UNIVERSITA' DEGLI STUDI DI MILANO

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THE IMPACT OF PHOSPHOROUS CONTROL IN CKD PATIENTS

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INDEX

THE EVOLVING WORLD OF CHRONIC KIDNEY DISEASE MINERAL BONE DISORDER

Chronic Kidney Disease Mineral Bone (CKD-MBD) disorder is associated with a significant morbidity and mortality. In vitro and animal models suggest that phosphorous, calcium, parathyroid hormone and vitamin D abnormalities mediate the cardiovascular and bone diseases that characterize CKD-MBD and increase the risk of death. Currently, mineral abnormalities are corrected through phosphorous restriction, phosphate binders, calcimimetics and vitamin D administration. Nonetheless, data in humans that support the use of these compounds are still scanty, mainly based on observational studies. Thus, a considerable number of doubts and questions still challenge clinicians dealing with CKD patients and mineral metabolism imbalances. We herein critically review clinical evidence that support the use of different drugs in CKD-MBD.

Introduction

Calcium, phosphate, vitamin D and parathyroid hormone (PTH) have been repeatedly recognized as predictor of outcome in chronic kidney disease (CKD))[1-4]Though the mechanisms are still poorly understood, numerous studies suggest that mineral homeostasis abnormalities are associated with bone and cardiovascular (CV) diseases that portend a poor survival[5]. Hence, biochemical, CV and bone abnormalities are now considered part of the multifaceted Chronic Kidney Disease - Mineral Bone Disorder (CKD-MBD) syndrome[5] **(Figure 1).**

In spite of convincing preclinical data linking mineral metabolism imbalances to cardiovascular and bone diseases, clinical evidence is still far from being conclusive[4, 6] and a considerable number of doubts and questions still challenge clinicians dealing with CKD patients and mineral metabolism imbalances. CKD-MBD is currently treated with nutritional interventions, native and active vitamin D phosphate binders and, calcimimetics administration **(Figure 2)**. Aim of the current review is to critically evaluate and summarize available evidence as well as highlight the numerous unanswered clinical questions on CKD-MBD management.

Diet: facts, promises and expectations

Hyperphosphatemia control is perceived by Nephrologists as one of the most relevant target to achieve in CKD[4]. Indeed, numerous studies have reported a close association between serum phosphorus levels and the risk of death in both subjects from the general population [7, 8] as well as subjects with various degree of renal function impairment[1-4]. Further, a large body of evidence suggests a direct link between phosphorous and the cardiovascular as well as bone system[5]. Thus, it is commonly accepted that phosphorus is a uremic toxin and current guidelines on mineral metabolism management recommend maintaining it within the range of normality[9, 10].

As kidney function declines, urinary phosphate excretion becomes insufficient and eventually hyperphosphatemia ensues if the phosphate daily intake remains constant [11]. It is estimated that the daily phosphate intake in a standard diet in the western countries is about 1500 mg/day [11, 12]. Considering that the fecal excretion is about 600 mg per day of which about 200 mg/day are secreted by the intestine, the amount of phosphorous absorbed by the gastrointestinal tract may approach 1100 mg/day[11, 12] **(figure 2).** To maintain phosphorous homeostasis and keep serum levels within the range of normality, renal excretion should match the daily intake at the expense of increasing the tubular workload of each functional nephron [13]. Notably, the average phosphate level in the general population varies according to sex and menopausal status[14, 15] and data suggest an increased risk of unfavorable outcome for phosphorous levels within the range of normality [8, 15] further corroborating the notion that serum phosphorus may not reflect adequately phosphorous balance.

Two different strategies to lower phosphorous intake are available: low phosphate diet and phosphate binders. A low phosphorous intake can be achieved via protein restriction and quality selection (5). Indeed, Moe et al. showed that a vegetarian rather than a meat-based diet significantly reduces serum phosphorous and the phosphaturic factor fibroblast growth factor 23 (FGF23)[16]. Notably, these differences were independent of the circadian serum and urine phosphorous changes suggesting that phosphorous contained in the vegetarian diet is less adsorbable in the gastrointestinal tract possibly due to the phosphate binding to phytate[16].

Cooking and food additives are two other factors that significantly affect phosphorous intake[17-22]. Cupisti and coworkers reported that 20-30 minutes boiling significantly reduce (30-

50%) phosphorous burden at the expense of a mnimal reduction of the protein content (9-17%) [18].

Food additives are another source of phosphorous of prepared meals. A recent survey of best-selling processed groceries concluded that phosphorus additive-containing foods averaged 67 mg phosphorus/100 g more than matched non additive-containing foods (about 736 mg more phosphorus per day compared with meals consisting of only additive-free foods)[23]. Phosphorous-based additives (phosphoric acid, Tetrasodium Pyrophosphate, Tricalcium Phosphate, Disodium Phosphate, Monopotassium Phosphate, Tricalcium Phosphate, etc) are used to enhance taste and consistency of different foods such as baked goods (baking powder, cakes, frozen dough, etc), beverages (colas, chocolate milk, buttermilk, fruit juices, sport drinks, canned milk, soy beverages) cereals, dairy, meat and egg products, fruit and vegetables, pasta and noodles.

Inorganic phosphorous contained in food additives is highly bioavailable and adsorbed in the gastrointestinal tract to a greater extent than the organic phosphorous. It is estimated that as much as 90% vs 60% of the ingested inorganic (food additives) and organic (vegetable and meat protein) phosphorous is absorbed, respectively[21, 22].

Though the mechanisms are still unclear, accumulating evidence suggest the high serum levels of phosphorous are associated with increased levels of FGF-23 that in turn have been independently associated with a significant risk of endothelial dysfunction[24], left ventricular hypertrophy[25], CKD progression and all-cause mortality [26]. In the absence of a randomized controlled clinical trial (RCT), it is unclear whether elevated serum phosphorous or FGF23 mediates the toxicity[1, 26] or, alternatively, both factors contribute to the organ damage and poor survival in CKD-MBD[27].

A balanced nutritional program should control both serum phosphorous and FGF23. Di Iorio et al [28] showed that a very low protein diet (0.3 g/kg of ideal body weight per day) supplemented with alpha-chetoanalogues and essential aminoacids significantly reduces FGF23 and phosphoremia. In 32 CKD subjects randomized to a cross-over sequential treatments with either standard low protein diet (60-70 g of protein/day) or very low protein diet (25-30 g of protein/day), they reported a significant 33.5%, 12% and 34% reduction of fibroblast growth factor 23, serum and urinary

phosphorous levels associated with very low protein diet (VLPD), respectively[28]. Of note, the 2 diet regimens did not differ only in the total protein intake but also in the animal/vegetal protein ratio (VLPD regimen based on vegetable protein only) and phosphorous content (350-420 mg/day versus 600-700 in VLPD and standard diet, respectively)[28]. Other groups have confirmed that phosphorous restriction with or without phosphate binders is effective in controlling FGF23[29, 30].

Low phosphate and protein diet has also been associated with proteinuria and CKD progression reduction[19, 31, 32]. In a seminal paper by Brunori at al, it was demonstrated that life expectancy among old patients with end stage renal disease was similar if patients were randomized to VLPD and conservative treatment or hemodialysis[32].

The most important drawback of low protein and phosphorous diet is the potential for malnutrition[33]. Indeed, a balanced nutritional program should be tailored on each individual and should provide the patient with the right amount of calories and nutrients[34]. In these regards, an observational study suggests that protein malnutrition maybe more detrimental than phosphorous intake and that the ideal nutritional regime should provide enough protein with minimal phosphorous burden[33].

Future RCT studies should investigate the safety and the impact of low protein and very low protein diets on long-term survival and CKD progression in both CKD patients not receiving and receiving dialysis. In consideration of the substantial increase of the mean age of dialysis patients, it is to be established if the recommended protein intake by current guidelines is still adequate in light of the considerable number of patients with increased levels of serum phosphorous[35]. Finally, a pharmacoeconomic analysis should evaluate the cost burden connected to aproteic foods, chetoanalogue or essential aminoacid supplements.

Phosphate binders: facts, promises and expectations

Phosphate binders are another strategy for reducing phosphate intake. All these compounds share the property to bind phosphorous in the intestinal lumen, prevent its absorption and increase the fecal excretion. Various drug are now available on the market with this indication[36, 37]. For easiness these compound can be divided into 2 different groups: calcium based phosphate binders

(calcium carbonate and calcium acetate) and calcium-free phosphate binders (aluminium hydroxide, lanthanum carbonate, magnesium carbonate, sevelamer hydrochloride, and sevelamer carbonate). Alternatively, these compounds can be divided into absorbable (calcium based binders, aluminium hydroxide, lanthanum carbonate, magnesium carbonate) and not absorbable (sevelamer hydrochloride, and sevelamer carbonate) in the gastrointestinal tract. Though all these compounds might have different affinity for phosphourous in the gastrointesinal tract and different doses have to be administered[38], clinical studies suggest that they all effectively lower serum phosphorous[36, 39, 40]. Nonetheless, due to the different adsorbability in the gastrointestinal tract the safety profile of these compounds can be profoundly different. Indeed, the prolonged use of aluminum based phosphate binder is not indicated due to its accumulation and toxicity [41].

The debate on calcium containing versus calcium free phosphate binders has characterized the last decade[36, 42]. Preclinical data suggest that both phosphorous and calcium can actively induce vascular calcification[43-45], a marker of vascular disease[46] and a risk factor for arterial stiffness[47] and mortality[46, 48]. A seminal paper by Cozzolino and coworkers demonstrated that the use of Sevelamer was associated with a similar phosphate control but lower extraosseous calcification that calcium based phosphate binder[49]. Observational data suggest that excessive calcium intake may result in a positive calcium balance that in turn has been associated with arterial stiffness and vascular calcification[50, 51], adynamic bone disease [52, 53]and, in some but not all studies, in excessive mortality[35, 54].

RCTs have also yielded somehow conflicting results. Up-to-date, 3 studies have tested the impact of calcium free and calcium containing phosphate binders on vascular calcification, CKD progression and all-cause mortality in moderate CKD[55-57]. In the first study ever published, Russo and coworkers[55] observed a significant reduction of coronary calcification (CAC) progression among patients with CKD stage 3-4 treated with sevelamer as compared to patients treated with calcium carbonate or low-protein diet[55]. Considering that the dose of both binders was based on a similar reduction in urinary phosphate excretion (i.e. phosphate binding equivalency), it is plausible that the different impact of sevelamer and calcium carbonate on vascular calcification is due to the excessive calcium load in the calcium carbonate treated arm. Indeed, recent evidence suggests that

a calcium intake greater than what usually ingested in a normal western county diet (about 800 mg/day) can induce a positive calcium balance in moderate CKD[58]. However, it is also possible that the additive effects of Sevelamer on FGF-23, fetuin-A, lipids, C-reactive protein, uric acid[59, 60] may account for some of these results. Block and coworkers[56] recently failed confirm the beneficial effect of non-calcium containing phosphate binders (sevelamer carbonate, lanthanum carbonate) on vasculature. Though the study was designed to address the phosphate lowering efficacy of calcium and non-calcium containing phosphate binders vs placebo in mild to moderate CKD, authors report among treated patients on a worrisome increase in CAC, measured as secondary endpoint[56]. However, it is unclear whether calcium or non-calcium containing phosphate binders drive this result. The limited statistical power of the study further limits the interpretation of this finding [56].

A third RCT designed to test the impact of sevelamer vs calcium carbonate on hard outcomes (all-cause mortality and CKD progression) in mild to moderate CKD patients (mean creatinine clearance 30 ml/min) with hyperphosphatemia supports the notion that a non-calcium containing phosphate binders maybe associated with a more favorable renal and life survival[57]. Of note, in this study a significant CAC progression attenuation was also noted [57]. Although Sevelamer treated patients showed a higher CAC prevalence and burden at baseline (prevalence of CAC 62.6% vs 47.6%; P=0.02; median CAC score: 122 AU [IQR, 0–180] versus 0 AU [IQR, 0–215]; P=0.01 in the Sevelamer and calcium carbonate group respectively], at study completion a significantly lower risk of CAC progression or *de novo* onset (12.8% in sevelamer-treated patients and 81.8% in calcium carbonate–treated patient) was noted [57].

Other studies in ESRD patients new to[48] or on maintenance dialysis[61] have also investigated the differential impact of calcium salts and calcium free phosphate binders on vascular calcification or hard outcome[48, 62]. Though the majority of these trials point toward a harmful potential of calcium containing phosphate binders, metanalyses have repeatedly failed to confirm this hypothesis [39, 63, 64]. A recent study by Di Iorio et al (*Sevelamer Versus Calcium Carbonate in Incident Hemodialysis Patients: Results of an Open-Label 24-Month Randomized Clinical Trial–Accepted for publication Am J Kidney Dis*) unfold an almost 10-fold reduction of CV and all-cause

mortality associated with sevelamer vs calcium carbonate in a large cohort (N=466) of patients new to dialysis.

Though these data suggest a different effect of calcium free phosphate binders on the cardiovascular system and survival, no study has ever tested whether serum phosphorous lowering is associated with a survival benefit. In light of the many adaptive mechanisms to hyperphosphatemia such as increase PTH and FGF23 that can modulate phosphorous toxicity and the potential calcium toxicity[65, 66], future studies should address when to start in the course of CKD and to what serum phosphorus target should we aim when prescribing phosphate binders. Finally, cost-effectiveness analyses of these compounds are needed in light of the expanding epidemiology of CKD[67].

Native Vitamin D: facts, promises and expectations

Native Vitamin D has received growing interest in the last ten years. Every year hundreds of manuscripts on native vitamin D associations with a variety of diseases such as osteoporosis [68], hypertension [69], cardiovascular disease[70, 71], insulin resistance [72], infections[73], cancer[74] and mortality [75] are published. Similarly, Nephrologists have traditionally linked native Vitamin D deficiency to CKD progression [76], secondary hyperparathyroidism (SHPT) [77] and survival [78] in renal patients. The widespread association between native Vitamin D and unfavorable outcomes in the general population, as well as in selected diseased sub-cohorts, together with the emerging knowledge of the extra-renal activation of native Vitamin D, support the hypothesis that vitamin D deficiency is an etiologic factor rather than a mere biomarker of frailty [79].

The term "native Vitamin D" refers to the 25 hydroxlate vitamin D (25(OH)D) forms. Vitamin D precursors ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are synthesized by the UV radiation in yeast and in animals starting from ergosterol and 7-dehydrocholesterol, respectively[80]. In turn, vitamin D precursors are hydroxilated in the liver to form 25(OH)D2 and 25(OH)D3, respectively [80]. These are the substrates that are subsequently activated to 1-25$(OH)_2$D (calcitriol) by the renal and, to a lesser extent, by the extra-renal 1 alpha hydroxylase [81].

Of note, humans do not synthesize Vitamin D2 [80] and almost 80% of Vitamin D is obtained by UVB irradiation with only a minor contribution of diet intake [81].

Though it is commonly prescribed as a supplement, we currently ignore what is the desirable level of 25(OH)D[68, 82]. It is commonly accepted that levels of 25(OH)D above 30 ng/ml, between 21 and 29 ng/ml and below 20 ng/ml define Vitamin D sufficiency, insufficiency and deficiency, respectively[81].

