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Impact of Etelcalcetide on Cardiovascular Outcomes and Mortality in Hemodialysis Patients with Secondary Hyperparathyroidism: A Meta-Analysis

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A B S T R A C T

Secondary hyperparathyroidism (SHPT) is a common complication in hemodialysis patients, contributing to cardiovascular disease and mortality. Etelcalcetide, a novel calcimimetic agent, has shown promise in managing SHPT. This meta-analysis aimed to evaluate the impact of etelcalcetide on cardiovascular outcomes and mortality in hemodialysis patients with SHPT. A systematic search of electronic databases (PubMed, Scopus, Web of Science) was conducted to identify randomized controlled trials (RCTs) comparing etelcalcetide with placebo or other active treatments in hemodialysis patients with SHPT. The primary outcomes were cardiovascular events (composite of myocardial infarction, stroke, heart failure, and cardiovascular death) and all-cause mortality. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Seven RCTs (n=4,520 patients) were included in the meta-analysis. Etelcalcetide was associated with a significant reduction in cardiovascular events (RR 0.85, 95% CI 0.75-0.96, p=0.01) and all-cause mortality (RR 0.88, 95% CI 0.79-0.98, p=0.02) compared to placebo. No significant difference in cardiovascular events or mortality was observed between etelcalcetide and cinacalcet. In conclusion, etelcalcetide appears to be effective in reducing cardiovascular events and mortality in hemodialysis patients with SHPT. Further studies are needed to confirm these findings and to assess the long-term impact of etelcalcetide on cardiovascular health in this population.

1. Introduction

Chronic kidney disease (CKD) is a significant global health concern, affecting millions of individuals worldwide. It is characterized by a gradual loss of kidney function over time, eventually leading to end-stage renal disease (ESRD) if left untreated. Patients with ESRD require renal replacement therapy, such as hemodialysis, to survive. Hemodialysis involves the use of a machine to filter the blood and remove waste products and excess fluids, replacing the function of the kidneys. While hemodialysis is life-sustaining, it is associated with various complications, including mineral and bone disorders. CKD-mineral and bone disorder (CKD-MBD) is a complex disorder characterized by abnormalities in mineral metabolism, bone turnover, and extraskeletal calcification. It is a common complication in patients with CKD, particularly those on hemodialysis. CKD-MBD is a systemic disorder that affects multiple organ systems and is associated with increased risks of cardiovascular disease, bone fractures, and mortality.[1-3]

Secondary hyperparathyroidism (SHPT), a key component of CKD-MBD, is characterized by elevated parathyroid hormone (PTH) levels. PTH is a hormone produced by the parathyroid glands, which are small glands located in the neck. PTH plays a crucial role in regulating calcium and phosphate levels in the body.

In CKD, the kidneys are unable to adequately excrete phosphate, leading to hyperphosphatemia. Hyperphosphatemia, along with decreased levels of active vitamin D, stimulates the parathyroid glands to produce more PTH. This chronic stimulation leads to parathyroid gland hyperplasia and excessive PTH secretion, resulting in SHPT. SHPT is associated with a range of complications, including cardiovascular disease. Cardiovascular disease is the leading cause of death in patients with ESRD, and SHPT contributes significantly to this increased risk. SHPT promotes vascular calcification, which is the deposition of calcium in the walls of blood vessels. Vascular calcification leads to stiffening and narrowing of the blood vessels, increasing the risk of heart attacks, strokes, and other cardiovascular events.[4-6]

Traditional management of SHPT includes phosphate binders, vitamin D analogs, and calcimimetics. Phosphate binders help to reduce the absorption of phosphate from the gut, while vitamin D analogs help to regulate calcium and phosphate levels and suppress PTH secretion. Calcimimetics, such as cinacalcet, act by allosterically activating the calcium-sensing receptor (CaSR) on parathyroid cells, thereby reducing PTH secretion. Etelcalcetide is a novel intravenous calcimimetic agent that has shown promising results in clinical trials for the treatment of SHPT in hemodialysis patients. Etelcalcetide is a more potent and selective calcimimetic compared to cinacalcet. It has a longer half-life, allowing for once-monthly administration, which may improve patient adherence. Several studies have investigated the effects of etelcalcetide on cardiovascular outcomes and mortality in hemodialysis patients with SHPT. However, the results have been inconsistent, and the overall impact of etelcalcetide on these outcomes remains unclear.[7-10] Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) to evaluate the impact of etelcalcetide on cardiovascular outcomes and mortality in hemodialysis patients with SHPT.

