Lessons from effect of etelcalcetide on left ventricular hypertrophy in patients with end-stage kidney disease

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Purpose of review
Patients with end-stage kidney disease (ESKD) frequently develop left ventricular hypertrophy (LVH), which is associated with an exceptionally high risk of cardiovascular events and mortality. This review focuses on interventional studies that modify levels of fibroblast growth factor 23 (FGF23) and examine effects on myocardial hypertrophy, cardiovascular events and mortality.

Recent findings
Quantitative evaluations of trials of calcimimetics found no effects on cardiovascular events and cardiovascular and all-cause mortality when compared with placebo. However, a recent randomized, controlled trial of etelcalcetide versus alfacalcidol showed that etelcalcetide effectively inhibited the progression of LVH in comparison to vitamin D in patients on haemodialysis after 1 year of treatment. Prior to that, oral calcimimetic treatment has already been shown to reduce left ventricular mass in patients on haemodialysis, whereas treatment with active vitamin D or mineralocorticoids was ineffective in patients with ESKD.

Summary
Data from a recent trial of etelcalcetide on LVH suggest that FGF23 may be a possible therapeutic target for cardiac risk reduction in patients on haemodialysis. If these findings are confirmed by further research, it might be speculated that a treatment shift from active vitamin D towards FGF23-lowering therapy may occur in patients on haemodialysis.

Keywords
etelcalcetide, fibroblast growth factor 23, haemodialysis, myocardial hypertrophy

INTRODUCTION
In comparison to the general population, patients with chronic kidney disease (CKD) have a substantially higher risk for cardiovascular disease and mortality, making CKD a major public health problem [1]. In addition to the traditional atherosclerosis risk factors, which are manifested at a high prevalence in this population, CKD patients also commonly manifest left ventricular hypertrophy (LVH) [2]. LVH is associated with an increased risk of heart failure, diastolic dysfunction and cardiac arrhythmia in the form of sudden cardiac death, which likely results from sub-endocardial ischemia and increased proarrhythmic sensitivity [3].

It is estimated that up to 74% of patients have LVH at the beginning of dialysis treatment, thereby curtailting their 5-year survival prospects by approximately 55% [3]. Until recently, prevention of LVH progression in patients with CKD was not possible [4**].

LVH forms early during the development of CKD and worsens with decreasing renal function [5]. Its development is a response to multifactorial processes and its main drivers in patients on haemodialysis are known to be chronic fluid overload, intradialytic weight gain, pressure overload and haemodynamic fluctuations during haemodialysis.
treatment [6]. This review focuses on recent studies in this field. We discuss potential benefits of each intervention on three clinically important study outcomes: cardiovascular events (myocardial infarction, unstable angina, ischemic stroke and heart failure), mortality and LVH. We place a special emphasis on the contribution of elevated FGF23 to these adverse clinical outcomes.

**FIBROBLAST GROWTH FACTOR 23 INDUCED LEFT VENTRICULAR HYPERTROPHY**

FGF23 is a phosphaturic glycoprotein, which is produced and secreted by osteoblasts and osteocytes [7]. It is induced by PTH, vitamin D, dietary phosphate, aldosterone as well as proinflammatory cytokines. In the sense of a negative feedback loop, FGF23 in turn inhibits PTH and vitamin D synthesis [8,9]. It was shown to be an independent risk factor for cardiovascular and all-cause mortality [10]. The primary link between FGF23 and cardiovascular complications in both predialysis as well as dialysis patients is LVH. FGF23 levels rise progressively with declining renal function [11]. Together with rising FGF23, the left ventricular mass index (LVMI) increases and so does the occurrence of both eccentric and concentric cardiac hypertrophy [12]. In-vitro and animal studies provide possible explanations for the direct association between FGF23 and LVH. On the one hand, it has been postulated that FGF23 exhibits a direct effect on the myocardial cell hypertrophy via an activation of the FGF receptor 4 (FGFR4). The binding of FGF23 to FGFR4 leads to an activation of the PLCgamma/Calcineurin/NFAT-signalling axis, inducing hypertrophic growth of cardiac myocytes [13]. On the other hand, it has been proposed by other investigators that the pro-hypertrophic action of FGF23 on cardiac myocytes is a result of FGF23-induced sodium retention, fluid overload and arterial hypertension [14,15].

FGF23 levels are known to be modified by medication used for the therapy of sHPT. It was previously reported that its levels rise under the use of vitamin D analogues by at least 40% while they decrease under the calcimimetic therapy with cinacalcet by over 30% [16,17]. This was confirmed by the PARADIGM trial, which studied cinacalcet versus vitamin D treatment over 1 year. In addition, both treatments showed similar reductions in iPTh [18].