Native Vitamin D deficiency is highly prevalent in the general population as well as in CKD and is almost ubiquitous in dialysis patients (greater than 80%) [83]. Three drugs are currently available for vitamin D supplementation (ergocalciferol, cholecalciferol and calcifediol) based on the precursor they are originated. A few subtle pharmacologic differences have been described [84, 85]. Several studies observed that ergocalciferol is less potent than cholecalciferol in restoring 25(OH)D levels[85], possibly due to a stronger affinity of cholecalciferol to the vitamin D binding protein[85]. Moreover, the activated form of vitamin D (1,25OHD – calcitriol) originated from cholecalciferol induces a sustained activation of the vitamin D receptor (VDR) due to a higher affinity of its catabolite 1-24-25(OH)D3 to the VDR than the ergocalciferol derived catabolite 1-24-25(OH)D2 [84]. Thus, it commonly accepted that 50.000 IU of ergocalciferol are pharmacologically equivalent to 5-15.000 IU of cholecalciferol [86]. However whether these 2 forms of vitamin D may have a different clinical implications is still unknown. Two RCTs are currently recruiting patients to compare the effect of Vitamin D2 vs Vitamin D3 on mineral metabolism in CKD stage 2-5 (NCT01633853, NCT01173848) to shed light on what 25OHD form is better suited in CKD. Current evidence suggests a potential role for 25OHD as PTH lowering agent. Indeed, A recent meta-analysis by Kandula and colleagues concludes based on the available observational studies that 25OHD compared to placebo reduces PTH levels in CKD (about 25 pg/ml) as well as in ESRD (about 60 pg/ml) patients[87]. However the heterogeneity of the studies precludes speculation on what could be the best 25OHD regimen in CKD(25). Whether 25OHD can be used instead of VDR activator for PTH suppression in CKD is still under debate, though preliminary data suggest that paricalcitol and doxercalciferol induce a stronger PTH reduction compared to ergocalciferol and cholecalciferol in CKD 3-4 [88, 89] and ESRD patients [85], respectively. Similarly, data concerning PTH reduction by

the co-administration of native and active Vitamin D are still inadequate, mainly based on observational and retrospective studies[90-92]. Further evidence is advocated before recommending the implementation of this combined approach.

In spite of the many pleiotropic effects described in the last decades and the substantial increase in the risk of death associated with low 25OHD levels [74], only few studies have investigated the impact of native vitamin D on surrogate endpoint such as renal osetodystrophy, vascular calcification, proteinuria, LVH or survival. However, numerous RCT are currently investigating the effect of native Vitamin D on left ventricular hypertrophy (NCT01323712), insulin resistance (NCT00893451), erythropoietin dosing (NCT01395823), proteinuria (NCT01426724), immunity (NCT00892099), ateriovenous fistulae maturation (NCT00912782) and physical and cognitive performance (NCT00511225, NCT01229878) to shed light on the potentials of this treatment. Finally, the NUTRIVITA study is actively randomizing dialysis patients to 25(OH)D versus placebo treatment to test the effect of 25OHD on survival, fatal myocardial infarction and non fatal stroke (NCT01457001).

Due to the scanty data available, current guidelines on mineral metabolism management[10], suggest 25(OH)D deficiency replenishment as the first step to correct SHPT in CKD stage 3-5[10], whereas no suggestion is provided for dialysis patients. These statement are *not-graded* and based on expert opinion rather than on evidence[10]. A considerable ongoing and future effort is needed to clarify the impact of 25OHD administration to CKD and dialysis patients.

Vitamin D analogs: facts, promises and expectations

Repeated observational data described an independent association between PTH levels and unfavorable outcomes in CKD stage 3-5[93, 94] as well as in ESRD[2, 3]**.** However, no randomized controlled trials (RCTs) have yet proven that an active reduction of PTH values improves patient-centered hard outcomes as hospitalizations, cardiovascular events, CKD progression and survival. Thus, the optimal PTH target is still uncertain in CKD as well as in ESRD subjects. KDIGO guidelines

provide a low-grade suggestion to maintain PTH levels into the range of normality in CKD 3-5 and between 2 and 9 times the normal range in ESRD [10].

The reduction of calcitriol levels, together with hypocalcemia and hyperphosphatemia, are the leading causes of increased PTH levels. Thus, KDIGO guidelines suggest the use of vitamin D in case of increased PTH values and its tailoring in case of PTH over-correction, hypercalcemia or hyperphosphatemia [10]. The risks related to high doses of Vitamin D are mainly due to phosphate and calcium overload that possibly contributes to the low achievement rate of calcium and phosphate recommended targets[95] and to a poor survival in dialysis patients[3]. However, selective vitamin D receptor activator (VDRA), with a stronger effect on PTH and a lesser impact on calcium and phosphate load, may improve the global achievement of serum PTH, calcium and phosphate targets reducing the Vitamin D toxicity [96-98].

In the recent years industries have provided multiple synthetic Vitamin D2 (paricalcitol and doxercalciferol) and Vitamin D3 analogs (alfacalcidol, falecalcitriol and maxacalcitol). However, comparison data of different Vitamin D analogs on mineral metabolism control, surrogate and patient-centered outcomes are currently still scanty.

Several studies suggest that VDRAs are superior to placebo and calcitriol in controlling PTH, calcium and phosphate, but the few available head to head comparisons between VDRAs led to heterogeneous and inconclusive results. Alfacalcidol was similar to calcitriol in suppressing PTH values with equal change in phosphate and calcium levels[99, 100], however recent data by Hansen et al did not observe significant differences between alfacalcidol and paricalcitol on similar targets [101]. Joist et al observed that paricalcitol at very high doses suppressed PTH with lower elevation of phosphate and calcium levels compared to doxercalciferol [102]. However, Fadem and coworkers could not detect any difference in PTH, calcium and phosphorous control when hemodialysis patients were switched from intravenous paricalcitol to doxercalciferol[103]. No clinical data comparing doxercalciferol with alfacalcidol in humans are currently available.

More recently a growing interest for Vitamin D pleiotropioc effects, related to the widespread regulation of the human genome played by VDR activation, has been observed. Albuminuria, left ventricular hypertrophy (LVH) and cardiac remodeling have all being tested as potential targets of

Vitamin D analogs. The activation of VDR can regulates the expression of several genes involved in glomerular and myocardial inflammation as renin[104], TGF-beta[105], antioxidant molecules[106], NFκB and RANTES[107]. The VITAL study, a randomized placebo controlled trial in diabetic CKD patients, documented a dose dependent trend toward reduction of albuminuria when paricalcitol was added to RAAS inhibitors[108]. Though the PRIMO study failed to demonstrate a significant LVH reduction[109], a post-hoc analysis documented a lower increase of brain natriuretic peptide and left atrial index in diabetic CKD patients receiving paricalcitol on top of ACE-I or ARBs compared to placebo[110]. Interestingly, paricalcitol was associated with lower risk of hospitalization in those patients with more severe LVH[109]. However, no RCT has tested the effect of different forms of vitamin D or VDRA on hard patient-centered outcomes.

Numerous albeit not all observational studies suggest potential benefits beyond mineral metabolism control linked to VDRA use on hospitalization, cardiovascular events and mortality. Kalantar-Zadeh and coworkers reported on a 14% reduction in all-cause hospitalization among patients receiving paricalcitol compared to those treated with calcitriol in a large cohort of 58,058 hemodialysis patients [3]. Paricalcitol [111-113] and doxercalciferol [113] use were both associated with lower mortality risk compared to calcitriol in other large series of patients on chronic hemodialysis. Recently published results from the Italian FARO survey unexpectedly showed a better survival in dialysis patients receiving Vitamin D also in the presence of PTH $\leq$ 150 pg/ml [114]. However, the dialysis Outcome and Practice Pattern Study (DOPPS) investigators failed to report on Vitamin D improved survival after adjustment for confounders and different practice patterns [115]. Hence, these encouraging observational data have to be confirmed in RCTs prior to orient stronger recommendations on Vitamin analogs prescription.

Future studies should shed definitive light of whether the use of VDRAs improve survival in CKD and ESRD as well as surrogate outcomes such as albuminuria and LVH. Finally, in consideration of the growing number of CKD patients and the high cost burden connected to CKD management, future studies should also verify the cost effectiveness of the use of VDRA in different stages of CKD.

Cinancalcet: facts, promises and expectations

The existing body of evidence suggests that cinacalcet effectively lowers serum PTH, phosphorous and calcium levels in ESRD modulating the parathyroid calcium sensing receptor affinity to serum calcium [6, 116-124]. Phase 2 and 3 studies show that on average a 40-50% (250-350 pg/ml) serum PTH, a 5-8% (0.5-0.8 mg/dl) serum calcium and a 5-10% (0.2-1.0 mg/dl) serum phosphorous reduction is expected when cinacalcet is administered [6, 116-124]. It is conceivable that the calcium-PTH setpoint shift and the metabolic change in bone metabolism induced by this drug explain these results [125, 126].

Whether calcimimetic are superior to VDRAs in controlling CKD-MBD is another unanswered question. Two large RCTs, the ACHIEVE[118] and the IMPACT[127] study investigated this issue in hemodialysis patients. The first study[118] concluded for a better PTH control with cinacalcet while the second study[127] showed a better PTH control among patients treated with intravenous paricalcitol. However, some major differences in the two study designs may account for some of the discrepant results: 1) in the ACHIEVE study both paricalcitol and doxercalciferol were allowed as VDRAs, while paricalcitol was the only VDRA administered in the D arm of the IMPACT study; 2) Cinacalcet was admitted as a recue therapy for hypercalcemia during VDRA treatment in the IMPACT study, whereas it was not allowed in the ACHIEVE study; 3) treatment algorithms for cinalcalcet or VDRA dose modulation were different in the two trials. In light of these study design differences it is unclear whether one of these two approaches is superior, though answering to this question might be of limited clinical utility in light of the different pharmacological profile of calcimimetic and VDRAs.

The presence of calcium sensing receptor in different tissues other than the parathyroid glands, could explain the positive impact of cinacalcet on the bones and vasculature detected in numerous preclinical data[128]. In vitro and animal evidence suggest that a reduction of functional calcium sensing receptor is associated with vascular calcification[128, 129], blood pressure[130], proteinuria[131], CKD progression[131], arterial stiffness and endothelial dysfunction improvement[132]. Large cohort prospective studies show that calcium sensing receptor modulation is associated with favorable clinically meaningful outcomes. Cunningham and coworkers[133] showed a significant reduction in the risk cardiovascular disease, bone fracture,

parathyroidectomy incidence and a parallel improvement in the general health perception among dialysis patients with secondary hyperparathyroidism. Block et al documented a substantial risk reduction in all-cause and cardiovascular mortality associated with cinacalcet in a large cohort of 25,292 chronic hemodialysis patients independent of several confounders[134].

However, the clinical impact of cinacalcet on hard outcome is far from being established in light of the recently published results of the ADVANCE[123] and EVOLVE [6] trials. The ADVANCE trial was conducted to investigate whether cinacalcet in combination with low dose of vitamin D (<6mcg paricalcitol equivalent/ week) vs flexible doses of vitamin D attenuates coronary, aorta and cardiac valves calcification progression in a cohort of 360 prevalent hemodialysis patients. After a relatively short period of follow-up of 12 months, a trend toward CAC reduction in the cinacalcet arm [Agatston CAC scores % change: 24% (95% confidence interval: - 22%, 119%) and 31% (- 9%, 179%), in the cinacalcet and flexible vitamin D group, respectively, P = 0.073] was noted. Notably the trend was consistent across all CV sites investigated for vascular calcification [123]. Furthermore, the large dose of calcium containing phosphate binders and vitamin D administered in the calcimimetic arm may contribute to explain these results[135]. Finally, the EVOLVE trial was designed to test the survival benefit of cinacalcet hypothesized by observational data in hemodialysis patients. At study completion, a statistically non-significant trend toward reduction (relative hazard in the cinacalcet group vs. the placebo group, 0.93; 95% confidence interval, 0.85 to 1.02; P=0.11) of the composite endpoint (time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event) was reported[6]. However, the lower than anticipated event rate, the high drop-in and -out rate during follow-up (about 20%)[6], significantly affected the statistical power (0.54)[6] and the interpretability of this inconclusive RCT.

In essence, data support the notion that cinacalcet is a safe and effective drug to lower PTH in secondary hyperparathyroidism. Nonetheless, future research projects should indentify the ideal candidate that would likely increase survival and quality of life while on this treatment. Finally, though the use of cinacalcet in predialysis stages of CKD is not approved because of the risk of hypocalcemia, future studies should evaluate its efficacy and safety in CKD not dialysis dependent

cases of secondary hyperparathyroidism characterized by normal-high calcium and high phosphate in which vitamin D may further aggravate phosphorous and calcium balance.

Conclusion

Treatment of CKD-MBD is currently based largely on opinion rather than evidence and many questions about CKD-MBD await answers. A tremendous effort has been performed in the attempt to clarify the natural history and pathogenic mechanisms that trigger CKD-MBD and modulate the astonishing risk connected to it. Nonetheless a substantial degree of uncertainty on the clinical relevance and use of different serological and tissue biomarkers used to individualize and titrate treatments still exists and affects patient care. Furthermore, the incompleteness **(table 1)** and inconclusiveness due to various methodological flaws in the few available RCTs complicate the interpretation of the available evidence and lead to a heterogeneous use of the different drugs we have in our armamentarium[95].

Future effort is therefore needed to elucidate mechanisms and treatment of these imbalances that, at least observational data, link to a substantial risk burden[2] in CKD patients.

Figure 1: CKD-MBD a multifaceted syndrome characterized by serum parameters abnormalities, bone and cardiovascular marker of disease and associated with poor outcome

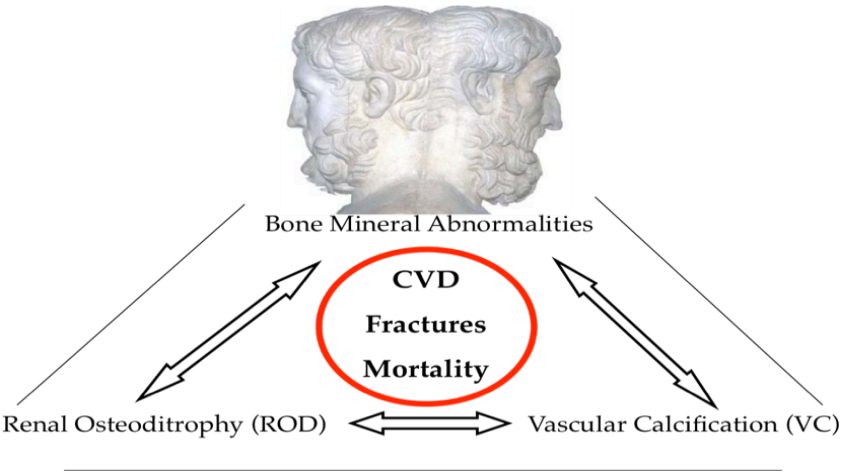

Figure 2: CKD-MBD pathophysiology is characterized by phosphate overload, PTH hypersecretion and Vitamin D depletion. Our armamentarium is composed by low protein diet and phosphate binder (light green circle) to lower phosphate overload; different forms of vitamin D (orange circle) to overcome vitamin D deficiency and inhibit PTH production and secretion; calcimimentics (light blue circle) to reduce PTH secretion.