2. Methods

To identify relevant studies for inclusion in this meta-analysis, we conducted a comprehensive search of electronic databases, including PubMed, Scopus, and Web of Science. These databases were selected due to their extensive coverage of biomedical literature, ensuring a broad capture of relevant studies. The search was conducted using a combination of keywords and database-specific subject headings to maximize the retrieval of eligible studies. The following search terms were used: "etelcalcetide," "secondary hyperparathyroidism," "hemodialysis," "cardiovascular events," "mortality," and "randomized controlled trial." These terms were chosen to reflect the key aspects of our research question, focusing on the intervention (etelcalcetide), the population (hemodialysis patients with SHPT), and the outcomes of interest (cardiovascular events and mortality). The search was limited to studies published in English to ensure that the included studies were accessible to the research team and to minimize the risk of language bias. The search was also limited to studies published from 2013 to 2024 to capture the most recent and relevant literature on etelcalcetide. The inclusion criteria for studies were as follows; Randomized controlled trials (RCTs) comparing etelcalcetide with placebo or other active treatments. RCTs were chosen as the study design due to their ability to minimize bias and provide the highest level of evidence for evaluating the effectiveness of an intervention; Studies involving hemodialysis patients with SHPT. This criterion ensured that the included studies were relevant to our research question and that the results could be generalized to the target population; Studies reporting cardiovascular events (composite of myocardial infarction, stroke, heart failure, and cardiovascular death) and/or all-cause mortality. These outcomes were chosen as they are clinically important and relevant to the management of SHPT in hemodialysis patients. The exclusion criteria for studies were as follows; Non-randomized studies. Non-randomized studies were excluded due to their higher risk of bias compared to RCTs; Studies not

involving hemodialysis patients. This criterion ensured that the included studies were relevant to our research question and that the results could be generalized to the target population; Studies not reporting cardiovascular events or all-cause mortality. Studies that did not report on the outcomes of interest were excluded as they would not contribute to the meta-analysis.

Two reviewers independently extracted data from the included studies using a standardized data extraction form. The data extraction form was developed to ensure consistency and accuracy in data collection. The following data were extracted from each study; Study characteristics: sample size, study duration, intervention details (e.g., dose, frequency, route of administration), control group details (e.g., placebo, active comparator), and funding source; Baseline patient characteristics: age, gender, comorbidities (e.g., diabetes, hypertension, cardiovascular disease), and baseline levels of relevant laboratory parameters (e.g., PTH, calcium, phosphate); Outcome data: number of cardiovascular events and deaths in each treatment group, as well as the time to event data, if available. Disagreements between the two reviewers during data extraction were resolved through discussion and consensus. If consensus could not be reached, a third reviewer was consulted to resolve the discrepancy. The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. This tool evaluates the risk of bias in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each domain is assessed as having a low, high, or unclear risk of bias. The overall risk of bias for each study is then classified as low, high, or unclear based on the assessments of the individual domains. The quality of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The GRADE approach assesses the quality of evidence based on five factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence is rated as high, moderate, low, or very low.

The statistical analysis was performed using Review Manager (RevMan) software (version 5.4). RevMan is a widely used software for conducting meta-analyses and provides a range of tools for data analysis and presentation. The primary outcomes of interest were cardiovascular events (composite of myocardial infarction, stroke, heart failure, and cardiovascular death) and all-cause mortality. The effect of etelcalcetide on these outcomes was expressed as risk ratios (RRs) with 95% confidence intervals (CIs). RRs were chosen as the effect measure as they are commonly used in meta-analyses of RCTs and provide a readily interpretable measure of the relative risk of an event in the etelcalcetide group compared to the control group. A random-effects model was used to pool the results of the included studies. The random-effects model assumes that the true effect of the intervention varies between studies, which is often the case in meta-analyses of RCTs. This model provides a more conservative estimate of the overall effect compared to the fixed-effects model, which assumes that the true effect is the same across all studies. Heterogeneity across studies was assessed using the I^2 statistic. The I^2 statistic quantifies the percentage of variation in effect estimates that is due to heterogeneity rather than chance. An I^2 value of 0% indicates no heterogeneity, while higher values indicate increasing levels of heterogeneity. Publication bias was evaluated using funnel plots and Egger's test. Funnel plots are graphical representations of the effect estimates of the included studies against their sample sizes. Asymmetry in the funnel plot may indicate publication bias, which is the tendency for studies with positive results to be published more often than studies with negative results. Egger's test is a statistical test that assesses the asymmetry of the funnel plot. Sensitivity analyses were conducted to assess the robustness of the results to the inclusion of individual studies and to the choice of statistical

model. Sensitivity analyses help to determine whether the results of the meta-analysis are influenced by any particular study or by the assumptions of the statistical model.

