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A Fresh Look

Brandi, L

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Review Article

Alfacalcidol in CKD-MBD - A Fresh Look

Brandt L*

Department of Cardiology, Nephrology and Endocrinology, University of Copenhagen, Denmark

*Corresponding author

Lisbet Brandt, Department of Cardiology Nephrology and Endocrinology H0642, North Zealand Hospital, Dyrehavevej 29, 3400 Hillerød, Denmark, Tel: 45 4829 5993; Mobile: 45 2054 2458; Email: Lisbet.Brandt@regionh.dk

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- Alfacalcidol
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- Uremia

Abstract

Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) is a result of metabolic changes that occur in patients with chronic kidney disease. The consequences are renal osteodystrophy and vascular calcifications, especially seen in the more advanced stages of chronic renal failure. Different treatment regimens including dietary phosphate restriction, oral phosphate binders and active vitamin D supplementation have been used during the last 30 years. Alfacalcidol ($1\alpha(\text{OH})\text{D}_3$) is an analog of vitamin D₃, a pro-drug of $1,25(\text{OH})_2\text{D}_3$, which is hydroxylated at position number 1 and therefore bypasses the impaired 1α -hydroxylation in the diseased kidneys of patients with chronic renal failure. Alfacalcidol was the first vitamin D analog produced in the 1970's, available for treatment of renal osteodystrophy in all stages of CKD. It has been used in most European countries since then, either alone or in combination with calcimimetics or bisphosphonates and shown to attenuate all aspects of CKD-MBD.

During the last 20 years, new vitamin D analogs with a potentially less effect on plasma calcium and phosphate and a more positive effect on the cardiovascular system have been on the market. None have demonstrated superiority compared to alfacalcidol. Based on the available clinical data, alfacalcidol can still be prescribed for treatment of secondary hyperparathyroidism in both early and late stages of CKD, besides being affordable to many patients, which is an important factor in many countries.

Hopefully, new drugs will be available in the future, which have positive effects on mortality and cardiovascular morbidity in CKD.

ABBREVIATIONS

BMD: Bone Mineral Density; CKD: Chronic Kidney Disease; CKD-MBD: Chronic Kidney Disease-Mineral and Bone Disorder; CVD: Cardiovascular Disease; FGF-23: Fibroblast Growth Factor 23; HPT: Hyperparathyroidism; HR-pQCT: High Resolution peripheral Quantitative Computed Tomography; KDIGO: Kidney Disease Improving Global Outcomes; PTH: Parathyroid Hormone; SHPT: Secondary Hyperparathyroidism; VDR: Vitamin D Receptor; VDRA: Vitamin D Receptor Activator; Wnt: Wingless-related Integration site

INTRODUCTION

Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) is a result of metabolic changes that occur in patients with chronic kidney disease (CKD). The consequences are renal osteodystrophy and vascular calcifications, especially seen in the more advanced stages of CKD. Different treatment regimens including dietary phosphate restriction, oral phosphate binders and active vitamin D supplementation have been used for the last 30 years, and during the last 15 years calcimimetics have also

become a part of the armamentarium [1]. Current understanding of CKD-MBD suggests that calcium, phosphate, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23) and vitamin D are key players in regulating mineral and bone metabolism. The factors are interrelated and their major target organs are the parathyroid glands, the kidneys, bone and the gastrointestinal tract (Figure 1). The increased levels of phosphate, PTH and FGF-23 contribute to the increased cardiovascular disease (CVD) in CKD [2,3]. Recent data has focused on the loss of *klotho* and crosstalk between bone and vessels as triggers for increased vascular calcification in CKD. The hypothesis is that bone affected by CKD predisposes to accelerated vascular calcification through the *Wingless*-related integration site pathway expressed by changes in sclerostin, osteocalcin, Dickkopf-related protein 1 and activin A [4-6]. In patients with CKD stage 5D and elevated or rising PTH, the KDIGO guidelines recommend: "calcitriol, or vitamin D analogs, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogs to lower PTH". In patients with CKD stage 3-5 not on dialysis, the KDIGO guidelines recommend: "in whom serum PTH is progressively