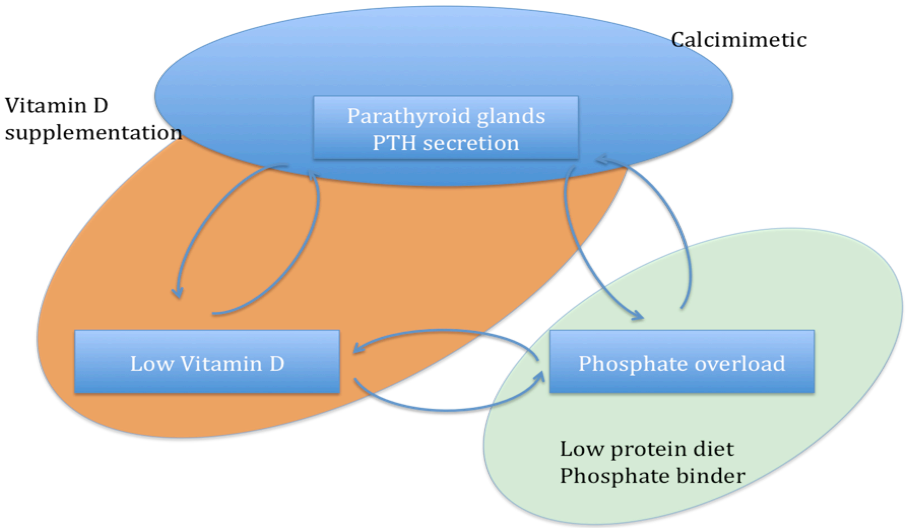

Figure 3: phosphorous balance is the net results of intake (diet), quota exchanged with bones and output (urine, feces)

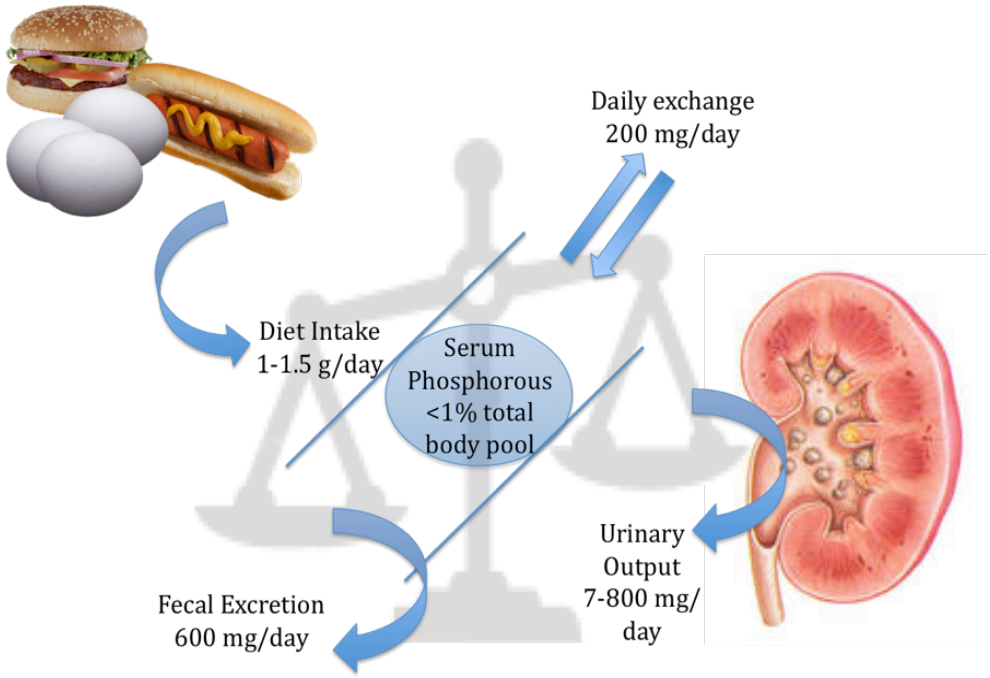

Table 1: available knowledge is mainly based on observational and inconclusive RCTs

Treatment	Type of evidence	Head to head comparisons between drugs of the same class	Mineral metabolism control	Tissue marker of organ damage	Survival data	Pharmacoeconomic evaluation
Low phosphate diet	Observational studies	NA	YES	NO	NO	NA
	RCTs	NA	YES	NO	NO	NO
Phosphate binders	Observational studies	YES	YES	YES	YES	NA
	RCTs	YES	YES	YES	YES	NO
Native vitamin D	Observational studies	YES	YES	YES	YES	NA
	RCTs	NO	NO	NO	NO	NO
Activated forms of Vitamin D (VDRA)	Observational studies	YES	YES	YES	YES	NA
	RCTs	NO	YES	YES	NO	NO
Cinacalcet	Observational studies	YES	YES	YES	YES	NA
	RCTs	NA	YES	YES	YES Inconclusive	NO

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INDEPENDENT STUDY: PRIMARY ANALYSIS RESULTS

Background: Whether the choice of sevelamer (SV) as a phosphate binder improves cardiovascular (CV) survival in patients receiving dialysis still remains to be elucidated. We aimed at evaluating the impact of SV on CV mortality in incident dialysis patients.

Study design: open label, randomized, controlled trial with parallel group

Settings and Participants: A total of 466 individuals incident to dialysis (requiring dialysis < 120 days) were recruited from 18 Centers in Italy.

Intervention: study participants were randomized in a 1:1 fashion to receive either SV or calcium salts (CS) as phosphate binders.

Outcomes: All individuals were followed until completion of 36 months of follow-up or CV death due to cardiac arrhythmias. All-cause mortality, all-CV-cause mortality and non-CV mortality were investigated as secondary endpoints.

Measurements: Event adjudication was performed by a committee masked to group allocation.

Results: The study subjects were middle-age (65±14 years); 49% men and 51% women. Hypertension (79%), CV disease (36%) and diabetes (29%) were the most common comorbid conditions. At baseline, patients allocated to SV had higher serum phosphorus levels and lower CAC scores (CACS) compared to patients allocated to CS. After a mean follow-up of 28 (± 10) months, SV treated patients experienced a 10-fold lower CV mortality due to cardiac arrhythmias compared to patients treated with CS ($p<0.001$). Similar results were noted for the all-cause, all-CV but not for non-CV mortality. Adjustments for potential confounders did not affect the results.

Limitations: open label design, higher baseline CAC burden among CS treated patients, better initial mineral metabolism control among SV treated patients, overall lower than expected mortality.

Conclusions: These results show that SV increases significantly CV survival in a cohort of Italian incident hemodialysis patients.

Introduction

Randomized controlled trials evaluating multiple potential interventions to reduce mortality in ESRD patients have largely been either negative or inconclusive. Observational studies have documented that increased serum phosphorous levels are associated with an excessive cardiovascular (CV) disease risk in incident as well as prevalent dialysis patients (CKD-5D).[1-3] This body of evidence has prompted recommends that correction of hyperphosphatemia should be attempted through a balanced approach of dietary phosphate restriction and phosphate binder administration.[4, 5] A recent prospective cohort study of 10,044 incident hemodialysis patients corroborates this recommendation showing a significant survival improvement in the first year of dialysis among patients treated with phosphate binders compared to peers not on phosphate binders.[6] These results where largely independent of serum phosphorous levels and type of phosphate binders.[6]

A few previous clinical trials[7-14] and systematic reviews[15-17] have investigated the impact of different phosphate binder regimens on clinical outcomes. In spite of a similar phosphate lowering ability, sevelamer is associated in numerous though not all studies with lower risk for CV calcification, arterial stiffening and ECG abnormalities when compared to calcium-based phosphate binders.[18, 19] Nonetheless, the impact of sevelamer on CV survival remains uncertain.[19, 20] We designed and conducted an open label, randomized controlled clinical trial to test specifically whether sevelamer compared to calcium-based phosphate binders attenuates the CV system deterioration in a cohort of incident hemodialysis (HD) patients and thus resulting in reduced CV mortality amongst these patients. The primary outcome of this study was cardiovascular mortality due to cardiac arrhythmias that are QT-dependent, secondary outcomes included all-cause mortality, all causes of cardiovascular mortality and deaths not classified as CV mortality. Similarly, changes in corrected (QTc), and QT dispersion (QTd), Pulse Wave Velocity (PWV) and Coronary Artery Calcification (CAC) associated to different phosphate binders were regarded as secondary endpoints. In this manuscript, we report on the effects of phosphate binder treatment allocation on cardiovascular mortality and all-cause mortality. The impact of treatment assignment on markers of vascular damage (i.e. CAC, QT tract and pulse wave velocity) will be reported separately.

Methods

A detailed description of the INDEPENDENT Study has been published elsewhere[21]. Study participants were randomized in a 1:1 fashion to receive as a phosphate binder either sevelamer or calcium carbonate / calcium acetate (Fig 1). Adult (>18 years) CKD-5 patients new to hemodialysis (requiring dialysis < 120 days) were enrolled at 18 dialysis center in Italy. Exclusion criteria include age older than 75 years, history of cardiac arrhythmia, syndrome of congenital prolongation of the QT segment interval, a corrected QT (QTc) longer than 440 ms or increased QT dispersion (QTd), history of coronary artery bypass (CABG), liver dysfunction and hypothyroidism and use of drugs that prolong the QT interval. Enrollment began in September 2006 and continued through July 2008. Study followup ended in July 2011.

To maintain allocation concealment, randomization was performed centrally. Patients were assigned to either sevelamer or a calcium-based phosphate binder (principally calcium carbonate with minimal calcium acetate; aluminum hydroxide was used as rescue therapy only as per KDOQI) in a 1:1 fashion (Fig. 1). The randomization process was blocked by recruitment site, and stratified by age, sex and diabetes status. Due to the unavailability of a CT scan in most study centers during patient recruitment, randomization was not stratified by baseline coronary artery calcium score (CACS). CACS were subsequently obtained on all subjects enrolled in the study in a single central location.

Investigators were instructed to adjust dosage of the phosphate binder to reduce serum phosphorous to between 2.7 - 5.5 mg/dl, as recommended by the KDOQI guidelines, available at the time of the study design.[4] Similarly, investigators were instructed to control blood pressure (≤130/80 mmHg), anemia (Hb>11 g/dl, TSAT >20%), acidosis (HCO_3 between 20-24 mmol/l), diabetes (HbA1c<7.0%), dyslispidemia (total cholesterol< 200 mg/dl; LDL cholesterol < 100 mg/dl; triglycerides <180mg/dl), and the other parameters of bone mineral metabolism (i.e., calcium, and iPTH between 8.0-9.9 mg/dl, and 150-300 pg/ml respectively) per KDOQI.[4] Investigators were free to adjust medication dosages to achieve these therapeutic targets.

Written informed consent was obtained from all participants prior to study entry and after approval from each institutional Ethical Review Board. The study was conducted in adherence to the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects. The Independent study was registered on ClinicalTrials.Gov as the Reduce Cardiovascular Calcifications to Reduce QT Interval in Dialysis (INDEPENDENT) Study, number NCT00710788.

Laboratory measurements and markers of CV disease.

Routine biochemical laboratory and imaging measurements were obtained at baseline and at six months intervals until completion of 24 months of follow-up. All blood samples were fasting and taken before the mid-week dialysis session. Serum parameters of mineral metabolism, electrolytes, inflammation, anemia, and dialysis adequacy were performed by each facilities' usual laboratory. The Nichols second generation immunoradiometric intact PTH assay was used to determine the iPTH levels.

Coronary Artery Calcium Score (CACS) was assessed by a multi-slice lightspeed (GE Medical Systems) equipment at one center (Solofra, AV), as previously described.[22] All scans were reviewed by one single reader blinded to patients' characteristics.

Primary and secondary study endpoint

The primary endpoint of the study was CV mortality QT related, defined as sudden cardiac death or death due to cardiac arrhythmias. Secondary endpoints were all-cause mortality, defined as any fatal event; all-CV mortality, defined as the composite of sudden cardiac death, death due to cardiac arrhythmias, acute myocardial infarction, cerebral vascular accident and heart failure and non-cardiovascular mortality, defined as all deaths not classified by the predefined definition for CV mortality. The non-cardiovascular deaths largely represented deaths classified as those due to cachexia, infectious disease, or neoplasia. By design, all patients were followed until death or study completion (36 months of follow-up). All patient charts were reviewed for correct adjudication of any lethal events by a committee masked to group allocation.

Statistical Methods

Demographic, clinical and laboratory characteristics were collected at enrollment. Continuous variables are presented as mean ± standard deviation or median (interquartile range) when appropriate. Categorical variables are presented as proportion. To gauge the association between phosphate binder and CV survival, all-cause survival and non-CV survival, we first plotted the incidence of these endpoint curves according to phosphate binder assignment using the Kaplan-Meier product-limit method. We, then, used the two-sided log rank test to calculate overall p-value for survival differences.[23] Finally, we calculated the age and multivariable adjusted Relative Risk (RR) by fitting the data to logistic regression models. RRs were calculated initially without adjustments. Subsequent models included adjustment for demographic variables (age, sex) and for the case-mix (diabetes mellitus, systolic and diastolic blood pressure, baseline CACS). The CACS were entered in the model as log(CACS+1) to normalize the CACS distribution and avoid zero scores exclusion. All analyses were conducted as *intention-to-treat* analyses. All probability values are two-tailed. P values ≤ 0.05 were considered statistically significant. All analyses were completed using R version 2.9.2 (2009-08-24) (The R Foundation for Statistical Computing).

Sample size calculation

Providing that the aim of the study was to assess the impact of sevelamer versus calcium-based phosphate binders on CV mortality, the sample size calculation was based on the following assumption: (1) time dependent exponential distribution of myocardial calcifications (this is the days during H>400 multiplied for the value of calcium content in the coronary artery and cardiac tissue) (2) hazard ratio according to the median survival time at 36 months in the sevelamer treated vs calcium treated patients equal to 0.667[8] (3) assignment fraction of 0.5; (4) statistical test: a 2-tailed test with type I error equal to 5%; (5) statistical test power equal to 80%; and (6) dropout rate of 10% per year. According to these assumptions, it was anticipated that a total of 194 fatal events and 360 study subjects would be required. Because of a lower than expected overall mortality rate after 12 months of study was observed in the total study population without consideration of group allocation, a new power calculation was performed using the same general

assumptions and a new lower event rate and the target number of enrolled patients was increased to 466 individuals. EaST 3.1 software was used for this calculation.

Results

A total of 466 patients were randomized to either sevelamer (N=232) or calcium carbonate (N=234). Of these, 33 (14.2%) in the sevelamer and 35 (15.0%) in the calcium arm exited the study for various reasons prior to study completion for a drop-out rate of less than 5% per year (Figure 1). Enrollment and drop-out rates were well balanced across all sites (Appendix 1). The mean age of the study cohort was 65+14 years. Males and females were equally represented; hypertension (79%), atherosclerotic CV disease (36%) and diabetes (29%) were the most common comorbidities. Baseline clinical characteristics of study subjects are shown in Table 1. Serum phosphorous was higher in the sevelamer group [mean (Standard Deviation, SD): 5.6 (1.7) versus 4.8 (1.4) mg/dl, in the sevelamer and calcium groups, respectively]. Otherwise, there were no significant differences in clinical characteristics between the sevelamer and the calcium treated subjects at study entry.