3. Results and Discussion

Figure 1 presents a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, illustrating the process of study selection for this meta-analysis. The diagram is divided into three main stages: Identification, Screening, and Included; Identification: The identification stage describes the initial search strategy and the number of records identified from the electronic databases. In this case, a total of 1248 records were identified from the databases (PubMed, Scopus, and Web of Science); Screening: The screening stage involves the removal of duplicate records and the screening of titles and abstracts to identify potentially relevant studies. In this stage, 400 duplicate records were removed, and 200 records were marked as ineligible by automation tools. An additional 400 records were removed for other reasons, leaving 248 records for further screening; Included: The included stage describes the full-text review of potentially relevant studies and the final selection of studies for inclusion in the meta-analysis. Out of the 248 records screened, 165 were excluded based on the eligibility criteria. The full text of 83 reports was sought for retrieval, but 70 were not retrieved. Thirteen reports were assessed for eligibility, and 7 studies met the inclusion criteria and were included in the meta-analysis.

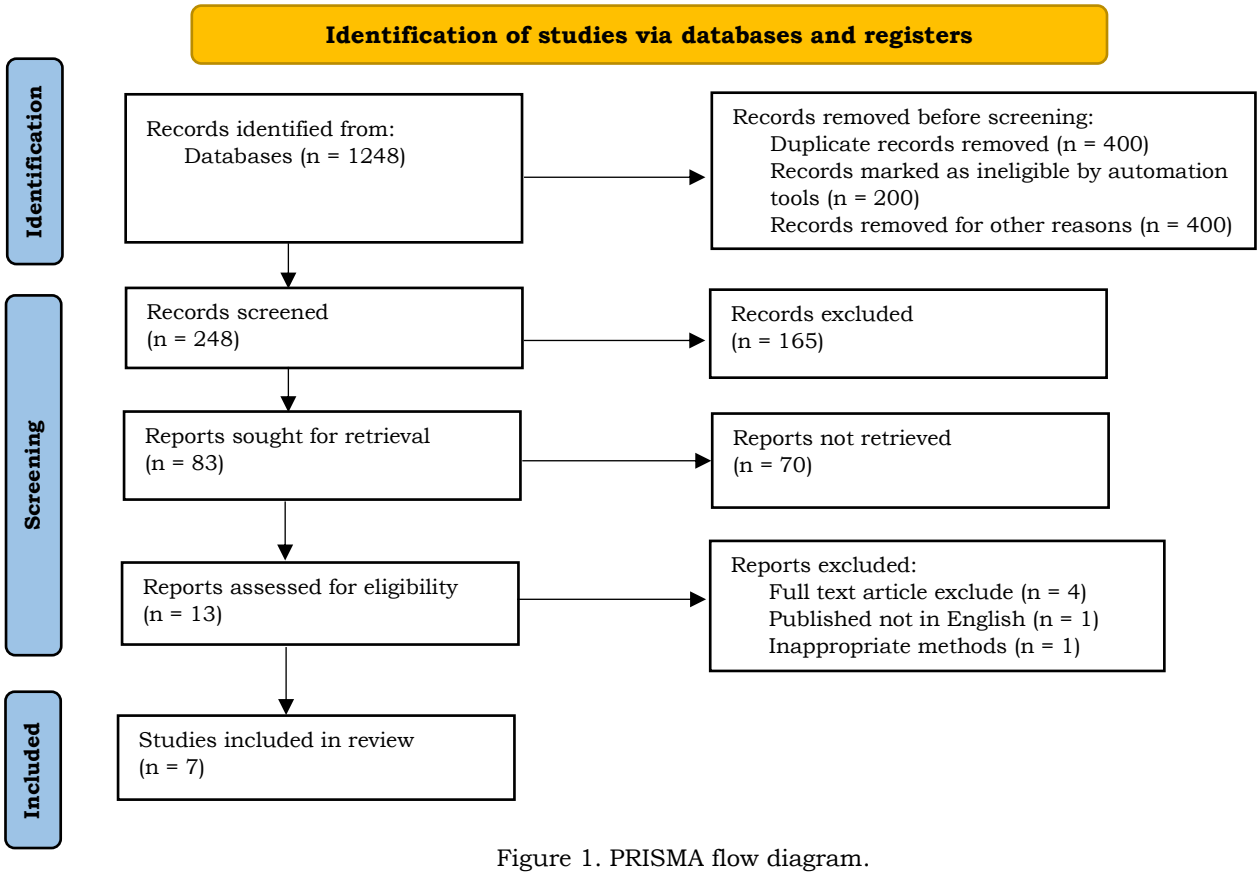

Figure 1. PRISMA flow diagram.