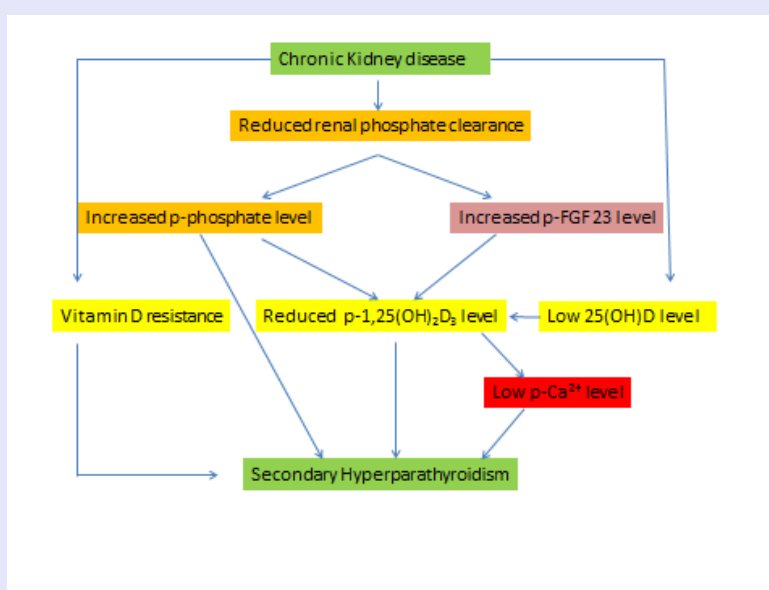


Figure 1 Pathogenesis of secondary hyperparathyroidism in Chronic Kidney Disease – role of vitamin D.

rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs” [7]. Repletion of 25-hydroxy vitamin D (25-OH-D₃) in patients with advanced CKD is still recommend, despite evidence for this being controversial [7-10].

The pro-drug alfacalcidol is a analog of vitamin D, which is hydroxylated at position number 1 (Figure 2). Alfacalcidol has the advantage of requiring only hydroxylation at the 25-position in the liver and in part locally in other tissues (e.g. bone) to become 1,25-hydroxy vitamin D (1,25(OH)₂D₃). Administration of alfacalcidol therefore bypasses the impaired 1 α -hydroxylation in the diseased kidneys in patients with CKD [11].

Alfacalcidol was produced by LEO Pharma in 1973 as an oral formulation, which was convenient, stable and inexpensive [12]. Preliminary reports showed a therapeutic effect of alfacalcidol already in 1973 in rats and human [12] and the drug became available in Denmark in 1974 as the first and only vitamin D analog for clinical use. Since then, it has been the most used active vitamin D analog in Denmark and in most countries worldwide for prophylaxis and treatment of secondary hyperparathyroidism (SHPT) and renal osteodystrophy. Alfacalcidol is also approved for treatment of renal bone disease, different forms of osteomalacia and postmenopausal, glucocorticoid-induced and senile osteoporosis in most countries worldwide.

The present article will focus on new knowledge about the pathogenesis of CKD-MBD and clinical use of alfacalcidol in CKD stage 3-5 and 5D, and whether newer vitamin D analogs provide further advantages in treatment of CKD-MBD compared to alfacalcidol.

REVIEW CRITERIA

A search for articles published between 2008 and 2016 focusing on alfacalcidol was performed in PubMed. The search

terms used were “alfacalcidol”, “one-alpha” “vitamin D analogs”, “PTH”, “FGF23”, “phosphate”, “secondary hyperparathyroidism”, “CKD” and “human”, alone and in combination. All articles identified were English language, full-text papers. Reference lists of identified articles were also searched for further relevant papers.