As previously shown, CAC was highly prevalent in this study cohort of incident hemodialysis patients. Indeed, only 138 (29.6%) individuals did not show any evidence of CAC at baseline. In contrast, mild (CACS 1-29), moderate (CACS 30 -99), high (CACS 100-399) and extremely high (CACS >400) CACS were detected in 108 (23.1%), 117 (25.1%), 40 (8.6%) and 64 (13.7%) study subjects, respectively. A lower average CACS was noted among patients randomized to sevelamer [median (interquartile range, IQR): 19 (0-30) vs 30 (7-180), in the sevelamer and calcium containing binder group, respectively] (Appendix 2). Through-out the study, no significant differences in the use of HMG Co-A reductase inhibitors, ACE inhibitors, beta-blockers, cinacalcet or vitamin D sterols could be detected between treatment groups. The average doses of sevelamer and calcium carbonate administered were 4300±1400 mg (median dosage 4800 mg) and 2200±1000 mg (median dosage 2000 mg), respectively.

In spite of higher serum phosphorous levels among patients allocated to sevelamer, no significant difference in serum PO_4 between the study groups (table 2) was detected at study

completion. The serum phosphorous reduction was coupled with a significant reduction in intact PTH in the sevelamer but not in the calcium study arm (comparisons between groups at study completion: p<0.001). Finally, serum calcium levels tended to be higher among calcium treated patients consistent with adherence to their prescribed binders (comparisons between groups at study completion: p<0.001) (table 2).

Patients were followed-up on average for 28 (± 10) months for the occurrence of any fatal CV or non-CV event. Specifically, 11.4% of subjects were treated for less than 12 months, 14.6% for 12–24 months, 14.6% for 24–36 months, and 59.4% for at least 36 months. At the end of the follow-up, 128 deaths [event rate: 113 (95% Confidence Interval (CI): 95-135) per 1000 patients/year] were recorded. Of these, 29 (22%) and 88 (68.7%) were adjudicated as CV due to cardiac arrhythmias [event rate: 25 (95%CI: 17-37) per 1000 patients/year] or all-CV deaths [event rate: 78 (95%CI: 63-96) per 1000 patients/year].

Survival analyses showed that sevelamer treated patients exhibited a significantly better CV survival (p<0.001) when compared to calcium treated patients (Fig 2A). Indeed, 2 [event rate: 3.3 (95%CI: 0.8-13) per 1000 patients/year] and 27 [event rate: 50 (95%CI: 34-73) per 1000 patients/year] CV deaths due cardiac arrhythmias were recorded among sevelamer and calcium treated patients, respectively. Notably a similar trend was noted when all-CV deaths were considered (9 [event rate: 15 (95%CI: 8-29)] vs 79 [event rate: 147 (95%CI: 118-184)] all-CV deaths among sevelamer and calcium treated patients, respectively). Adjustments for potential confounding factors (age, gender, presence of diabetes, systolic and diastolic blood pressures, and CAC scores at baseline) did not significantly affect this association. Sevelamer treated patients experienced a significant ten-fold reduction in the risk of death due to fatal cardiac arrhythmias (Relative Risk (RR): 0.08; 95%CI 0.02-0.37; p=0.001) (table 3). (table 3). Similar results were noted for the all-cause but not for the non-CV survival (Figure 2B,2C, 2D). Indeed, patients allocated to sevelamer experienced a significant 3.5-fold relative risk reduction (RR: 0.28; 95%CI: 0.22-0.35; p<0.001) of dying from any cause at follow-up (Table 3). Adjustment for different factors associated with poor prognosis in CKD-5D patients did not significantly affect these results (Table 3). On univariable or multivariable analyses there was no association between phosphate binder

assignments and non-CV mortality. Thus, the all-cause survival benefit was most likely driven principally by the lower CV mortality in the sevelamer group. The study was not sufficiently powered to determine if a small difference in non-cardiovascular mortality was present.

To explore the impact of sevelamer on CV survival independent of baseline CAC score, we tested whether sevelamer improved survival among patients with different CAC burden at baseline. After adjustment for age, sex, diabetes, systolic and diastolic blood pressure, and baseline CAC, sevelamer treatment was associated with a substantial reduction in CV events among patients without CAC (RR 0.16; 95%CI: 0.08 -0.30; p=0.004); with CACS greater than 0 but less than 400 (RR 0.05; 95%CI: 0.02-0.11; p<0.001); and CACS greater than 400 (RR: 0.31; 95%CI: 0.12 – 0.79; p=0.01).

Discussion

In this study, a large cohort of incident hemodialysis patients was randomized to receive either sevelamer or calcium salts for treatment of hyperphosphatemia. An important objective of the study was to test the impact of phosphate binder choice on both CV and all-cause survival. Previous randomized clinical trials (RCT) showed that sevelamer may significantly attenuate cardiovascular calcification progression in both incident and prevalent dialysis patients.[7-9] Other observational studies[18-24] suggest that sevelamer use is also associated with a significantly lower arterial stiffness, another marker of CV disease[25]. Nonetheless, prior to the current study, a beneficial impact of sevelamer on hard patient-centered outcomes has been uncertain.[15-20] A secondary analysis of the Renagel In New Dialysis patients (RIND) study, showed a substantial 3.1-fold reduction in the all-cause mortality among incident hemodialysis patients receiving sevelamer[8]. This benefit became evident after 2 years of treatment and persisted after multivariable adjustment (hazard ratio for death associated with calcium vs sevelamer treatment: 3.1, 95% CI 1.23–7.61; p=0.02). The generalizability of these results is limited by the small sample size of the RIND study and by the inconclusive results of the Dialysis Clinical Outcomes Revisited (DCOR) study.[11]DCOR failed to demonstrate a mortality reduction with sevelamer treatment for the entire population (hazard ratio of sevelamer vs calcium treatment: 0.93, 95% CI: 0.79–1.10; P=0.40). A significantly better

survival was noted for subjects older than 65 years of age assigned to treatment with sevelamer [RR 0.77; 95%CI: 0.61-0.96; p=0.02].[11, 26] The high dropout rate (about 50% of the entire DCOR study cohort), the lower than expected event rate for the entire study population, and the relatively short follow-up (38% of subjects were treated for less than 12 months, 20% for 12–24 months, 25% for 24–36 months, and only 17% for more that 36 months) may partly explain the failure of DCOR to demonstrate conclusively an overall survival benefit with sevelamer. A *post hoc* analysis of DCOR demonstrated that patients who received sevelamer for at least 24 months exhibited a significantly better survival (Relative Risk for sevelamer vs calcium treatment: 0.66; 95%CI: 0.48-0.94; p=0.02)[26].

The current study, the Independent study, adds to the existing body of evidence by showing that sevelamer is associated to a significantly lower CV and all-cause mortality in a large cohort of old (overall mean age: 65.6±14.8 years) incident dialysis patients, treated for a relatively longer period of time (74% of study subjects were treated for at least 24 months). Notably, the Independent study results on the all-cause mortality (the least susceptible to misclassification) are consistent with a 3-fold reduction previously documented in the RIND study. Furthermore, the fact that no effect on non-CV mortality could be demonstrated, suggests that the positive impact of sevelamer on all-cause mortality is mainly driven by the significantly lower CV mortality. Additionally, overall mortality in this cohort of incident dialysis patients was lower than expected; thus the study was likely insufficiently powered to demonstrate an impact of treatment on the less common causes of mortality.

The Independent study exhibits limitations worth noting. One limitation is the higher baseline CAC burden among patients allocated to calcium containing phosphate binders since CAC is a marker of cardiovascular disease risk in CKD-5 patients.[8, 27] Nonetheless, adjustment for baseline CAC did not change the strengths of the association between sevelamer treatment and CV survival, supporting the conclusion that the effect is independent of CAC burden.

The open label design represents another possible limitation. Effective blinding was deemed impossible due to the predictable lowering of serum total and LDL cholesterol by sevelamer. An impact of unblinding on differential care of patients by group allocation was minimized by

protocolizing all other aspects of patient management according to KDOQI. Additionally, outcomes were adjudicated independently by investigators masked to treatment allocation. Patients allocated to Sevelamer exhibited better initial mineral metabolism control. However, after therapy was established, the serum phosphorous levels were comparable between study groups throughout the remainder of the study. Finally, the overall lower mortality observed in this study was consistent with mortality rates reported for cohorts of incident dialysis patients with normal QTc values and hence, less advanced cardiovascular disease. Thus, it is possible that the beneficial effects of sevelamer observed in this RCT might not be seen in patients with more advanced cardiovascular disease. However, in most clinical conditions the magnitude of benefit increases and hence, the number needed to treat decreases when baseline risks are higher.

In summary, we have demonstrated in an Italian cohort of incident CKD-5D patients that sevelamer treatment improves CV and all-cause survival. The current study differs importantly with previous published studies in that it is larger, evaluates a hard patient-centered outcome and has achieved significantly more complete follow-up of substantially longer duration. This study helps meet the acknowledged need for well-conducted RCTs addressing patient centered outcomes of sufficient duration and size to inform the major therapeutic choices in nephrology. In keeping with the existing evidence, the data from the current study lend compelling support to the view that older and / or incident dialysis patients may benefit greatly from treatment of hyperphosphatemia with the non-calcium containing phosphate binder, sevelamer when compared to treatment with calcium-based binders.

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Table 1: Demographic, clinical and laboratory characteristics of study cohort at baseline and according to phosphate binder assignments

	Total (N = 466)	Sevelamer (n = 232)	Calcium Carbonate (n = 234)	*P*
Male sex	49	50	48	0.7
Age (y)	65.6 ± 14.8	66.6 ± 14.1	64.6 ± 15.4	0.1
Atherosclerotic CVD	36	36	34	0.7
Hypertension	79	78	80.5	0.6
Diabetes	29	30	29	0.9
Body weight (kg)	69.2 ± 14.1	70.8 ± 15.2	67.6 ± 12.7	0.01
SBP (mm Hg)	137 ± 18	137 ± 18	137 ± 17	0.9
DBP (mm Hg)	76 ± 9	76 ± 9	76 ± 9	0.9
Use of vitamin D	42	42	41	0.9
Use of cinacalcet	53	50	54	0.4
Use of EPO	88	87	88	0.9
Creatinine (mg/dL)	7.8 ± 2.5	7.9 ± 2.3	7.7 ± 2.7	0.4
Sodium (mmol/L)	139 ± 3	138 ± 3	139 ± 3	<0.001
Phosphorus (mg/dL)	5.2 ± 1.5	5.6 ± 1.7	4.8 ± 1.4	<0.001
Calcium (mg/dL)	8.9 ± 0.7	9.0 ± 0.8	8.8 ± 0.7	0.004
Hemoglobin (g/dL)	11.0 ± 1.5	11.1 ± 1.5	11.0 ± 1.5	0.5
Intact PTH (pg/mmol)	274 ± 207	265 ± 187	283 ± 226	0.4
Albumin (g/dL)	3.8 ± 0.4	3.9 ± 0.5	3.7 ± 0.4	<0.001
LDL cholesterol (mg/dL)	99 ± 29	98 ± 30	100 ± 28	0.5
CRP (mg/dL)	7.4 ± 10.7	8.8 ± 13.4	5.9 ± 6.8	0.003
Kt/V	1.2 ± 0.3	1.2 ± 0.4	1.3 ± 0.3	0.002

Note: Values for categorical variables are given as percentages; values for continuous variables are given as mean ± standard deviation. Conversion factors for units: creatinine in mg/dL to μmol/L, ×88.4; phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495; LDL cholesterol in mg/dL to mmol/L, ×0.02586.

Abbreviations and definitions: atherosclerotic CVD, atherosclerotic cardiovascular disease (defined as cerebrovascular disease, peripheral vascular disease, angina pectoris, history of myocardial infarction, aortic aneurysm, history of percutaneous coronary angioplasty with or without stenting); CRP, C-reactive protein; DBP, diastolic blood pressure; EPO, erythropoietin; LDL, low-density lipoprotein; PTH, parathyroid hormone; SBP, systolic blood pressure.

Table 2. Mineral metabolism control at study entry and completion between the two study arms. Data are experessed as mean and standard deviation or median and interquartile range when appropriate.

Table 2. Mineral Metabolism Control at Study Entry and Completion Between Study Arms

	Sevelamer (n = 232)			Calcium Carbonate (n = 234)			Sevelamer vs Calcium Carbonate	
	Baseline	24 mo	Baseline vs 24 mo	Baseline	24 mo	Baseline vs 24 mo	Baseline	24 mo
Phosphorus (mg/dL)	5.6 ± 1.7	4.2 ± 1.2	−1.37 ± 1.93; $P < 0.001$	4.8 ± 1.4	4.8 ± 1.1	−0.10 ± 1.67; $P = 0.4$	0.75 ± 0.14	−0.65 ± 0.12; $P < 0.001$
Calcium (mg/dL)	8.9 ± 0.8	8.2 ± 0.5	−0.70 ± 0.91; $P < 0.001$	8.8 ± 0.7	9.6 ± 1.1	0.84 ± 1.21; $P < 0.001$	0.15 ± 0.07	−1.37 ± 0.09; $P < 0.001$
Intact PTH (pg/mL)	208 [135-265]	120 [78-137]	−153.7 ± 188.4; $P < 0.001$	218 [135-283]	240 [142-398]	2.1 ± 313.5; $P = 0.4$	17.5 ± 19.2	−173.7 ± 15.85; $P < 0.001$

Note: Values are given as mean ± standard deviation or median [interquartile range]. Conversion factors for units: phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495.

Abbreviation: PTH, parathyroid hormone.