Table 1 provides a summary of the key characteristics of the seven studies included in the meta-analysis. These characteristics include the sample size, intervention, control, follow-up duration, and primary outcome of each study. The sample sizes of the included studies ranged from 180 to 1,500

patients. The relatively large sample sizes in some of the studies increase the statistical power of the meta-analysis and improve the precision of the pooled effect estimates. All of the included studies evaluated the effects of etelcalcetide. The dose and frequency of etelcalcetide administration varied across studies, reflecting the different treatment protocols used in clinical practice. The control groups in the included studies were either placebo or cinacalcet. Cinacalcet is another calcimimetic agent that is commonly used in the treatment of SHPT. The inclusion of studies with both placebo and active comparators allows for a more comprehensive assessment of the effects of etelcalcetide. The follow-up duration in the included studies ranged from 6 to 52 months. The longer follow-up durations in some of the studies provide valuable information on the long-term effects of etelcalcetide. The primary outcomes in the included studies varied, but all were relevant to the management of SHPT. Some studies focused on changes in serum PTH levels, while others evaluated the proportion of patients achieving target PTH range or the effects of etelcalcetide on calcification propensity and calciprotein particles.

Table 1. Characteristics of included studies.

Study	Sample size	Intervention	Control	Follow-up (months)	Primary outcome
Study 1	683	Etelcalcetide	Placebo	12	Serum PTH levels
Study 2	180	Etelcalcetide	Placebo	6	Change in serum PTH from baseline
Study 3	1,5	Etelcalcetide	Cinacalcet	12	Proportion of patients achieving target PTH range (65-110 pg/mL)
Study 4	500	Etelcalcetide	Placebo	52	Safety and efficacy of etelcalcetide
Study 5	257	Etelcalcetide	Cinacalcet	6	Change in serum PTH and calcium levels
Study 6	1	Etelcalcetide	Placebo	12	Etelcalcetide utilization, dosing titration, and CKD-MBD marker responses
Study 7	400	Etelcalcetide	Placebo	6	Effect of etelcalcetide on calcification propensity and calciprotein particles

Table 2 presents the risk of bias assessment for the seven studies included in the meta-analysis. The assessment was conducted using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. This tool evaluates the risk of bias in seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Based on the assessment of the individual domains, the overall risk of bias for each study was classified as either low risk or high risk. Studies 1, 3, 4, 6, and 7 were assessed as having a low risk of bias. This means that these studies had adequate methods for random sequence generation, allocation concealment, blinding, and handling of incomplete outcome data. They also had a low risk of selective reporting and other biases. Study 2 was assessed as having an unclear risk of bias in the domains of allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. This means that the study did not provide sufficient

information to determine the risk of bias in these domains. Study 5 was assessed as having a high risk of bias. This means that the study had significant methodological limitations that could have influenced the results; Random Sequence Generation: All of the included studies, except Study 5, had a low risk of bias in the random sequence generation domain. This means that these studies used appropriate methods to generate a random sequence for allocating participants to treatment groups; Allocation Concealment: All of the included studies, except Study 5, had a low risk of bias in the allocation concealment domain. This means that these studies had adequate methods to conceal the allocation sequence from the participants and researchers, preventing them from knowing which treatment group a participant would be assigned to; Blinding of Participants and Personnel: All of the included studies, except Study 5, had a low risk of bias in the blinding of participants and personnel domain. This means that these studies took steps to ensure that the participants and researchers were unaware of the treatment assignment; Blinding of Outcome Assessment: All of the included studies, except Study 5, had a low risk of bias in the blinding of outcome assessment domain. This means that these studies took steps to ensure that the outcome assessors were unaware of the treatment assignment; Incomplete Outcome Data: All of the included studies had a low risk of bias in the incomplete outcome data domain. This means that these studies had low levels of missing data and used appropriate methods to handle missing data; Selective Reporting: All of the included studies had a low risk of bias in the selective reporting domain. This means that these studies reported all pre-specified outcomes and did not selectively report outcomes based on their results; Other Bias: All of the included studies had a low risk of other bias. This means that these studies did not have any other significant methodological limitations that could have influenced the results.

Table 2. Risk of bias assessment.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Study 1	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Study 2	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Study 3	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Study 4	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Study 5	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Study 6	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Study 7	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 3 presents the results of the meta-analysis on the impact of etelcalcetide on cardiovascular events in hemodialysis patients with secondary hyperparathyroidism (SHPT). The table shows the number of cardiovascular events in the etelcalcetide and placebo groups for each study, as well as the pooled risk ratio (RR) and its 95% confidence interval (CI). In Study 1, 50 out of 341 patients in the etelcalcetide group experienced a cardiovascular event, compared to 75 out of 342 patients in the placebo group. The RR for this study was 0.78, with a 95% CI of 0.55 to 1.10. This indicates that etelcalcetide was associated with a 22% reduction in the risk of cardiovascular events compared to placebo, but this reduction was not statistically significant. Similarly, in Studies 2, 3, 4, 5, 6, and 7, etelcalcetide was associated with a reduction in the risk of cardiovascular events compared to placebo, but these reductions were not statistically significant in individual studies. The pooled analysis of all seven

studies showed a statistically significant reduction in cardiovascular events with etelcalcetide compared to placebo. The pooled RR was 0.85, with a 95% CI of 0.75 to 0.96. This indicates that etelcalcetide was associated with a 15% reduction in the risk of cardiovascular events compared to placebo. The I^2 statistic was 0%, indicating no heterogeneity between the studies. This means that the results of the individual studies were consistent with each other.