CLINICAL USES OF ALFACALCIDOL

Many different (mainly small) studies demonstrate an effect of alfacalcidol on both PTH level, bone and vessels. The effects of alfacalcidol as treatment and prophylaxis of SHPT in CKD patients on chronic dialysis are well documented [13,14]. Brandi et al., demonstrated that it was possible with both intravenous and oral administration of alfacalcidol to suppress PTH without inducing hypercalcemia, when plasma calcium was closely monitored and dose of alfacalcidol carefully adjusted [13]. Gonzalez et al., demonstrated that intravenous administration of alfacalcidol suppressed PTH at all levels of PTH in patients on chronic hemodialysis. The effect was greater at mild to moderate levels of PTH and therefore, initiation of therapy should be in the early stages of the SHPT [15]. Oral alfacalcidol also effectively suppressed PTH in children [16]. In 1995, the effect of oral alfacalcidol on bone was clearly demonstrated in a randomized controlled trial in CKD stage 3-4, by improving bone histology and preventing increases in alkaline phosphatases (Figure 3) [17]. In 2004, Rix et al., demonstrated that alfacalcidol improved Bone Mineral Density (BMD) and decreased PTH, osteocalcin and alkaline phosphatases (Figure 4) [18]. Further, in kidney transplant recipients, alfacalcidol in combination with bisphosphonate produced a superior effect on BMD compared to either of the two drugs alone [19]. In another study, Brandi et al., demonstrated an increase in BMD in dialysis patients treated with intravenous alfacalcidol [13].

The main cause of mortality in CKD patients is CVD [20]. Therapies with active vitamin D and analogues, independent of

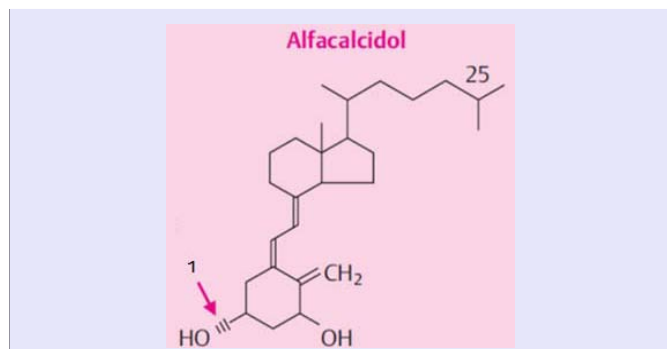


Figure 2 The chemical structure of the vitamin D analog alfacalcidol. Position 1 is marked with an arrow.

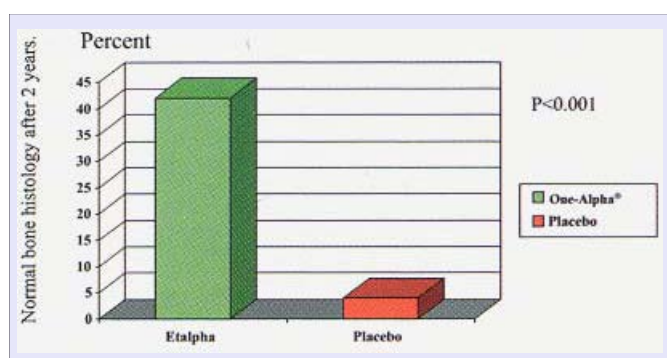


Figure 3 In a randomized clinical trial Hamdy et al., demonstrated that treatment with alfacalcidol corrects abnormal bone histology in mild to moderate renal failure [17]. Data kindly provided by LEO Pharma, Denmark.

drug type, are associated with reduced mortality in CKD patients [21], in particular, those suffering from SHPT. These results, based on observational evidence, are supportive of prescribing vitamin D therapies to CKD patients, while respecting good practice guidelines [21]. In a large cohort of hemodialysis patient treatment with vitamin D receptor activators (VDRA), (type not further specified), the use of VDRA was associated with a lower risk of incident CVD, but not with death from CVD [22]. As the vitamin D receptor (VDR) is expressed on cardiomyocytes, direct actions of vitamin D in the heart as a target organ are expected and demonstrated [23]. A retrospective study showed that oral administration of alfacalcidol for patients with CKD stage 3-5, was associated with reduced risk of CVD [24], similar to results presented in 2004 [25]. In CKD, low plasma levels of $1,25(\text{OH})_2\text{D}_3$ increases renal renin production. Activation of the renin-angiotensin-aldosterone system, in turn, reduces renal expression of klotho. The resulting high FGF-23 levels suppress 1-alpha hydroxylase and further lower $1,25(\text{OH})_2\text{D}_3$ [26]. In a retrospective study, treatment with alfacalcidol for SHPT reduced albuminuria by 16% in patients with CKD stage 3-5 [27], probably by inhibition of the renin-angiotensin system. The combination of olmesartan and alfacalcidol inhibited the progression of renal damage in 5/6 nephrectomized rats through a strong antihypertensive effect as well as upregulation of klotho [28].