Table 3: Risk reduction for the primary and secondary endpoints amongst subjects assigned to sevelamer

Outcome	Value	*P*
CV mortality from cardiac arrhythmias		
No. of deaths		
Sevelamer	2	
Calcium carbonate	27	
HR (95% CI)		
Unadjusted model	0.06 (0.01-0.25)	<0.001
Adjusted model	0.08 (0.02-0.34)	<0.001
All-cause CV mortality		
No. of deaths		
Sevelamer	9	
Calcium carbonate	80	
HR (95% CI)		
Unadjusted model	0.09 (0.05-0.19)	<0.001
Adjusted model	0.11 (0.05-0.22)	<0.001
All-cause mortality		
No. of deaths		
Sevelamer	28	
Calcium carbonate	100	
HR (95% CI)		
Unadjusted model	0.23 (0.15-0.35)	<0.001
Adjusted model	0.26 (0.17-0.41)	<0.001
Non-CV mortality		
No. of deaths		
Sevelamer	19	
Calcium carbonate	20	
HR (95% CI), unadjusted model	0.75 (0.39-1.40)	0.4
HR (95% CI), adjusted model		
Patients with f/u <25 mo	2.74 (0.81-9.30)	0.3
Patients with f/u ≥25 mo	0.19 (0.06-0.61)	0.01

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Legend: CV: Cardiovascular; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; CAC: coronary artery calcification at baseline

Figure 1: study flowchart

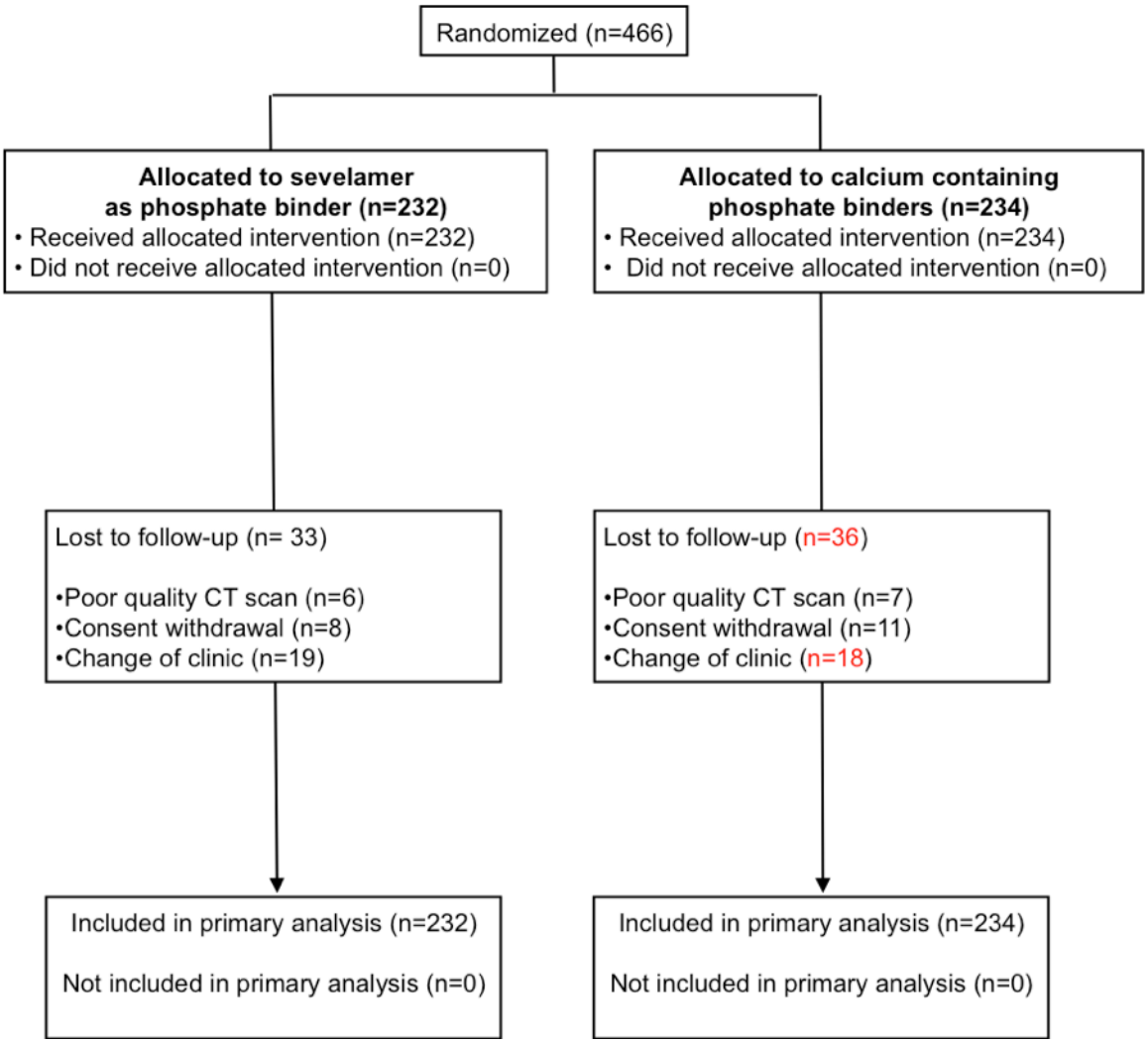
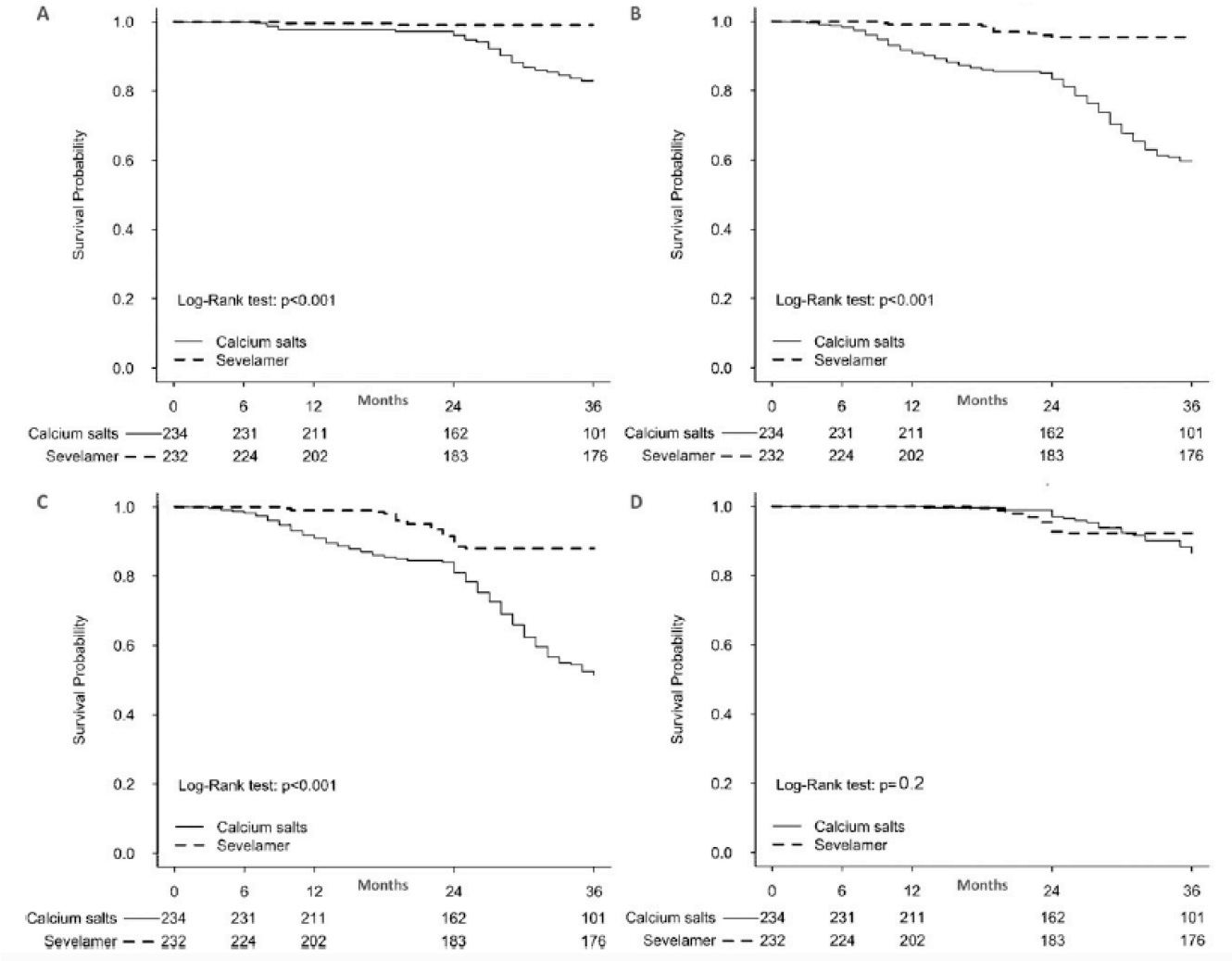


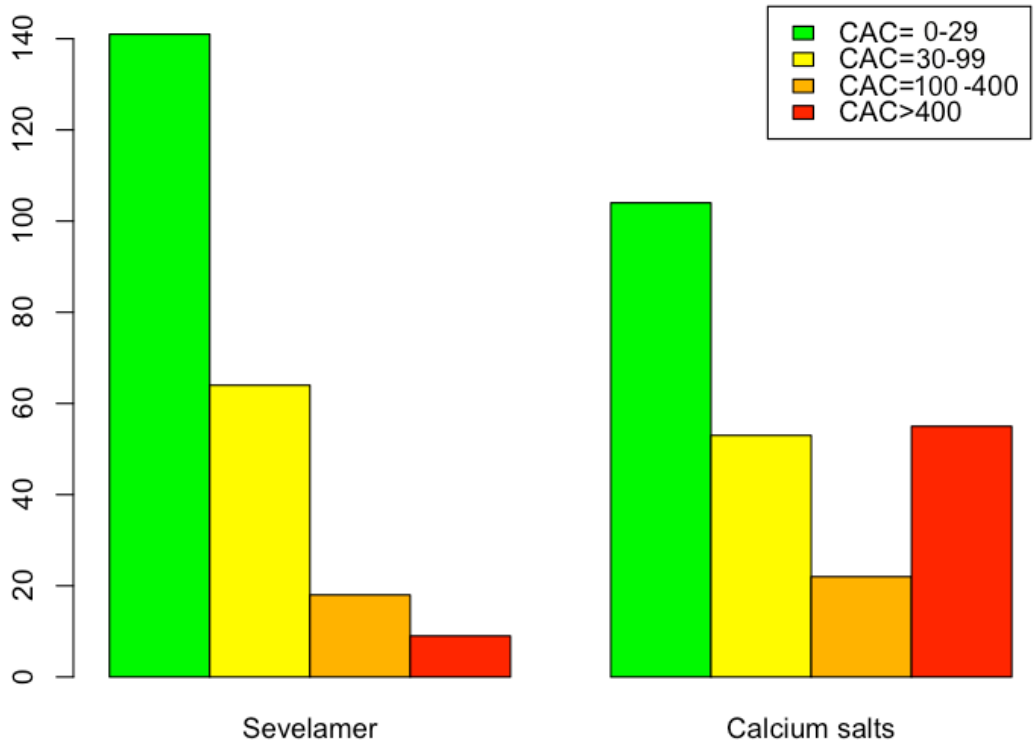
Figure 2: Kaplan-Meier CV survival due to cardiac arrhythmias (A), all-CV survival (B), all-cause survival (C) and non-CV survival (D) according to phosphate binder assignment



APPENDIX 1: Overall allocation and outcomes by site.

Overall	# patients	withdrawn	study completed	Sevelamer	Calcium	Deaths
	466	69	397	200	197	128
By study site	# patients	withdrawn	study completed	Sevelamer	Calcium	Deaths
1	30	4	26	13	13	6
2	28	4	24	13	11	7
3	16	2	14	7	7	5
4	14	5	9	5	4	4
5	32	2	30	14	16	9
6	54	8	46	24	22	10
7	24	4	20	11	9	10
8	22	3	19	9	10	9
9	26	2	24	12	12	8
10	36	6	30	14	16	11
11	42	1	41	21	20	16
12	22	0	22	10	12	10
13	18	7	11	6	5	4
14	16	4	12	5	7	5
15	18	2	16	9	7	4
16	16	3	13	6	7	5
17	20	5	15	8	7	2
18	32	7	25	13	12	3

Appendix 2: Coronary Artery Calcification (CAC) burden according to phosphate binder assignment.



INDEPENDENT STUDY: PHARMACOECONOMIC ANALYSIS RESULTS

Background: The recent multicenter, randomized, open-label INDEPENDENT study demonstrated that sevelamer improves survival in new to hemodialysis (HD) patients compared with calcium carbonate. The objective of this study was to determine the cost-effectiveness of sevelamer versus calcium carbonate for patients new to HD, using patient-level data from the INDEPENDENT study.

Study design Cost-effectiveness analysis.

Setting and population Adult patients new to HD in Italy.

Model, perspective, timeframe A patient-level cost-effectiveness analysis was conducted from the perspective of the Servizio Sanitario Nazionale, Italy's national health service. The analysis was conducted for a 3-year time horizon. The cost of dialysis was excluded from the base case analysis.

Intervention Sevelamer was compared to calcium carbonate.

Outcomes Total life years (LYs), total costs, and the incremental cost per LY gained were calculated. Bootstrapping was used to estimate confidence intervals around LYs, costs, and cost-effectiveness and to calculate the costeffectiveness acceptability curve.

Results Sevelamer was associated with a gain of 0.26 in LYs compared to calcium carbonate, over the 3-year time horizon. Total drug costs were **€**3,282 higher for sevelamer versus calcium carbonate, while total hospitalization costs were **€**2,020 lower for sevelamer versus calcium carbonate. The total incremental cost of sevelamer versus calcium carbonate was **€**1,262, resulting in a cost per LY gained of **€**4,897. The bootstrap analysis demonstrated that sevelamer was cost effective compared with calcium carbonate in 99.4 % of 10,000 bootstrap replicates, assuming a willingness-to-pay threshold of **€**20,000 per LY gained.

Limitations Data on hospitalizations was taken from a post hoc retrospective chart review of the patients included in the INDEPENDENT study. Patient quality of life or health utility was not included in the analysis.

Conclusions Sevelamer is a cost-effective alternative to calcium carbonate for the first-line treatment of hyperphosphatemia in new to HD patients in Italy.

Introduction

Hyperphosphatemia is a common and serious consequence of chronic kidney disease (CKD). It is most prevalent among CKD patients receiving dialysis, with published estimates of prevalence ranging from 47 to 80 % [1–4]. A recent report from the COSMOS study found that most hemodialysis patients (70.5 %) had serum phosphorus levels that were above the normal range recommended by the kidney disease: improving global outcomes (KDIGO) guidelines (3.0–4.5 mg/dL) [4]. Left untreated, hyperphosphatemia leads to an increased risk of morbidity, including vascular calcification (abnormal deposition of calcium-phosphate in connective tissues and solid organs such as the arteries and heart), cardiovascular disease and cardiovascular events, metabolic bone disease and bone fractures, and an increased risk of mortality [5, 6]. Given these consequences, international treatment guidelines recommend lowering serum phosphorus towards normal levels in CKD patients on dialysis through the control of dietary phosphorus and use of phosphate binders [7].

Commonly used phosphate binders include calciumbased binders (CBBs) such as calcium carbonate and calcium acetate and non-CBBs such as sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate. While CBBs are effective at reducing serum phosphorus in CKD patients on dialysis, the resulting increased exposure to calcium via calcium from these binders has been shown to contribute to positive calcium balance in patients, resulting in an increased risk of vascular calcification, cardiovascular morbidity and mortality [8–13]. In response to mounting evidence and growing concerns regarding calcium overloading and its sequelae in patients with CKD, the KDIGO guidelines include recommendations regarding restricting the usage/dosage of calcium-based binders in CKD patients who have hyperphosphatemia in the presence of persistent/recurrent hypercalcemia, calcification, persistently low parathyroid hormone (PTH), and/or adynamic bone disease [7].