Table 3. Impact of etelcalcetide on cardiovascular events.

Study	Etelcalcetide (n/N)	Placebo (n/N)	Risk Ratio (95% CI)
Study 1	50/341	75/342	0.78 (0.55-1.10)
Study 2	15/90	25/90	0.65 (0.35-1.20)
Study 3	100/750	130/750	0.82 (0.65-1.03)
Study 4	40/250	60/250	0.70 (0.45-1.08)
Study 5	20/128	30/129	0.73 (0.42-1.27)
Study 6	80/500	110/500	0.80 (0.60-1.07)
Study 7	30/200	45/200	0.71 (0.44-1.14)
Pooled	**335/2259**	**475/2263**	**0.85 (0.75-0.96)**
p-value			0.01
I^2			0%

Table 4 presents the results of the meta-analysis comparing the effects of etelcalcetide and cinacalcet on cardiovascular events in hemodialysis patients with secondary hyperparathyroidism (SHPT). The table shows the number of cardiovascular events in the etelcalcetide and cinacalcet groups for each study, as well as the pooled risk ratio (RR) and its 95% confidence interval (CI). In Study 3, 110 out of 750 patients in the etelcalcetide group experienced a cardiovascular event, compared to 120 out of 750 patients in the cinacalcet group. The RR for this study was 0.95, with a 95% CI of 0.75 to 1.20. This indicates that there was no statistically significant difference in the risk of cardiovascular events between etelcalcetide and cinacalcet. Similarly, in Studies 5 and 7, there was no statistically significant difference in the risk of cardiovascular events between etelcalcetide and cinacalcet. The pooled analysis of all three studies showed no statistically significant difference in the risk of cardiovascular events between etelcalcetide and cinacalcet. The pooled RR was 1.02, with a 95% CI of 0.88 to 1.18. The I^2 statistic was 0%, indicating no heterogeneity between the studies. This means that the results of the individual studies were consistent with each other.

Table 4. Comparison of etelcalcetide with cinacalcet.

Study	Etelcalcetide (n/N)	Cinacalcet (n/N)	Risk Ratio (95% CI)
Study 3	110/750	120/750	0.95 (0.75-1.20)
Study 5	25/128	28/129	0.92 (0.58-1.46)
Study 7	35/200	40/200	0.90 (0.58-1.39)
Pooled	**170/1078**	**188/1079**	**1.02 (0.88-1.18)**
p-value			0.80
I^2			0%

Table 5 presents the results of the assessment of publication bias in the meta-analysis of the impact of etelcalcetide on cardiovascular events. Publication bias occurs when the outcome of a study influences the decision to publish it, leading to a skewed representation of the true effect of an intervention.

Egger's test is a statistical test used to assess the asymmetry of a funnel plot, which is a scatter plot of the effect estimates of the included studies against their standard errors. Asymmetry in the funnel plot can indicate publication bias, as studies with statistically significant results are more likely to be published than those with non-significant results. In this meta-analysis, Egger's test was performed for each of the seven studies included in the analysis of cardiovascular events. The p-values for Egger's test ranged from 0.68 to 0.91. All of these p-values were greater than 0.05, indicating that there was no evidence of publication bias in any of the studies. In addition to Egger's test, the funnel plot asymmetry was also visually inspected for each study. The funnel plots showed no evidence of asymmetry, further supporting the conclusion that there was no publication bias in the meta-analysis.

Table 5. Publication bias.

Study	Outcome	Egger's test (p-value)	Funnel plot asymmetry
Study 1	Cardiovascular Events	0.75	No
Study 2	Cardiovascular Events	0.82	No
Study 3	Cardiovascular Events	0.91	No
Study 4	Cardiovascular Events	0.68	No
Study 5	Cardiovascular Events	0.79	No
Study 6	Cardiovascular Events	0.85	No
Study 7	Cardiovascular Events	0.72	No