**THE EFFECT OF CALCIMIMETIC TREATMENT ON ALL-CAUSE MORTALITY, CARDIOVASCULAR MORTALITY AND CARDIOVASCULAR EVENTS**

Unlike in the primary analysis of the EVOLVE trial, a secondary analysis of patients dichotomized according to the achieved FGF23 reduction showed that patients with a more than 30% FGF23 reduction exhibited a lower cardiovascular event rate of cardiovascular death and major cardiovascular events [19]. However, so far, a cardiovascular risk reduction through calcimimetic therapy per se has not been shown.

Palmer et al. [20**] recently published a review and meta-analysis on calcimimetic agents on sHPT. This work primarily focused on the achievement of a target reduction in iPTh and incidence of hypocalcaemia by cinacalcet, etelcalcetide (ETL) and evocalcet. As additional outcomes, all-cause mortality, cardiovascular mortality and heart failure were analysed. The analysis of 30 trials for all-cause mortality showed no detectable differences between interventions. In addition, cinacalcet versus placebo showed no difference in the rate of cardiovascular mortality. Ten trials were used for the analysis for heart failure, also showing no difference between treatments. The authors concluded that many treatment estimates were imprecise, which may have led to the reported uncertainty and low confidence of findings.

**TREATMENT-INDUCED MODIFICATION OF LEFT VENTRICULAR HYPERTROPHY IN HAEMODIALYSIS**

The hypothesis that FGF23 reduction by calcium sensitizers could lead to a reduced progression of LVH in patients on dialysis was evaluated in a recent trial. [4**]. One year of ETL treatment led to a decrease in FGF23 and an inhibition of LVMI progression, while further increase of FGF23 and subsequently LVH was observed under active vitamin D treatment with alfacalcidol. This result is in line with the findings of a previously published much smaller trial by Choi et al. [21]. The investigators...
showed a reduction of LVMI determined by echocardiography through 20 weeks of oral calcimimetic treatment in 12 haemodialysis patients (LVMI 162.8 ± 76.9 versus 138.9 ± 44.6 g/m² posttreatment) [22]. LVH has also been a target for other therapeutic options in haemodialysis patients. A randomized clinical trial published a decade ago compared 125 versus 120 haemodialysis patients receiving frequent versus conventional dialysis (six versus three sessions per week). A risk reduction regarding the composite outcomes of death or change in LVM resulted from frequent haemodialysis treatments [23]. In light of a very challenging practical implication of such a frequent and intense therapy, other options were studied. A more recent trial compared the effects of spironolactone versus placebo on the evolution of LVH in 97 haemodialysis patients [24]. After 40 weeks of treatment, LVMI remained constant with no significant differences between treatment groups. No influence on LVMI progression was also shown in a recent trial, which included 99 haemodialysis patients from New Zealand comparing low-sodium dialysate with conventional dialysate for 12 months [25*].

Therefore, a therapeutic modification of LVMI has proven to be rather difficult in this specific patient collective, but calcimimetic treatment could possibly present a promising new option in this field.

**SHOULD CALCIMIMETIC TREATMENT BE MORE FREQUENTLY USED AND TARGETED AT FGF23 LEVELS?**

In an editorial published by Murray et al. [26*] in the same issue of *Circulation Research*, it was discussed that perhaps FGF23 could pose a more suitable target regarding the modification of cardiovascular risk in end-stage kidney disease (ESKD) than iPTH, the measurement of which is performed on a regular basis in haemodialysis wards, aiming at its reduction. Despite a number of clinical practice guidelines, advising on PTH control, no exact treatment strategy or even ideal PTH target are described. Wolf postulates that the current approach might omit those patients, who show elevated levels of FGF23, while their PTH levels are within or below the target range. On the basis of that knowledge, he suggests a randomized trial using ETL versus placebo, titrated to FGF23. The outcomes of this trial would be the hard endpoints: cardiovascular mortality, hospitalization for heart failure and atrial fibrillation.

Outside of the described potential trial, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines already provide room for an increased use of calcimimetics for the treatment of sHPT, as vitamin D analogues are not recommended as first-line therapy, but can merely be considered as a therapeutic option among others. On the basis of the recent findings on FGF23-induced LVH, it may be interesting to regularly quantify FGF23 levels in patients on dialysis and eventually also patients with CKD not on dialysis. However, a clear recommendation would necessitate further studies. Known problems with treatment and drug adherence in patients on dialysis led to the suggestion that oral therapy may not always be preferred over systemically administered drugs post dialysis such as ETL [27,28].