Sevelamer hydrochloride and sevelamer carbonate are calcium-free, non-absorbed phosphate binders that effectively lower serum phosphorus without contributing to positive calcium balance in patients with CKD. Several studies have demonstrated that sevelamer lowers the progression of coronary artery and aortic calcification compared with calcium-based binders in CKD

patients on

maintenance hemodialysis [14 –21], and in CKD patients new to hemodialysis [22 –24]. Most importantly, several randomized controlled trials (RCTs) have suggested that sevelamer may improve survival in CKD patients on hemodialysis compared with calcium-based binders [23 –26]. The most recent of these RCTs was the INDEPENDENT study; a multicenter, randomized, open-label study comparing sevelamer to calcium carbonate for the treatment of hyperphosphatemia in incident dialysis patients in Italy [24]. All patients were followed up for 36 months or until death or study discontinuation. The primary endpoint of the study was cardiovascular mortality due to cardiac arrhythmias (defined as death attributed to either cardiac arrhythmia or sudden cardiac death defined as death coded as cardiac arrest, cause unknown or cardiac arrhythmia); all-cause cardiovascular mortality (defined as the composite of fatal event due to sudden cardiac death, cardiac arrhythmias, acute myocardial infarction, cerebral vascular accident, and heart failure), all-cause mortality (defined as any fatal event), and non-cardiovascular mortality were secondary endpoints in the study. Survival analyses found that sevelamer-treated patients exhibited a significant reduction in the risk of cardiovascular death due to cardiac arrhythmias compared with calcium carbonate [hazard ratio (HR) 0.06, 95 % confidence interval (CI) 0.01–0.25, **p**\ 0.001). A significant risk reduction was also noted for all-cause mortality (HR 0.20, 95 % CI 0.13–0.31, **p**\ 0.001).

We conducted a cost-effectiveness analysis (CEA) of sevelamer versus calcium carbonate in CKD patients on dialysis using patient-level data from the INDEPENDENT study, in order to assess whether sevelamer represents good value for its added cost relative to calcium carbonate in Italy.

Methods

Individual patient-level data from the INDEPENDENT study (NCT#00710788) was used to perform the CEA of sevelamer versus calcium carbonate in CKD patients new to hemodialysis. A detailed description of the study design, methods and results for the INDEPENDENT study has

been published elsewhere [21, 24]. Briefly, the study enrolled adult (age [18 years) CKD patients who were new to hemodialysis (\120 days of hemodialysis) from 18 nephrology clinics across Italy. Exclusion criteria included age older than 75 years of age, history of cardiac arrhythmia, syndrome of congenital prolongation of the QT segment interval, a corrected QT longer than 440 ms or increased QT dispersion, history of coronary artery bypass, liver dysfunction, hypothyroidism and use of drugs that prolong the QT interval. A total

of 466 eligible participants were randomized in a 1:1 fashion to open-label treatment with either sevelamer or calcium-based binders, with clinicians

free to adjust treatment dosage to achieve serum phosphorus target of 2.7–5.5 mg/dL. Although not required by the study protocol, all patients in the calcium-based binder group received calcium carbonate. Participants were followed for 36 months or until a fatal event or lost to

follow-up. A total of 68 participants, 35 (15 %) in the calcium-based binder group and 33 (14 %) in the sevelamer group, were lost to follow-up. The results of the INDEPENDENT study and this CEA were based on the intention-to-treat patient population of 232 sevelamer patients and 234 calcium carbonate patients. For the CEA, patient-level data from the INDEPENDENT study for time to death from all causes or time to end of follow-up (for patients remaining alive at 36 months) was used to calculate life years (LYs). Mean per-patient daily dose of sevelamer and calcium carbonate and hospitalization data were also based on the INDEPENDENT study and were included in the calculation of total costs. Since the INDEPENDENT study did not collect data regarding quality of life or patient utility, the incorporation of quality-adjusted life years (QALYs) in the analysis would have required the use of data external to the clinical trial. In order to avoid introducing external data and associated assumption, LYs were used as the outcomes when calculating the incremental cost-effectiveness ratio (ICER). The CEA was performed from the perspective of the Servizio Sanitario Nazionale (SSN), Italy's national health service and included only direct medical costs, and not indirect costs such as those associated with productivity loss. The time horizon for the analysis was 3 years, as treatment and follow-up data from the INDEPENDENT study were available for this period. No discounting was applied to costs or outcomes. Bootstrapping was employed to estimate 95 % confidence intervals around the point estimates for LYs, total costs, and the ICER.

Direct medical resource use and costs

Direct medical costs included in the CEA were the costs of sevelamer, calcium carbonate, and hospitalizations during the clinical trial. Costs associated with outpatient visits, concomitant medications, and adverse events were not included in the analysis, as choice of phosphate binder was assumed not to impact these costs. Dialysis costs were also excluded from the analysis for methodological reasons explained elsewhere [27]. Discounting was not applied to outcomes or costs, as the analysis was limited to 3 years. All costs are expressed in 2012 Euros (**€**).

Drug costs

Patient-level dosages for sevelamer and calcium carbonate were obtained from the INDEPENDENT study. Daily doses of sevelamer and calcium carbonate for years one, two, and three of the analysis were informed using daily doses at study start and at 12 and 24 month follow-ups, respectively, for each participant. Assuming an 800-mg pill for sevelamer and a 500-mg pill for calcium carbonate, the mean number of pills per day was calculated. Total drug costs were calculated using costs for sevelamer (**€** 0.75 per pill) and calcium carbonate (**€** 0.0165 per pill) provided by the hospital pharmacy at Solofra Hospital, Avellino, Italy and the Farmadati Italia database.

Hospitalization costs

Data regarding hospitalizations were not directly collected in the INDEPENDENT study. However, because hospitalizations represent the largest component of resource utilization in patients with CKD [28] and because sevelamer has been shown previously to reduce the risk of hospitalizations in patients with CKD [29

], it was deemed important to capture the frequency and cost of hospitalizations in the CEA. Post hoc to the INDEPENDENT study, a retrospective chart review of the patients included in the INDEPENDENT study was conducted to collect data regarding hospitalizations. The hospitalizations considered in the analysis of the costs were related to arrhythmias, angina pectoris, myocardial infarction, stroke, heart failure, shortness of breath not from pulmonary sepsis. Were excluded arteriovenous fistula surgery, respiratory tract infections and sepsis, trauma, and all the diseases that were not related to cardiovascular disease. Specific data for each hospitalization, including length of stay (LOS) and discharging ward, were collected for each patient from the point of randomization to the point of study completion (3 years), death or lost to follow-up. Unit costs for hospitalizations were taken from the Italian diagnosis-related group (DRG) tariffs and were applied, according to discharging ward, to each hospitalization for each patient to arrive at a total cost of hospitalization over the 3 years. The unit costs for a hospitalization discharged from the intensive care unit (ICU), nephrology ward, or cardiology ward was **€** 3,730, **€** 3,746, and **€** 3,694, respectively. The analyses assumed no differences in the unit cost of hospitalization between the treatment groups.

Statistical methods

Frequencies and percentages were used to describe discrete variables and mean [standard deviation (SD)] was used to

report continuous variables. Variance around the mean difference was reported as a 95 % CI. Fischer's exact test and Student's t test were used to determine statistical significance between treatment groups for discrete and continuous data, respectively, with p\ 0.05 signifying significance for both tests. Mean cumulative LYs and costs were calculated using the total LYs and costs for each participant and were reported for both treatments arms. The cost effectiveness of sevelamer versus calcium carbonate was calculated as the difference in the mean cumulative 3-year costs between sevelamer and calcium carbonate divided by the difference in the mean 3-year cumulative LYs. Variance around the point estimates for mean cumulative costs and LYs and the ICER, in the form of 95 % CI, was estimated using parametric bootstrapping methods [30]. In brief, the original dataset was randomly sampled with replacement to generate 10,000 new sets of data. For each bootstrap dataset, the mean cumulative survival and costs were calculated and then used to calculate the ICERs. The net monetary benefit statistic was calculated for the bootstrap samples and was used to determine the probability of sevelamer being cost effective versus calcium carbonate over a reasonable range of willingness-to-pay thresholds (WTPs). A cost-effectiveness acceptability curve (CEAC) was plotted using the probability estimates of sevelamer's cost effectiveness over a range of WTP thresholds.

Sensitivity analysis

Since data regarding dialysis was not collected in the INDEPENDENT study and because phosphate binder choice was not expected to have an impact on the frequency of dialysis, the cost of dialysis was excluded from the base case analysis. A sensitivity analysis was conducted to explore the impact on the results of including dialysis costs. For the sensitivity analysis, all patients were assumed to undergo thrice weekly hemodialysis for the duration of their follow-up in the study; that is, until death, lost to follow-up or 36 months. The unit cost for a hemodialysis session (**€** 176.98) was taken from regional ambulatory tariff.

Results

Patient population for the economic evaluation

A total of 466 patients (sevelamer n = 232, calcium carbonate 234) were included in the efficacy analysis of the INDEPENDENT study and were included in this CEA. Patients were a mean age of 65 (SD 14.8) years; 49 % of patients were male, 79 % had hypertension, 36 % had atherosclerotic cardiovascular disease, and 29 % had diabetes (Table 1). Baseline serum phosphorus level was higher in the sevelamer group [5.6 (SD 1.7) mg/dL] compared to the calcium carbonate group [4.8 (1.4) mg/dL]. There were no significant differences between treatment groups ± cinacalcet, and vitamin D [24]. In fact 97 (42 %) in sevelamer group and 96 (41%) in calcium group received vitamin D (p = 0.9), and 116 (50 %) in sevelamer group and 126 in calcium group received cinacalcet (p = 0.4). On average, vitamin D costs were **€** 721.45 higher per patient/year treated with sevelamer compared with calcium carbonate; and cinacalcet cost were **€** 523.93 higher per patient/year treated with sevelamer compared with calcium carbonate (total costs for vitamin D and cinacalcet per pts/year were 1,245.36 (Appendix 1 Supplementary data). These costs were higher for sevelamer because patients receiving sevelamer had more life years and therefore more dialysis sessions versus calcium carbonate.

Between the two groups there was no difference for the use of hemofiltration (49/200 pts in Sevelamer group, 24.5 %, versus 47/197 in calcium group, 23.8 %). The two groups showed no difference with regard to the efficiency

calculated as dialysis Kt/V (1.22 ± 0.22 and 1.27 ± 0.27 and 1.26 ± 0.26 in sevelamer group versus 1.26 ± 0.29 and 1.27 ± 0.20 and 1.28 ± 0.27 in calcium group at baseline and first and second year of observation, respectively), neither for the protein catabolic rate (1.09 ± 0.04 versus 1.11 ± 0.05 in sevelamer and calcium group, respectively) (Appendix 2, Supplementary data).

Base-case analysis

Clinical outcomes

Table 1 summarizes the trial-based LYs, and hospitalizations associated with sevelamer and calcium carbonate for the base case analysis over 3 years. A total of 28 (12 %) deaths occurred among sevelamer patients in contrast to 100 (43 %) deaths among calcium carbonate patients (p

= 0.000); the rate of all-cause mortality was significantly less frequent among patients randomized to sevelamer (p< 0.001) [24]. The mean number of LYs per patient treated with sevelamer was 2.54 ± 0.86, while the mean number of LYs per patient treated with calcium carbonate was 2.28 ± 0.82; the gain of 0.26 (95 % CI 0.11–0.41) LYs for sevelamer was statistically significant at p< 0.05.

The total number of patients admitted to hospital in the sevelamer group (n = 27; 12 %) was significantly fewer than those admitted to hospital in the calcium carbonate group (n = 100; 43 %; p< 0.0001). The total number of hospitalizations was also significantly fewer for patients treated with the sevelamer than for patients treated with calcium carbonate (51 hospitalizations for sevelamer versus 178 hospitalizations for calcium carbonate; p<0.0001). This trend was significant at the p< 0.05 level across all ward types: nephrology (46 for sevelamer versus 133 for calcium carbonate), cardiology (3 versus 22, respectively), and ICU (2 versus 23, respectively).

Economic outcomes

Table 2 summarizes the mean per-patient phosphate binder, hospitalization, and total costs associated with sevelamer and calcium carbonate for the base case analysis over 36 months. The mean drug cost per patient for sevelamer was €3,282.12 (95 % CI 3,098.82–3,288.56) higher than that of calcium carbonate (p<0.05). The mean per-patient cost for all hospitalizations was significantly lower among those treated with sevelamer than those treated with calcium carbonate (€822.66 versus €2,843.06, respectively; p = 0.0001). By ward type, mean costs per patient were lower for patients treated with sevelamer: €1,386, €300, and €334 lower for hospitalizations to the nephrology, cardiology, and ICU wards, respectively. Any differences in the mean costs between treatment groups were derived solely from clinical data demonstrating a reduction in the mean number of hospitalizations with sevelamer. The cost savings associated with the reduction of hospitalizations for patients treated with sevelamer partially offset the higher acquisition cost for sevelamer; total per patient costs were € 1,261.73 (95 % CI 666.16–1,857.30) higher for sevelamer compared with calcium carbonate (p = 0.0001).

Cost-effectiveness analysis and bootstrap analysis

In the base-case CEA, sevelamer resulted in greater Lys (incremental 0.26) and higher total costs

(incremental € 1,261.73) per patient than calcium carbonate over 36 months, resulting in a cost per LY gained of € 4,897. The bootstrap analysis resulted in a mean incremental LY of 0.26 (95 % CI 0.25–0.27) and mean incremental cost of € 1,262.92 (95 % CI 1,224.24–1,301.60) (Fig. 1). In nearly all (99.94 %) of the bootstrap samples, sevelamer was more effective and more costly than calcium carbonate. In the remainder of the bootstrap samples (0.06 %), sevelamer was less effective and more costly than calcium carbonate. Notably, in 99.6 % of the 10,000 bootstrap samples, the ICER for sevelamer versus calcium carbonate was below a willingness-to-pay threshold of € 25,000 per life year gained. In 94.9 % of the bootstrap samples, the ICER for sevelamer versus calcium carbonate was below a willingness-to-pay threshold of € 10,000 per life year gained. Plotting of the probability estimates that sevelamer was cost effective over a range of WTP thresholds found that sevelamer had a 95 % chance of being cost effective versus calcium carbonate at a WTP threshold of € 10,000 per LY gained (Fig. 2).

Sensitivity analysis

We conducted a sensitivity analysis that included the cost of dialysis. The analysis assumed thrice weekly hemodialysis for all patients for their duration of time in the study, at a unit cost of (€ 176.98) per hemodialysis session. Because of the survival advantage for sevelamer versus calcium carbonate, patients receiving sevelamer had more dialysis sessions versus calcium carbonate. The mean number of dialysis sessions for sevelamer-treated patients was 396.30 ± 134.32 versus 356.11 ± 127.59 for calcium-treated patients, resulting in a mean difference of 40.19 dialysis sessions (95 % CI 16.40–56.61, p = 0.07). On average, dialysis costs were € 7,113.32 higher per patient treated with sevelamer compared with calcium carbonate (95 % CI 2,902.86–10,006.55, p = 0.03). As a consequence, total incremental costs were € 8,375.04 higher for sevelamer versus calcium carbonate (95 % CI 4,073.62–12,676.47, p = 0.02). With the inclusion of the cost of dialysis, the ICER increased from € 4,897 in the base-case analysis to € 32,506 per LY gained. The bootstrap analysis resulted in mean incremental LYs of 0.26 (95 % CI 0.25–0.27) and mean incremental costs of € 8,350.67 (95 % CI 8,068.35–8,632.98) per patient (Fig. 3 a). Similar to the base case analysis, sevelamer was more effective and more costly than calcium carbonate in 99.95 % of the bootstrap samples. In the remainder of the bootstrap samples (0.05 %), sevelamer was

less effective and more costly than calcium carbonate. The ICER for sevelamer versus calcium carbonate fell between a WTP threshold of € 30,000 and € 50,000 per life year gained in 96.8 % of the bootstrap samples. Figure 3 b plots the results of the bootstrap analysis using the probability estimates of sevelamer's cost effectiveness over the range of WTP thresholds.