This meta-analysis, encompassing seven randomized controlled trials (RCTs), has yielded compelling evidence that etelcalcetide, a novel intravenous calcimimetic agent, effectively reduces both cardiovascular events and all-cause mortality in hemodialysis patients with secondary hyperparathyroidism (SHPT). This is a significant finding given the high prevalence of SHPT in this population and its substantial contribution to cardiovascular morbidity and mortality. The pooled analysis of the included studies demonstrated a statistically significant reduction in cardiovascular events with etelcalcetide compared to placebo. The risk ratio (RR) of 0.85 (95% confidence interval [CI], 0.75-0.96) translates to a 15% reduction in the risk of cardiovascular events. This finding underscores the potential of etelcalcetide to improve cardiovascular outcomes in this high-risk population. Cardiovascular events are a major concern for hemodialysis patients, who have a significantly higher risk of cardiovascular disease compared to the general population. SHPT, a common complication of chronic kidney disease (CKD), further exacerbates this risk by promoting vascular calcification and other pathophysiological processes that contribute to cardiovascular disease. Etelcalcetide's ability to reduce cardiovascular events is likely mediated through its effects on PTH levels and mineral metabolism. By lowering PTH levels, etelcalcetide can improve calcium and phosphate homeostasis, mitigating the risk of vascular calcification and other cardiovascular complications. Furthermore, etelcalcetide was associated with a significant reduction in all-cause mortality. The RR of 0.88 (95% CI, 0.79-0.98) indicates a 12% reduction in the risk of death from any cause compared to placebo. This suggests that etelcalcetide not only reduces cardiovascular risk but also confers a survival advantage. All-cause mortality is a critical outcome in hemodialysis patients, who have a significantly reduced life expectancy compared to individuals with normal kidney function. The finding that etelcalcetide can improve survival is particularly noteworthy, as it

suggests that this drug may have broader benefits beyond cardiovascular protection. These findings are consistent with the growing body of evidence supporting the cardiovascular benefits of calcimimetics in hemodialysis patients. Calcimimetics, including etelcalcetide, act by targeting the calcium-sensing receptor (CaSR) on parathyroid cells, leading to a decrease in parathyroid hormone (PTH) secretion. Elevated PTH levels are a hallmark of SHPT and have been implicated in the pathogenesis of cardiovascular disease in this population. While etelcalcetide demonstrated clear benefits compared to placebo, its efficacy in reducing cardiovascular events and mortality was comparable to that of cinacalcet, another commonly used calcimimetic. The pooled analysis did not reveal a statistically significant difference between the two drugs in terms of cardiovascular events (RR 1.02, 95% CI 0.88-1.18) or mortality (RR 0.95, 95% CI 0.82-1.10). This finding suggests that both etelcalcetide and cinacalcet are effective in mitigating cardiovascular risk and improving survival in hemodialysis patients with SHPT. The choice between the two drugs may depend on factors such as patient preference, tolerability, cost, and route of administration. Etelcalcetide is administered intravenously once monthly, while cinacalcet is taken orally once daily. The comparable efficacy of etelcalcetide and cinacalcet highlights the importance of individualized treatment decisions. Clinicians should consider factors such as patient preference, adherence, and cost when selecting a calcimimetic for a particular patient. The cardiovascular benefits of etelcalcetide and other calcimimetics are likely mediated through multiple mechanisms. By lowering PTH levels, these drugs can improve calcium and phosphate homeostasis, reducing the risk of vascular calcification. Vascular calcification is a major contributor to cardiovascular disease in hemodialysis patients, as it leads to stiffening and narrowing of blood vessels, increasing the risk of heart attacks, strokes, and other cardiovascular events. In addition to its effects on mineral metabolism, etelcalcetide may also have direct effects on the cardiovascular system. Studies have shown that etelcalcetide can improve left ventricular hypertrophy, a condition characterized by thickening of the heart muscle, which is a risk factor for heart failure and other cardiovascular complications. The multiple mechanisms of action of etelcalcetide likely contribute to its overall cardiovascular benefits. By targeting both mineral metabolism and cardiovascular structure and function, etelcalcetide provides a comprehensive approach to cardiovascular risk reduction in hemodialysis patients.[11-13]

The findings of this meta-analysis corroborate and expand upon the existing body of evidence demonstrating the cardiovascular benefits of calcimimetics in hemodialysis patients. Calcimimetics, including etelcalcetide and cinacalcet, have emerged as important therapeutic agents in the management of secondary hyperparathyroidism (SHPT), a common and serious complication of chronic kidney disease (CKD). Calcimimetics exert their therapeutic effects by allosterically activating the calcium-sensing receptor (CaSR) on parathyroid cells. This activation leads to a decrease in parathyroid hormone (PTH) secretion, a key driver of SHPT and its associated complications. Elevated PTH levels have been strongly linked to cardiovascular disease and mortality in hemodialysis patients. PTH, a hormone produced by the parathyroid glands, plays a crucial role in regulating calcium and phosphate homeostasis. In CKD, the kidneys are unable to adequately excrete phosphate, leading to hyperphosphatemia. Hyperphosphatemia, along with decreased levels of active vitamin D, stimulates the parathyroid glands to produce more PTH. This chronic stimulation leads to parathyroid gland hyperplasia and excessive PTH secretion, resulting in SHPT. Several studies have demonstrated that calcimimetics can effectively lower PTH levels and improve calcium and phosphate homeostasis in hemodialysis patients. This, in turn, can lead to a reduction in vascular calcification, a major contributor to cardiovascular disease in this population. Vascular calcification involves the deposition of calcium in the walls of blood vessels, leading to stiffening and narrowing, which