In a hemodialysis population, treatment with alfacalcidol was associated with reduced development of vascular calcification as assessed by chest-x-ray [29].

Also, an open-label randomized clinical trial of alfacalcidol versus to no active vitamin D treatment in dialysis patients demonstrated that treatment with alfacalcidol had no effect on microvascular endothelial function in diabetic patients, but significantly improved central systolic blood pressure with trends toward improvement in arterial stiffness and peripheral blood pressure [30]. In another study, intravenous administration of alfacalcidol reduced left ventricular mass index, but simultaneously left ventricular function became hyperdynamic and less effective [31]. In a single-center retrospective observational study, pharmacological doses of alfacalcidol were associated with accelerated progression of aortic stiffness. This study suggests that the vascular safety of active vitamin D may need to be specifically addressed in the treatment of CKD [32]. Another study of hemodialysis patients, the prescription of alfacalcidol was associated with lower pulse wave velocity [33].

PLEIOTROPIC EFFECTS OF ALFACALCIDOL

Vitamin D plays a role in the crosstalk between the innate and the adaptive immunity. The paracrine response of $1,25(\text{OH})_2\text{D}_3$ seems to have an effect on monocytes and immature dendritic cells. The local production of $1,25(\text{OH})_2\text{D}_3$ is assumed to enhance a tolerogenic immune response and possess immunosuppressive properties [34]. Therefore alfacalcidol could be interesting in

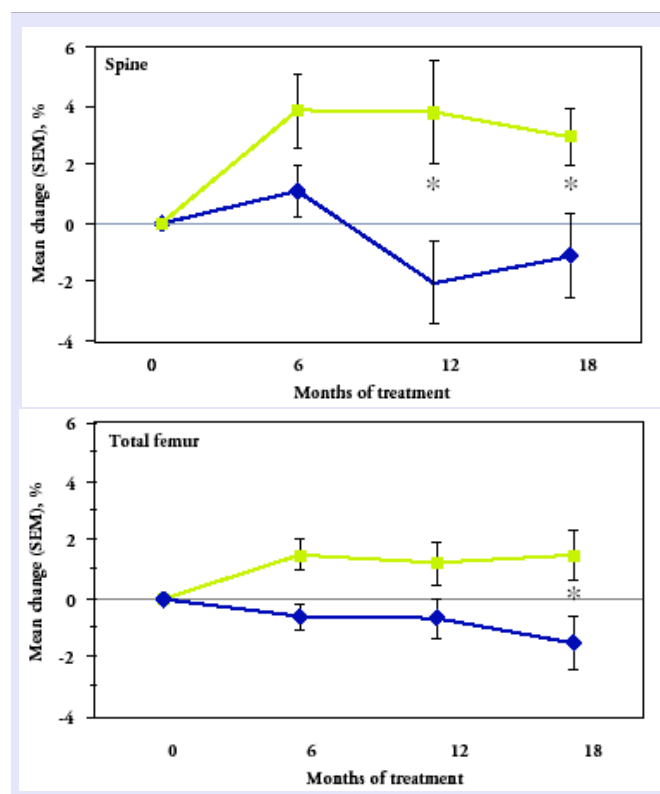


Figure 4 In a randomized clinical trial Rix et al., demonstrated that treatment with alfacalcidol preserved bone mass in the spine and femur in mild to moderate renal failure [18]. Data kindly provided by LEO Pharma, Denmark.

treatment of autoimmune diseases. A recent randomized clinical trial demonstrated a positive effect of alfacalcidol on multiple sclerosis-related fatigue compared to placebo. The kidney function was not described [35].

Further, increased insulin sensitivity in CKD and reduced need for erythropoietin stimulating agents (ESA) are reported with alfacalcidol [34]. Some older studies are also available regarding alfacalcidol and effects related to ESA treatment [36], immunity [37] and insulin resistance [38] in CKD.