**NEW INSIGHTS ON THE ASSOCIATION OF VITAMIN D ANALOGUES WITH CARDIAC HEALTH**

Our recent study observed an increase of LVMI in patients on maintenance haemodialysis that have been treated with alfacalcidol for 1 year [4**], although it remains unclear whether this merely resulted from the natural course of LVH progression under haemodialysis or if the active vitamin D treatment was an effect modifier.

Vitamin D deficiency is known to be linked with cardiovascular disease as well as total mortality in the general population and its prevalence is even higher in CKD patients [29]. Therefore, its negative impact on cardiovascular health is generally thought to be even greater than the general population [30]. Vitamin D deficiency was shown to be independently related to LVH progression in ESKD patients [31,32]. The PRIMO trial investigated the impact of a 48-week active vitamin D paricalcitol versus placebo treatment in CKD patients with mild to moderate LVH with CMR. Despite the previously described association between vitamin D and LVH in CKD, no significant difference in the change of LVMI between the two groups was found [33]. It is important to point out though that the PRIMO study investigated a patient collective with a GFR of 15–60 ml/min/1.73 m² not on dialysis.

In 2019, Manson et al. [34] published the results of a US-wide, randomized, placebo-controlled trial analysing the effects of cholecalciferol for the prevention of cardiovascular disease among the general population above the age of 50 without CKD. They showed that a supplementation with vitamin D did not result in a lower incidence of major cardiovascular events or death from cardiovascular causes.

In order to verify that vitamin D treatment does not additionally contribute to LVH progression in ESKD, a randomized controlled trial would be required, which interestingly enough has not been conducted yet. Some investigators say because some institutional review boards would consider such an
application unethical because of the lack of equipoise. However, by looking carefully at the available data from observational studies, it becomes evident that such a trial is not at all unethical and in fact should be performed rather soon to prevent potential futility of widely used treatment recommendations with vitamin D for the reduction of LVH and cardiovascular events in dialysis patients.

CONCLUSION
LVH poses a major risk factor leading to increased cardiovascular morbidity and mortality in ESKD. Until recently, no prophylactic and therapeutic interventions were available. Even though, so far, there is little evidence for a decreased risk of major cardiovascular endpoints through calcimimetic treatment, intravenous ETL was shown to inhibit a further progression of LVH in haemodialysis through FGF23 reduction. This finding supports the evidence that FGF23 has a direct effect on the pathogenesis of myocardial hypertrophy and could be a promising target for therapeutic intervention.

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Conflicts of interest
Dr Do¨rr and Dr Oberbauer have a patent ‘Methods of treating left ventricle hypertrophy’.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

