained even after adjusting for baseline variables including CKD, diabetes, hypertension, and statin use.

In patients with chronic hypoparathyroidism, disordered phosphate metabolism caused by the lack of phosphaturic PTH effect and the presence of higher serum phosphate levels [1] are plausible contributing causes for the observed increased risk of cardiovascular disease.
disease. Conventional therapy of calcium supplements can restore calcium levels but fails to lower the threshold for phosphate reabsorption. Stimulation of gastrointestinal phosphate absorption with active vitamin D could further increase serum phosphate levels. In addition, the use of conventional therapy is frequently associated with fluctuating elevated serum calcium levels \([11, 42]\), which, when coupled with elevated serum phosphate levels, can further contribute to increased serum calcium-phosphate product and extraskeletal calcifications \([43, 44]\), which could also include vascular calcifications, resulting in cardiovascular disease. A study from Turkey reported a positive correlation between elevated phosphate level \((r = 0.449; \ P = 0.003)\) or calcium-phosphate product and pulse wave velocity \((r = 0.416; \ P = 0.006)\) in patients with chronic hypoparathyroidism \((n = 42)\) \([45]\). The attenuation of the phosphaturic effects of fibroblast growth factor 23 (FGF-23) resulting from PTH deficiency may also contribute to elevated serum phosphate levels \([46]\). In addition, therapy with supplemental active vitamin D stimulates FGF-23 production \([47, 48]\), which has been implicated as a risk factor for

| Characteristic | Development of a cardiovascular event |
|----------------|--------------------------------------|
|                | HR        | 95% CI   | \(P\) value |
| **Unadjusted model** |           |          |            |
| Treatment with rhPTH(1–84) (vs no rhPTH [1–84], unadjusted) | 0.27 | 0.10–0.72 | 0.010 |
| **Adjusted model** |           |          |            |
| Treatment with rhPTH(1–84) (vs no rhPTH[1–84], adjusted) | 0.25 | 0.08–0.81 | 0.02  |
| Age, years     | 1.04 | 1.02–1.06 | < 0.001 |
| Male (vs female) | 1.17 | 0.70–1.96 | 0.559 |
| Race (vs White) | 1.66 | 0.99–2.77 | 0.054 |
| **Baseline clinical conditions** |           |          |            |
| Hypocalciuria   | 0.42 | 0.06–3.11 | 0.399 |
| Hypertension    | 1.11 | 0.71–1.73 | 0.644 |
| Type 2 diabetes | 1.90 | 1.19–3.04 | 0.007 |
| Acute hypoparathyroidism event* | 1.41 | 0.89–2.23 | 0.147 |
| CKD††          | 1.45 | 0.91–2.32 | 0.120 |
| Hyperlipidemia  | 0.99 | 0.60–1.62 | 0.968 |
| Baseline statin use | 1.43 | 0.87–2.36 | 0.158 |
| Baseline serum calcium‡ | 1.15 | 0.60–2.22 | 0.676 |

CI confidence interval, CKD chronic kidney disease, eGFR estimated glomerular filtration rate, HR hazard ratio, rhPTH(1–84) recombinant human parathyroid hormone (1–84)
*Defined as at least one diagnosis for hypercalcemia, hypocalcemia, laryngeal spasm, muscle spasm, other convulsions, tetanic cataract, tetany, cardiac dysrhythmia, palpitations, or tachycardia
†CKD was defined as eGFR < 60 mL/min/1.73 m\(^2\)
‡Closest measurement before index date (within 6 months pre-index date)
cardiovascular disease in patients with CKD and in the general population [49–51].

In patients treated with rhPTH(1–84) in long-term clinical trials, serum levels of phosphate and calcium-phosphate product were maintained within reference ranges for patients with chronic hypoparathyroidism that were lower than pretreatment levels and did not differ from normal population reference ranges [34, 35]. In addition, there was reduction in the use of oral calcium and active vitamin D supplements, which in turn would result in lesser calcium influx needed to maintain normocalcemia. Taken together, these data suggest that the lower cardiovascular risk associated with treatment with rhPTH(1–84) may be the result of better restoration of mineral homeostasis compared with conventional therapy alone.

The strengths of this study include a study design used to select patients for the control cohort that was similar to the enrollment criteria of the clinical trials, including inclusion and exclusion criteria, and availability of baseline laboratory measurements. Multivariable regression models accounted for potential differences between patients treated with rhPTH(1–84) and controls by adjusting for potential confounding variables. The limitations of this study include the relatively small sample size, reflecting the rarity of the disease, and the uneven cohort sizes. Patients who received rhPTH(1–84) were enrolled in clinical trials and may have had more frequent monitoring of their condition and measurement of biochemical parameters than those in the control cohort, who were treated in real-world clinical practice. Thus, despite careful selection of the control cohort using the trial inclusion and exclusion criteria, there may be remaining differences in the two patient cohorts because of differences in patient management and how study variables were measured. Because this was an observational study, there may be unrecorded and/or unmeasured confounding variables between cohorts that were not accounted for in the analyses that persist after adjusting for baseline differences. Data for medications could not be made. Complete medical histories were not available, limiting information regarding some important confounders, such as family history of cardiovascular disease or smoking history and duration of hypoparathyroidism. The number of cardiovascular events in the study was low; however, owing to the serious nature of cardiovascular disease, it is unlikely that events were underreported in either study cohort. Future studies involving larger samples would be helpful to support the findings of this study.

CONCLUSIONS

Long-term treatment with rhPTH(1–84) was associated with a lower risk of developing a cardiovascular event compared with a control cohort of patients who did not receive rhPTH(1–84). rhPTH(1–84) may confer cardiovascular benefits to patients with chronic hypoparathyroidism, and further research is warranted to understand the relationship better in a real-world setting.

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Compliance with Ethics Guidelines. Permission to access and use the trial data was granted by the data owner, Takeda. All patients enrolled in the clinical trials provided written informed consent. Permission to access and use the IBM® Explorys EMR database was granted by IBM. The Explorys database is a nationally representative EMR resource maintained by IBM. Institutional review board approval was not required as the Explorys database consists of pre-existing data that is de-identified in accordance with the Health Insurance Portability and Accountability Act.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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