ANALOGS

The dose limiting factors regarding active vitamin D for treatment of SHPT in CKD are hyperphosphatemia and hypercalcemia [1]. In a direct single-dose comparative set-up, there was no difference in the PTH suppressive effect of alfacalcidol and $1,25(\text{OH})_2\text{D}_3$ following administration of 4 μg of the two drugs, while a smaller effect for alfacalcidol than $1,25(\text{OH})_2\text{D}_3$ was seen following administration of 10 μg . The hypercalcemic effect was higher for $1,25(\text{OH})_2\text{D}_3$ than alfacalcidol [13]. The smaller clinical effect per dose was underlined in another more recent study [39]. The main reason for developing new vitamin D analogs was initially to produce drugs that suppressed PTH sufficiently, but with less development of hypercalcemia and hyperphosphatemia. Focus later expanded to all parts of the CKD-MBD syndrome such as renal osteodystrophy, vascular calcification and also non-classical vitamin D effects, especially in oncology and dermatology [40]. Paricalcitol was the first analog on the market with a suspected lower calcemic effect than $1,25(\text{OH})_2\text{D}_3$. That drug nearly replaced $1,25(\text{OH})_2\text{D}_3$ in USA and other parts of the world and has been used intensively for the last 10 years [41]. A recent meta-analysis between paricalcitol and other active non-selective vitamin D receptors (including alfacalcidol) concluded that it was not possible to demonstrate any superiority of paricalcitol [42]. In a randomized clinical trial set-up between alfacalcidol and 19-nor- D_2 the two drugs were equal for treatment of disturbances in mineral metabolism in hemodialysis patients. There was no difference regarding effect on PTH or safety profile [43]. Recently clinical data from a new vitamin D_3 analog, 2 MD (a 19-nor- D_3 analog), has been published [44,45]. Promising results are demonstrated, but a study including a control group treated with another active vitamin D analog is needed. An eight-week direct comparison between alfacalcidol and falecalcitriol has been performed in 1998. In that study, falecalcitriol was superior to alfacalcidol regarding suppression of PTH [46]. In a later study directly comparing falecalcitriol with calcitriol, no difference was found [47]. Vitamin D analogs available for use in CKD are described in Table (1).

DIFFERENT ROUTES OF ADMINISTRATION

Most active vitamin D analogs are available both as oral

and intravenous formulation. The intravenous formulation of alfacalcidol was developed in the 1980's. The first intravenous formulation of active vitamin D on the market was $1,25(\text{OH})_2\text{D}_3$. The intention was to enhance the delivery of the drug directly to the target, improve the effect and reduce side-effect such as hypercalcemia and hyperphosphatemia compared to oral administration [48]. To characterize the intravenous formulation of alfacalcidol, pharmacokinetic studies were performed. The plasma concentration of $1,25(\text{OH})_2\text{D}_3$ was higher after intravenous than oral administration of alfacalcidol [13,49], but not as high as after intravenous administration of $1,25(\text{OH})_2\text{D}_3$ [13]. The long-term effect of intravenous administration of alfacalcidol has been intensively investigated. The suppressive effect on PTH was marked, with manageable effects on plasma calcium and phosphate [13]. The intravenous formulation is only useful for the hemodialysis patients, where it is administered at the end of each dialysis session. A single study compared daily oral alfacalcidol with intermittent intravenous alfacalcidol, and found that the effect of intermittent alfacalcidol on PTH suppression was faster in all patients and also greater in those patients with PTH between 200 and 500 pg/ml compared to higher levels [50]. Another group has tested regime with intravenous administration 1,2 or 3 times weekly and found no difference in the effect on PTH [51]. The dosing regime thereafter changed from daily to intermittent. During the recent years, direct comparative studies have been performed between intravenous and oral administration in patients on chronic hemodialysis of both alfacalcidol [13,52,53] and doxercalciferol (1- α -(OH) D_2) [54]. The effects on PTH, calcium and phosphate were similar. Based on the available pharmacological and clinical data, the intravenous formulation is likely to be superior only in a highly selected group.

From the patients perspective, the intravenous formulation could have a huge advantage. Patients with CKD have an extremely high pill burden [55] and it is clearly documented that the adherence to medication decreases as the number of pills increases [55]. Poor compliance will presumably result in worse clinical outcomes. In this situation, intravenous administration easily overcomes the problem with adherence.