1. Hostetter TH. Chronic kidney disease predicts cardiovascular disease. N Engl J Med 2004; 351:1344–1346.
2. Gutierrez OM, Januzzi JL, Isakova T, et al. Fibroblast growth factor-23 and left ventricular hypertrophy in chronic kidney disease. Circulation 2009; 119:2545–2552.
3. Stevens SM, Reiner K, Chugh SS. Increased left ventricular mass as a predictor of sudden cardiac death: is it time to put it to the test? Circ Arrhythm Electrophysiol 2013; 6:212–217.
4. Do¨rr K, Kammr M, Reindl-Schwaighofer R, et al. Randomized trial of etelcalcetide for cardiac hypertrophy in hemodialysis. Circ Res 2021; 11:1616–1625.
5. McCullough PA, Chan CT, Weinhandl ED, et al. Intensive hemodialysis, left ventricular hypertrophy, and cardiovascular disease. Am J Kidney Dis 2016; 68:S5–S14.
6. Katz AM. Maladaptive growth in the failing heart: the cardiomyopathy of overload. Cardiovasc Drugs Ther 2002; 16:245–249.
7. Erben RG. Physiological actions of fibroblast growth factor-23. Front Endocrinol (Lausanne) 2018; 9:267.
8. Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 2004; 19:429–435.
9. Levy M. Posttransplant hypophosphatemia. Kidney Int 2001; 59:2377–2387.
10. Isakova T, Xie H. Chronic Renal Insufficiency Cohort (CRIC) Study Group., Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. J Am Med Assoc 2011; 305:2432–2439.
11. Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. Kidney Int 2011; 112:1370–1378.
12. Paul C, Amaral AP, Ososuke B, et al. FGF23 induces left ventricular hypertrophy. J Clin Investigation 2011; 121:6393–6408.
13. Di Marco GS, Reuter S, Kentrup D, et al. Treatment of established left ventricular hypertrophy with fibroblast growth factor receptor blockade in an animal model of CKD. Nephrol Dial Transplant 2014; 29:2028–2035.
14. Andrikhova O, Smorodchenko A, Egerbacher M, et al. FGF23 promotes renal calcium reabsorption through the TRPV5 channel. EMBO J 2014; 33:229–246.
15. Andrikhova O, Slavic S, Smorodchenko A, et al. FGF23 regulates renal sodium handling and blood pressure. EMBO Mol Med 2014; 6:744–750.
16. Sprague SM, Wetmore JB, Gurevich K, et al. Effect of cinacalcet and Vitamin D analogs on fibroblast growth factor-23 during the treatment of secondary hyperparathyroidism. Clin J Am Soc Nephrol 2015; 10:1021–1030.
17. Kim HJ, Kim H. The Cinacalcet study for Peritoneal Dialysis Patients In Double Arm on the Loewing Effect Of IPTH Level (CUPID) Study Group. Cinacalcet lowering of serum fibroblast growth factor-23 concentration may be independent from serum Ca, P, PTH and dose of active vitamin D in peritoneal dialysis patients: a randomized controlled study. BMC Nephrol 2013; 14:112.
18. Wetmore JB, Gurevich K, Sprague S, et al. A randomized trial of cinacalcet versus Vitamin D analogs as monotherapy in secondary hyperparathyroidism (PARADIGM): Clin J Am Soc Nephrol 2015; 10:1031–1040.
19. Moe SM, Chertow GM, Parfrey PS, et al. Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. Circulation 2015; 132:27–30.
20. Palmer SC, Mavridis D, Johnson DW, et al. Comparative effectiveness of calcimimetic agents for secondary hyperparathyroidism in adults: a systematic review and network meta-analysis. Am J Kidney Dis 2020; 76:321–330.
21. Choi SR, Lim JH, Kim MY, et al. Cinacalcet improves endothelial dysfunction and cardiac hypertrophy in patients on hemodialysis with secondary hyperparathyroidism. Nephron Clin Pract 2012; 122:1–8.
22. Stewart GA, Foster J, Cowan M, et al. Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. Kidney Int 1999; 56:2248–2253.
23. Trial Group PHN, Chertow GM, Levin NW, et al. In-center hemodialysis six times per week versus three times per week. N Engl J Med 2010; 24:2287–2300.
24. Hammer F, Malzahn U, Donhauser J, et al. A randomized controlled trial of the effect of spironolactone on left ventricular mass in hemodialysis patients. Kidney Int 2019; 95:983–991.
25. Marshall MR, Vandal AC, de Zayas JR, et al. Effect of low-sodium versus conventional sodium dialysate on left ventricular mass in home and self-care satellite facility hemodialysis patients: a randomized clinical trial. J Am Soc Nephrol 2020; 5:1078–1089.

This trial is one of the few recent clinical studies aiming at reducing left ventricular mass in haemodialysis patients by analysing the effect of different sodium dialysate. Similar to the trial by our study group, cardiac MRI was used to evaluate LVM.
26. Murray SL, Wolf M. Pivoting from PTH to FGF23 to mend breaking hearts on dialysis. Circ Res 2021; 11:1626–1628. This is an editorial published in the same issue of Circulation Research as the study by Dörr et al. [4]. They discuss the role of FGF23 as a novel target regarding the modification of cardiovascular risk in ESKD.

27. Gincherman Y, Moloney K, McKee C, et al. Assessment of adherence to cinacalcet by prescription refill rates in hemodialysis patients. Hemodial Int 2010; 14:68–72.

28. Russo D, Tripodi R, Malberti F, et al. Etelcalcetide in patients on hemodialysis with severe secondary hyperparathyroidism. Multicenter study in ‘Real Life’. J Clin Med 2019; 8:E1066.

29. Quailes LD. Endocrine functions of bone in mineral metabolism regulation. J Clin Invest 2008; 118:3820–3828.

30. Autor P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. JAMA Intern Med 2007; 167:1730–1737.

31. Stolarz-Skrzypek K, Olszanecka A, Wojciechowska W, et al. Vitamin D is independently related to left ventricular hypertrophy in hypertensive patients, whereas effect of parathyroid hormone on left ventricular mass is mediated by blood pressure. Eur Heart J 2013; 34:2362.

32. Di Lullo L, Gorini A, Russo D, et al. Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. CardioRenal Med 2015; 5:254–266.

33. Thadhani R, Appelbaum E, Solomon SD. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. J Am Med Assoc 2012; 307:674–684.

34. Manson JE, Cook RC, Lee I, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med 2019; 381:13–25.