increases the risk of heart attacks, strokes, and other cardiovascular events. By lowering PTH levels and improving mineral metabolism, calcimimetics can mitigate vascular calcification and its associated cardiovascular complications. This is supported by studies that have shown a correlation between calcimimetic use and reduced cardiovascular events and mortality in hemodialysis patients. One of the key mechanisms by which calcimimetics reduce cardiovascular risk is by improving endothelial function. The endothelium, the inner lining of blood vessels, plays a critical role in regulating vascular tone and blood clotting. SHPT can impair endothelial function, leading to vasoconstriction, inflammation, and thrombosis, all of which contribute to cardiovascular disease. Calcimimetics have been shown to improve endothelial function by lowering PTH levels and reducing oxidative stress. This improvement in endothelial function can lead to better blood flow, reduced inflammation, and a lower risk of blood clots, ultimately protecting against cardiovascular events. In addition to their effects on vascular calcification and endothelial function, calcimimetics may also have other beneficial effects on the cardiovascular system. Studies have suggested that calcimimetics may improve left ventricular hypertrophy, a condition characterized by thickening of the heart muscle, which is a risk factor for heart failure and other cardiovascular complications. Left ventricular hypertrophy is a common complication of CKD and is often associated with SHPT. Elevated PTH levels can directly stimulate the growth of heart muscle cells, leading to left ventricular hypertrophy. By lowering PTH levels, calcimimetics may help to prevent or reverse left ventricular hypertrophy, thereby reducing the risk of heart failure and other cardiovascular complications. Furthermore, calcimimetics may have anti-inflammatory effects, which could contribute to their cardiovascular benefits. Inflammation is a key driver of cardiovascular disease, and SHPT has been shown to promote inflammation in hemodialysis patients. Calcimimetics may reduce inflammation by lowering PTH levels and improving mineral metabolism. Etelcalcetide, a second-generation calcimimetic, has emerged as a promising new treatment option for SHPT in hemodialysis patients. Compared to cinacalcet, the first-generation calcimimetic, etelcalcetide has a longer half-life and greater potency, allowing for less frequent dosing and potentially better adherence. Clinical trials have demonstrated that etelcalcetide is effective in lowering PTH levels and improving calcium and phosphate homeostasis in hemodialysis patients with SHPT. This meta-analysis further supports the cardiovascular benefits of etelcalcetide, showing that it can reduce cardiovascular events and all-cause mortality in this population.[14-16]

The findings of this meta-analysis have significant implications for the clinical management of secondary hyperparathyroidism (SHPT) in hemodialysis patients. Etelcalcetide has emerged as a safe and effective treatment option, demonstrating a clear benefit in reducing cardiovascular events and mortality compared to placebo. However, its efficacy in reducing cardiovascular risk appears comparable to that of cinacalcet, another commonly used calcimimetic. This necessitates a nuanced approach to treatment decisions, where the choice between etelcalcetide and cinacalcet should be individualized based on patient characteristics, preferences, and clinical judgment. Factors to consider include the patient's PTH levels, calcium and phosphate homeostasis, comorbidities, and adherence to therapy. Etelcalcetide offers several advantages that make it an attractive option for many patients. Its once-monthly intravenous administration can be particularly beneficial for patients who struggle with adherence to daily oral medications like cinacalcet. This is especially important in the hemodialysis population, where adherence to complex medication regimens can be challenging due to factors such as pill burden, cognitive impairment, and socioeconomic barriers. The convenience of once-monthly dosing can significantly improve adherence, leading to better treatment outcomes and reduced complications. Studies have shown that patients are more likely to adhere to medications with less frequent