Discussion

Our study represents the first CEA to use patient-level data from a RCT to evaluate the cost effectiveness of sevelamer versus calcium-based binders for the first-line treatment of hyperphosphatemia in CKD patients new to dialysis. The INDEPENDENT study found a statistically significant improvement in both cardiovascular and all-cause survival was observed in patients receiving sevelamer compared to those receiving calcium carbonate [24]. The CEA of this study found sevelamer to result in greater LYs (incremental 0.26) and higher total costs (incremental €1,261.73) per patient than calcium carbonate over 36 months, resulting in a cost per LY gained of €4,897. In 95 % of the bootstrap samples, the ICER for sevelamer versus calcium carbonate was below a willingness-to-pay threshold of €10,000 per LY gained.

Our findings differ from three previous sevelamer CEAs [31–33]. In the most recent of these, Bernard and colleagues [24] modeled a lifetime analysis using hospitalization rates and extrapolated overall survival data derived from the Dialysis Clinical Outcomes Revisited (DCOR) study [31]. In the base case analysis, the incremental cost per QALY gained was £22,157 (2009 GBP) and the incremental cost per LY gained was £13,427, using the perspective of the publicly-funded healthcare system in the UK, the National Health Service (NHS).

In 2008, Taylor et al. [32] reported a model-based CEA that utilized data from the renagel in new to dialysis (RIND) study to compare the associated costs and outcomes of treating hyperphosphatemia with either sevelamer or calcium-based binders in patients new to dialysis. From the perspective of a UK payer, sevelamer was found to be cost-effective compared with calcium-based binders over a 5-year time horizon, with a cost per LY gained of £15,508 (2007 GBP) and a cost per QALY gained of £27,120. In contrast to the results reported by Bernard et al. and Taylor et al., the Canadian analysis of sevelamer by Manns and colleagues found much higher ICERs. In their study, the efficacy

of sevelamer was based on the DCOR study and was evaluated using four unique models that varied assumptions regarding survival benefit of sevelamer [33]. Results ranged from no benefit and an added cost of $17,000 (2004 CDN dollars) for sevelamer to sevelamer being more effective and more costly with ICERs of $105,500 to $278,100 per QALY (cost per LY gained was not reported). The PSA revealed that there was significant uncertainty in the cost per QALY gained, regardless of the model considered. An important distinction between the Mann's study and the other publications, is that the Mann's study included the cost of dialysis in all analyses. When dialysis costs were excluded, ICERs were substantially reduced to $43,800 to $186,800.

The current analysis found sevelamer to be moderately more cost effective versus calcium-based binders compared to the results reported by Bernard et al. and Taylor et al., and significantly more cost effective compared to the results reported Manns et al. The discrepancy between the results may be explained by differences in the underlying patient population, hospitalization rates for calcium-based binders and sevelamer, and, in the case of Manns et al., assumptions regarding the inclusion of dialysis costs. As mentioned previously, the Bernard et al. and Manns et al. CEAs were conducted in patients receiving prevalent hemodialysis using data from the DCOR study. In contrast to the INDEPENDENT study, which was conducted in new to dialysis patients, the DCOR study failed to demonstrate a statistically significant all-cause mortality reduction with sevelamer for the entire patient population (HR of sevelamer versus calcium-based phosphate binder 0.93, 95 % CI 0.79–1.10, p = 0.400). The high dropout rate (50 % of the entire DCOR study cohort), the lower than anticipated event rate for the entire study population, and the relatively short follow-up (38 % of patients were followed for failure of the DCOR study to conclusively demonstrate a survival benefit with sevelamer compared with calciumbased binders. More conservative benefits in all-cause mortality reductions for sevelamer in the DCOR study may have translated into smaller incremental LYs for sevelamer versus calcium-based binders and thus higher ICERs in the CEAs that used the DCOR study to inform survival. Incidentally, a significant reduction in all-cause mortality was noted for sevelamer versus calcium-based binders in a subgroup analysis of patients older than 65 years of age in the DCOR study (HR 0.77, 95 % CI 0.61–0.96, p = 0.02). In a subgroup CEA reported by Bernard et al. that used data for patients older than 65 years of age in the DCOR study, the ICERs

improved significantly.

Previous CEAs also utilized hospitalization data from either the DCOR study or Collins et al. [34]. to inform hospitalization costs in the analyses. Both the DCOR and Collins et al. studies reported reductions in days of hospitalization for sevelamer versus calcium-based binders that were lower than what was observed in the INDEPENDENT study. The relative risk reduction in days of hospitalization for sevelamer versus calcium-based binders was 0.15 in the DCOR study and the relative risk of hospitalization for sevelamer versus calcium-based binders was 0.46–0.54 for sevelamer versus calcium-based binders in the Collins et al. study [24]. In addition, Taylor et al. only applied the reduction in hospitalization for sevelamer to the first 18 months of the analysis and assumed no benefit thereafter [24]. The INDEPENDENT study reported a relative risk of 0.27 for hospitalizations in the sevelamer group compared with the calcium-carbonate group, and we applied this value for the full duration of our analysis. As a consequence, the incremental costs associated with hospitalizations in our CEA may have been lower for sevelamer versus calcium-based binders compared with previous CEAs, resulting in lower ICERs.

Finally, in the CEA reported by Manns et al., the main analyses included the cost of dialysis in the total cost of treatment, resulting in significantly higher incremental costs and ICERs for sevelamer versus calcium-based binders, then if dialysis costs were excluded. We excluded dialysis costs from the base case analysis of our CEA, as did the studies by Bernard et al. and Taylor et al. Inclusion of dialysis cost creates analyses which are not comparable as dialysis costs can dramatically influence an economic analysis. As argued by Grima et al. [27], dialysis costs should not be included in cost-effectiveness analyses of therapies that extend the lives of dialysis patients, but do not reduce the need for or the frequency of dialysis. For even if the life extending therapy were free, the cost per LY gained for the therapy will be at least as great as the cost of dialysis. In Italy, where patients on hemodialysis consume over € 27,000 in healthcare costs for dialysis during each year of life, interventions for dialysis patients that improve survival without reducing the need for dialysis will be associated with a cost per LY gained of at least € 27,000. Indeed, when we included the cost of dialysis in a sensitivity analysis, the cost per LY gained increased from € 4,897 in the base-case analysis to € 32,506 per LY gained. As suggested by Bernard et al. [31], the risk of including dialysis

costs in CEAs of therapies that extend the life of dialysis patients without impacting dialysis itself is that dialysis patients could be denied access to any current or future therapy that would extend their life, simply because those additional years of life on dialysis are too costly. Similar to Grima et al. and Bernard et al., we argue that it is unreasonable to include the cost of dialysis in CEAs of phosphate binders that extend the lives of dialysis patients but do not impact the need for or the frequency of dialysis. Exclusion of dialysis costs is also consistent with health economic guidelines [27].

The primary strength of this CEA is that it uses patient level data from an RCT of patients initiating dialysis. As such the analysis avoids some of the assumptions required in modeled cost-effectiveness analyses; instead it uses final outcomes (mortality) as observed within an RCT. The INDEPENDENT study sought to provide an unbiased, real world, estimate of all-cause mortality, phosphate binder utilization, and hospitalization in patients receiving either sevelamer or calcium carbonate in patients initiating. For example, attempts were made in the INDEPENDENT study to limit the invasiveness normally associated with an RCT. For example, phosphate binders were given in an open-label fashion and clinicians were free to increase the initial dose of binder at their discretion to maintain serum phosphorus concentrations in the ranges suggested by KDOQI guidelines. This would mitigate the risk of a lack of generalizability of the results to real-world practice also typical of RCTs.

The study, however, is not without limitations. Since the INDEPENDENT study did not collect data on hospitalizations, a post hoc retrospective chart review of the patients included in the INDEPENDENT study was conducted to collect data regarding frequency of hospitalization, overall LOS, and discharging ward for the study duration. It would have been preferable that this data was collected at the time of the study as part of the study protocol; however, since complete hospitalization data were able to be collected for all patients included in the study, we feel that any bias introduced as a consequence of the retrospective data collection was minimal. The INDEPENDENT study also did not collect data regarding patient quality of life or utility to allow the calculation of QALYs for the economic evaluation. In order to comply with the RCT and to minimize the use of external data and assumptions in the analysis, the ICER was reported as cost per LY gained only. As a consequence, comparison of results of this CEA to CEAs for other products or diseases for the purposes of allocating scarce resources across all health care is limited. This study represents the only patient-

level CEA of sevelamer versus calcium-based binders for the treatment of hyperphosphatemia in patients receiving dialysis and the first CEA of sevelamer conducted in an Italian patient population. For a complete vision of the costs incurred in the patients, we also analyzed the costs that the increased survival produced in economic terms for dialysis administered during the 36-month follow-up (Appendix 3, Supplementary data). The number of dialysis was 88660 in the sevelamer group and 75556 in the calcium group (difference 13104), who produced a greater cost for hemodialysis made of 2,096,640,00 euros in sevelamer group. An analysis, however, the cost per single patient, during 36 months study analysis, spending for dialysis was 68,179.56 (range 18,720.00–74,880.00) in the sevelamer group and 61,066.24 (range from 6,240.00 to 74,880.00) euros in calcium group. On average, dialysis costs were **€** 7,113.32 higher per patient treated with sevelamer compared with calcium carbonate (95 % CI 2,902.86–10,006.55, p = 0.03). Dialysis costs were higher for sevelamer because patients receiving sevelamer had more life years and therefore more dialysis sessions versus calcium carbonate.

Conclusions

Using patient-level data from the recently published INDEPENDENT study, this CEA demonstrated that sevelamer versus calcium carbonate represents good valuef or money in the first-line treatment of hyperphosphatemia in CKD patients initiating dialysis. The cost per LY gained was **€** 4,897.

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Table 1 Baseline characteristics and 3-year clinical outcomes for the base case cost-effectiveness analysis

Clinical outcome	Sevelamer ($n = 232$)	Calcium carbonate ($n = 234$)	Difference (95 % CI)	p value[a]
Baseline characteristics				
Age (years)	66.6 (SD 14.1)	64.6 (SD 15.4)		0.1
Male (%)	50	48		0.7
Diabetes (%)	30	29		0.9
Atherosclerotic cardiovascular disease (%)	36	34		0.7
Hypertension (%)	78	80.5		0.6
3-year outcomes				
Survival				
All-cause deaths	28 (12.1 %)	100 (42.7 %)	−72 (−94 to −58)	0.0001
Life years per patient	2.54 (SD 0.86)	2.28 (SD 0.82)	0.26 (0.11–0.41)	0.05
Hospitalizations				
Patients admitted	27 (11.6 %)	100 (42.7 %)	−31 % (−61 to −12 %)	0.0001
Total hospitalizations	51	178	−127 (−184 to −67)	0.05
Nephrology	46	133	−87 (−116 to −41)	0.05
Cardiology	3	22	−19 (−52 to −2)	0.05
Intensive care unit	2	23	−21 (−47 to −6)	0.05

[a]Statistical significance between treatment groups was determined using t test and Fischer's exact test for continuous and discrete variables, respectively; significance was set at 5 % for all tests

Table 2: Total costs over 36 months for the base-case cost-effectiveness analysis

Cost outcomes per patient mean (SD)	Sevelamer ($n = 199$)	Calcium carbonate ($n = 198$)	Difference (95 % CI)	p value[a]
Phosphate binder costs	€3,347.45 (1,424.11)	€65.33 (32.99)	€3,282.12 (3,098.82–3,288.56)	0.05
Hospitalization costs				
Nephrology	€742.74 (2,375.32)	€2,129.14 (3,448.02)	−€1,386.40 (−1,923.61 to −944.57)	0.05
Cardiology	€47.77 (418.24)	€347.30 (1,183.87)	−€299.53 (−460.48 to −147.82)	0.1
Intensive care unit	€32.16 (345.57)	€366.62 (1,112.83)	−€334.47 (−483.83 to −191.87)	0.0001
Total	€822.66 (2,603.32)	€2,843.06 (3,876.97)	−€2,020.40 (−2,619.54 to −1,523.61)	0.0001
Total costs	€4,170.11 (2,551.20)	€2,908.39 (3,878.37)	€1,261.73 (666.16–1,857.30)	0.0001

[a] Statistical significance between treatment groups was determined using t test and Fischer's exact test for continuous and discrete variables, respectively; significance was set at 5 % for all tests

Fig. 1 Results of the bootstrap analysis plotted on the cost-effectiveness plane

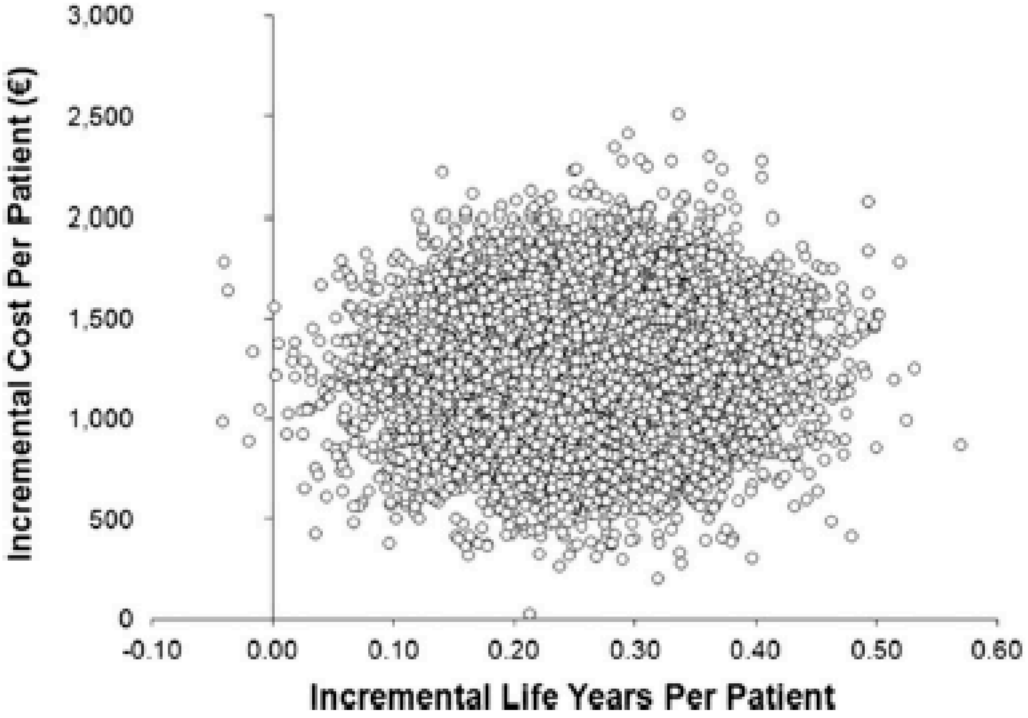


Fig. 2 Cost-effectiveness acceptability curve for sevelamer versus calcium carbonate