FUTURE PERSPECTIVES

Since vitamin D was introduced on the therapeutic arena in CKD, it has successfully been supplemented with calcimimetics for better control of SHPT [56,57]. An intravenous formulation of a new calcimimetic drug has been developed and is now FDA approved [58,59].

Renal osteodystrophy is associated with 2- to 14-fold increased fracture risk compared to the general population [60]. Risk of fractures is also increased in kidney transplant

Table 1: Native vitamin D and Vitamin D analogs available for clinical use in CKD.

Native vitamin D	Non-selective VDRA	Non-selective VDRA	Selective VDRA	Selective VDRA
D_2 -Ergocalciferol	Doxercalciferol $1\alpha(\text{OH})\text{D}_2$		Paricalcitol 19-nor- D_2	
D_3 - Cholecalciferol	Alfacalcidol $1\alpha(\text{OH})\text{D}_3$	Calcitriol $1,25(\text{OH})_2\text{D}_3$	Maxacalcitol 22-oxa- D_3 Falecalcitriol 26,27-F6- $1,25(\text{OH})_2\text{D}_3$	2 MD (19-nor- D_3)

recipients [61]. Proper screening and management of CKD bone complications is critical to improving clinical outcomes. Methods to establish the severity of osteoporosis in non-CKD patients are analysis of BMD. This method alone has not been of use in CKD and new promising methods are being explored. One of these is high-resolution peripheral quantitative computed tomography (HR-pQCT) [62], an imaging method that provides detailed images of bone geometry and microarchitecture. Bisphosphonate in combination with active vitamin D (including alfacalcidol) is standard treatment of osteoporosis in patients with normal kidney function, CKD stages 1-3, and kidney transplant recipients [61,63]. Due to the risk of a dynamic bone disease, bisphosphonate are not recommended in CKD stage 4-5 [63]. Newer anti-osteoporotic medications such as RANKL-ligands are currently under investigation. A recent retrospective study in non-CKD patients with osteoporosis demonstrated a significantly higher increase in BMD of the femoral neck and distal forearm in patients treated by denosumab and alfacalcidol compared to denosumab and inactive vitamin D [64]. In prospective non-randomized study in hemodialysis patients, it was found that the combination of denosumab and $1,25(\text{OH})_2\text{D}_3$ decreased PTH secretion and allowed supraphysiological doses of $1,25(\text{OH})_2\text{D}_3$ [65]. In a "letter to editor", experience, also in a hemodialysis population are published. An increase in PTH has also been described with denosumab in combination with different active vitamin D analogs (including alfacalcidol) in hemodialysis patients, perhaps in response to calcium lowering by denosumab [66]. Further studies are awaited.

The usefulness of biomarkers in clinical studies has been unclear and the findings so far remain inconclusive. Biochemical markers that might be valuable in evaluation of both vascular calcification and bone in CKD are now tested [4-6]. Sclerostin, a protein suppressing osteoblast activity and inhibiting bone formation, is associated with plasma level of 25-hydroxy vitamin D in patient both with normal kidney function and CKD. In hemodialysis patients with low PTH levels, sclerostin is associated with phosphate and FGF-23. New data is available for sclerostin on vascular stiffness [67] and fracture risk [68]. The influence of vitamin D treatment on the plasma levels of sclerostin is unknown.

CONCLUSION

Alfacalcidol was the first vitamin D analog available for treatment of renal osteodystrophy, a pioneer in the arena in the 1970's. In the CKD population the indication expanded to include treatment of SHPT and post-transplant osteoporosis. Further, it has been shown to attenuate both bone and vessel disease. More new vitamin D analogs are on the market today. This has increased the understanding of CKD-MBD and the role of vitamin D in this context. None of these new vitamin D analogs have been shown to have different effects than alfacalcidol in randomized clinical trials. Based on the available clinical data, alfacalcidol can still be prescribed for treatment of SHPT in both early and late stages of CKD. Because the drug is old and inexpensive, it is affordable to many patients in many countries. Hopefully, in the future newer drugs with effects on mortality and cardiovascular morbidity in CKD will be available.

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