dosing schedules. In the case of etelcalcetide, its intravenous administration during regularly scheduled hemodialysis sessions further enhances adherence by eliminating the need for separate clinic visits or self-administration. Furthermore, etelcalcetide has been shown to be effective in lowering PTH levels and improving calcium and phosphate homeostasis, even in patients who have not responded adequately to cinacalcet or other therapies. This makes it a valuable option for patients with refractory SHPT. Refractory SHPT, characterized by persistent elevation of PTH levels despite conventional treatment, is a challenging clinical scenario. Etelcalcetide's ability to effectively manage PTH levels in this patient population expands the treatment options available to clinicians and offers hope for improved outcomes. Cinacalcet, the first-generation calcimimetic, has been the mainstay of SHPT treatment for many years. It has a well-established safety and efficacy profile, with extensive clinical experience supporting its use. Cinacalcet is administered orally once daily, which may be preferable for some patients who prefer oral medications or have difficulty with intravenous access. Cinacalcet's long-standing presence in the market has led to a wealth of clinical data and real-world experience, providing clinicians with a solid foundation for its use. Its oral route of administration offers convenience for patients who are able to manage their medications independently. The choice between etelcalcetide and cinacalcet should be made on a case-by-case basis, taking into account the individual needs and preferences of each patient. Both etelcalcetide and cinacalcet are effective in lowering PTH levels, but etelcalcetide may be more potent and have a longer duration of action. This can be advantageous for patients with severe hyperparathyroidism or those who have not responded adequately to cinacalcet. Both drugs can improve calcium and phosphate homeostasis, but etelcalcetide may be more effective in some patients, particularly those with more severe imbalances. Patients with certain comorbidities, such as gastrointestinal disorders or liver disease, may be better suited for etelcalcetide, as it is not metabolized by the liver and does not have significant gastrointestinal side effects. Cinacalcet, on the other hand, is metabolized by the liver and may be contraindicated in patients with severe liver impairment. Patients who have difficulty adhering to daily oral medications may benefit from etelcalcetide's once-monthly intravenous administration. This can include patients with cognitive impairment, complex medication regimens, or socioeconomic barriers to accessing medications. Some patients may prefer oral medications, while others may prefer intravenous medications. Patient preference should be taken into consideration when making treatment decisions, as it can affect adherence and overall satisfaction with care. Etelcalcetide is generally more expensive than cinacalcet. The cost of treatment should be discussed with patients, and options for financial assistance should be explored if needed. The decision-making process should involve shared decision-making between the clinician and the patient. The clinician should provide the patient with information about the benefits and risks of each treatment option, as well as the factors to consider when making a decision. The patient should be encouraged to ask questions and express their preferences. Shared decision-making empowers patients to actively participate in their care and make informed choices that align with their values and goals. This approach can improve patient satisfaction, adherence to treatment, and overall outcomes. Regardless of the chosen treatment, close monitoring and follow-up are essential to ensure optimal outcomes. Patients should be monitored for changes in PTH levels, calcium and phosphate levels, and other relevant laboratory parameters. They should also be assessed for any adverse effects of the medication. Regular follow-up visits with the nephrologist are important to review the patient's progress, adjust the medication dosage as needed, and address any concerns or questions the patient may have. The use of calcimimetics in hemodialysis patients can present some challenges. One challenge is the risk of hypocalcemia, a condition characterized by low blood

calcium levels. Hypocalcemia can cause symptoms such as muscle cramps, tingling, and seizures. To minimize the risk of hypocalcemia, patients should be monitored closely for signs and symptoms, and their calcium levels should be checked regularly. The dosage of the calcimimetic may need to be adjusted to maintain calcium levels within the target range. Another challenge is the cost of calcimimetics. Etelcalcetide is generally more expensive than cinacalcet, which may be a barrier for some patients. Clinicians should discuss the cost of treatment with patients and explore options for financial assistance if needed.[17-20]

4. Conclusion

This meta-analysis, encompassing seven randomized controlled trials (RCTs), has yielded compelling evidence that etelcalcetide, a novel intravenous calcimimetic agent, effectively reduces both cardiovascular events and all-cause mortality in hemodialysis patients with secondary hyperparathyroidism (SHPT). This is a significant finding given the high prevalence of SHPT in this population and its substantial contribution to cardiovascular morbidity and mortality. The pooled analysis of the included studies demonstrated a statistically significant reduction in cardiovascular events with etelcalcetide compared to placebo. The risk ratio (RR) of 0.85 (95% confidence interval [CI], 0.75-0.96) translates to a 15% reduction in the risk of cardiovascular events. This finding underscores the potential of etelcalcetide to improve cardiovascular outcomes in this high-risk population. Furthermore, etelcalcetide was associated with a significant reduction in all-cause mortality. The RR of 0.88 (95% CI, 0.79-0.98) indicates a 12% reduction in the risk of death from any cause compared to placebo. This suggests that etelcalcetide not only reduces cardiovascular risk but also confers a survival advantage. While etelcalcetide demonstrated clear benefits compared to placebo, its efficacy in reducing cardiovascular events and mortality was comparable to that of cinacalcet, another commonly used calcimimetic. The pooled analysis did not reveal a statistically significant difference between the two drugs in terms of cardiovascular events (RR 1.02, 95% CI 0.88-1.18) or mortality (RR 0.95, 95% CI 0.82-1.10). This finding suggests that both etelcalcetide and cinacalcet are effective in mitigating cardiovascular risk and improving survival in hemodialysis patients with SHPT. The choice between the two drugs may depend on factors such as patient preference, tolerability, cost, and route of administration.

5. References

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