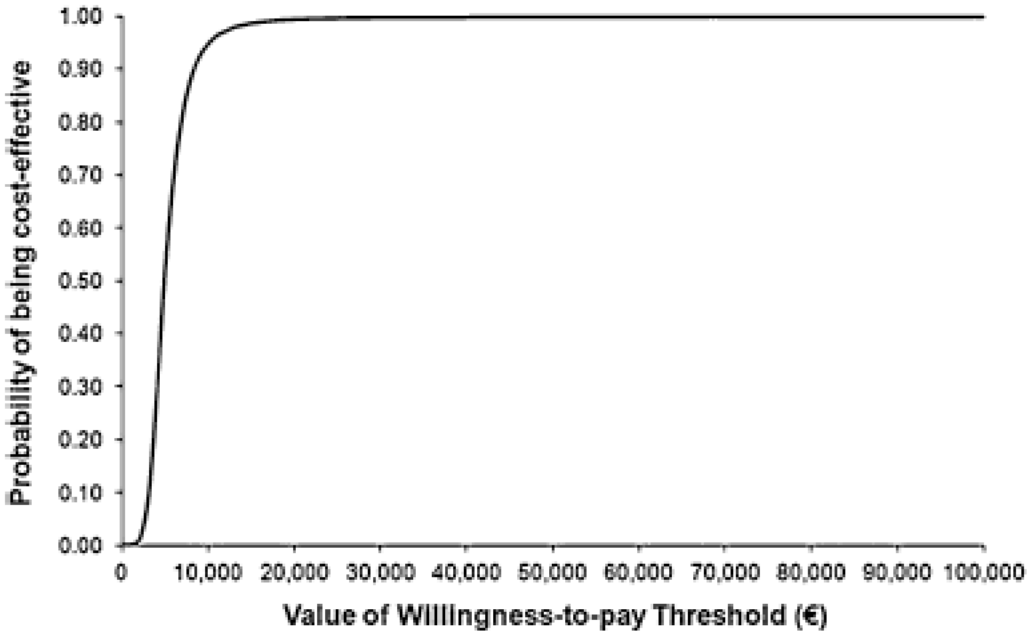
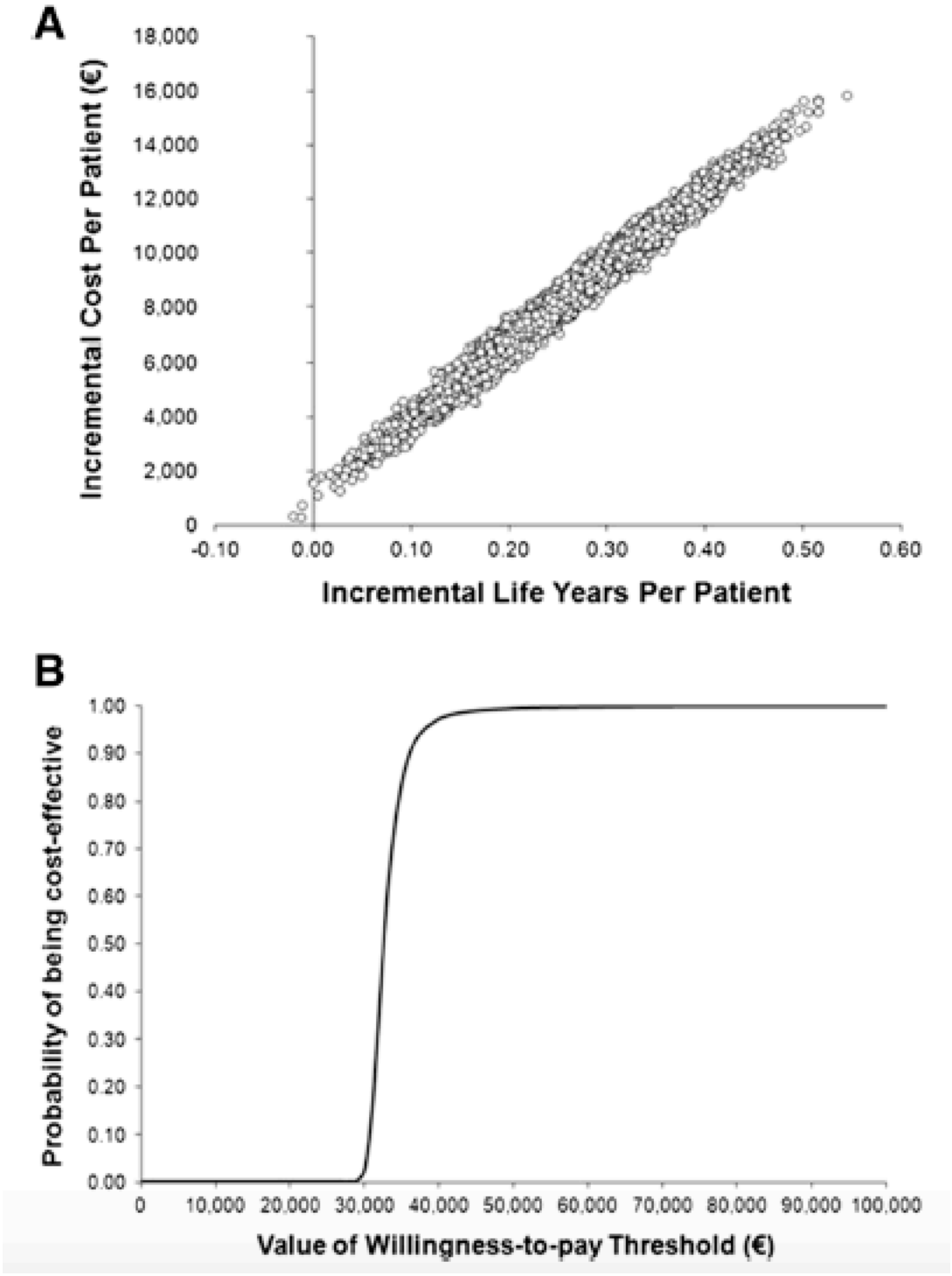


Fig. 3 Results of the bootstrap analysis (a) and cost-effectiveness acceptability curve (b) for the sensitivity analysis that included dialysis costs



INDEPENDENT STUDY: IMPACT OF CINACALCET AND SEVELAMER ON MORTALITY

Whether the concurrent use of calcium sensing modulator or vitamin D with either a calcium free or calcium containing phosphate binder impacts patient-centered outcomes remains to be elucidated. This is a post hoc analysis of an open label, randomized, controlled trial designed to evaluate the impact of sevelamer (SV) vs calcium salts (CS) on survival in incident dialysis patients. All individuals were followed until study completion or death. Cinacalcet and vitamin D were administered to a portion of patients as part of routine care (52% and 42%, respectively). We tested the impact of cinacalcet and vitamin D on survival for the overall study cohort and in both treatment arms of the original study. Overall, we recruited 466 middle-age (65$\pm$14 years) men (49%) and women (51%). After a mean follow-up of 28 ($\pm$10) months, SV but not cinacalcet administration was associated with a survival benefit. However, a significant (p=0.006) interaction on mortality was observed. Cinacalcet use was associated with improved survival when administered in combination with SV (HR 0.34, 95%CI 0.14-0.81, p=0.01 for SV treated subjects receiving or not cincalcet) but not with CS (HR 1.28, 95%CI 0.82-2.00; p=0.26 for CS treated subjects receiving or not cinacalcet). No effect on mortality or interaction with phosphate binder use was noted with vitamin D. Though hypothesis generating, these results lend support to a hypothesis that use of a calcium free vs containing phosphate binder may increase survival in incident hemodialysis patients, in particular, when patient are treated concurrently with a calcium sensing modulator.

Introduction

Chronic Kidney Disease Mineral Metabolism (CKD-MBD) is a common finding in advanced stages of renal failure and it has been associated with poor outcome[1, 2]. Although only a few randomized controlled studies have shown survival benefit associated with mineral metabolism management strategies in chronic kidney disease (CKD) patients[3, 4], it is commonly accepted that serum metabolites such as calcium, phosphorous, vitamin D, and parathyroid hormones should carefully be monitored and controlled[5]. Available therapeutic strategies rely on phosphate-restricted diets, parathyroidectomy and administration of phosphate binders, nutritional and/or activated vitamin D, and calcium sensing receptor (CaSR) agonist [6].

Studies testing the impact on survival of single interventions aimed at reversing one aspect of the deranged mineral metabolism in CKD and ESRD have often failed to show a substantial survival benefit[7, 8], especially in regards to potential side effects and relative cost. However, in light of the complex cross-talk of calcium, phosphate, vitamin D, and parathyroid hormone, it is possible that these findings may be partly explained by effect modification of various combinations of available drugs on outcomes. We herein aim at testing for an interaction on survival of cinacalcet, vitamin D, and phosphate binders in a cohort of incident dialysis patients treated with either calcium carbonate or sevelamer as part of a randomized controlled clinical trial, the INDEPENDENT Study.[4]

Results

In the INDEPENDENT Study, a total of 466 patients were randomized to either sevelamer (N=232) or calcium carbonate (N=234) phosphate binders. Of these, 33 (14.2%) in the sevelamer and 35 (15.0%) in the calcium arm exited the study for various reasons prior to study completion[4]. Study participants characteristics according to the use of phosphate binder type and cinacalcet use are summarized in **table 1**. Overall, a total of 232 (52%) of the study cohort, almost equally distributed in the two study arms, were treated with cinacalcet.

At univariate and multivariate analyses, cinacalcet was not associated with all-cause survival for the entire cohort (HR 0.93; 95% CI: 0.65 – 1.31; p=0.68). However, a significant interaction was noted with the phosphate binder regimen (P=0.029, interaction test). Subject allocated to

Sevelamer experienced a significant survival benefit when concurrently treated with cinacalcet. Progressive adjustment for potential confounders did not affect the interaction between sevelamer and cinacalcet (p=0.007 for interaction test) (**table 2**).

Analyses performed in each arm of the study, confirmed a significant 60% (Fully adjusted HR: 0.34; 95% CI: 0.14-0.81; p=0.015) risk reduction among cinacalcet treated patient in the sevelamer arm as opposed to a trend toward an increase risk (Fully adjusted HR: 1.28; 0.82-2.00; p=0.26) with the combination of calcium carbonate and cinacalcet use (**Supplemental table 1**).

To better gauge the effect of the combined use of sevelamer or calcium carbonate and cinacalcet, the study cohort was then divided in 4 different groups according to the drug regimens study participants were prescribed. Overall, sevelamer treated individuals experienced significant survival benefits (**figure 1**) as reported previously.[4] However, while no effect on mortality was noted when calcium carbonate was administered in combination with cinacalcet (Fully adjusted HR: 1.39; 0.90-2.15; p=0.15), a substantial 86% risk reduction was observed when sevelamer and cinacalcet were concurrently prescribed (Fully adjusted HR for sevelamer-cinacalcet compared to sevelamer-only: 0.14; 95%CI: 0.06-0.32; p<0.001) (**table 3, figure 2**). Propensity matched and adjusted analyses yielded similar results (Fully adjusted HR: 0.15; 95%CI: 0.06-0.39; p<0.001) (**Supplemental Table 2 and Supplemental Figure 3**).

Finally, no association between Vitamin D and mortality, as well as, no significant interactions between vitamin D and phosphate binder use were detected (***data not shown***).

Discussion

The main findings of these *post hoc* analyses of the Independent study[4] suggest that cinacalcet may modify the survival benefit observed with sevelamer in incident dialysis patient. Indeed, in the current analysis, concurrent use of sevelamer and cinacalcet was associated with improved survival, in distinct contrast to the finding that concurrent use of calcium carbonate and cinacalcet was associated with a trend towards an increase in mortality. Notably, no effect on mortality or significant interaction of vitamin D and phosphate binder use was noted.

Current results should be evaluated in light of the existing data. Much evidences suggest that as renal function declines calcium homeostasis is progressively disrupted and CKD individuals are exposed to a net positive calcium balance[9, 10]. In turn, calcium accumulation in soft tissue may trigger vascular calcification deposition and progression and thereby, likely contributes to the abysmal cardiovascular (CV) risk observed in patients with advanced CKD[11]. These observations may explain why calcium containing phosphate binders are linked to reduced survival when compared to calcium free phosphate binders[3, 12].

It is plausible that patients on maintenance dialysis are chronically exposed to an even larger amount of calcium and hence at an even higher risk of pathologic calcium accumulation[13, 14]. High calcium concentration in the dialysis bath[13, 14] as well as generous doses of calcium-based phosphate binders administered to control hyperphosphatemia may ultimately results in a significant positive calcium balance[13]. However, little is known about the impact of the interaction of drugs that modulate calcium balance at different potentially synergistic mechanisms on survival.

Cinacalcet is a commonly prescribed Calcium Sensing Receptor (CaSR) modulator that reduces serum levels of both serum parathyroid hormone (PTH) and calcium by inducing a shift of the calcium-PTH-response curve[15, 16]. Furthermore, intestinal CaSR activation may affect electrolyte secretion in the gastro-intestinal tract and possibly alter the net absorption of calcium[17]. Although still requiring clinical validation, CaSR activation may reduce vascular calcification (VC) deposition and progression[18, 19, 22]. Though speculative, it is possible that the concurrent administration of calcium and cinacalcet may result in an increased positive calcium balance. Lower levels of pre-dialysis serum calcium as one might see with cinacalcet therapy increase the chemical gradient between plasma and dialysate [20] potentially promoting intradialytic calcium transfer to the patient. The net positive balance is potentially exacerbated further by the chronic intake of large quantities of calcium as phosphate binder (mean dose of elemental calcium in the INDEPENDENT study: 2,2$\pm$1.0 g/day). Notably, serum calcium levels may not accurately reflect calcium loading and hence, the exposure risk for the individual dialysis patient.

The use of cinacalcet and calcium free phosphate binders have both been associated with significants reduction of serum levels of fibroblast growth factor 23 (FGF23)[21-23]. Increased FGF23

has been associated with left ventricular hypertrophy[24], endothelial dysfunction[22] and adverse outcome in CKD patients[25]. In contrast, calcium containing phosphate binders do not affect FGF23 levels[23, 26]. Although available evidence warrant confirmation, it is possible that FGF23 lowering also contributes to an improvement in survival[27]. Hence, the concurrent use of cinacalcet and sevelamer may results in a greater reduction in FGF23 when compared to concurrent calcium and cinacalcet administration. It is tempting to speculate that drug induced changes in FGF23 may explain some of the observed differential impact of cinacalcet on mortality noted in the two arms of the INDEPENDENT study.

Vitamin D can modify intestinal absorption of calcium and phosphorous however we failed to document an interaction between phosphate binder and vitamin D use on mortality (**data not shown**). The relative small sample size of patients on vitamin D, the use of different vitamin D compounds and dosages[28,31] and the imbalance of vitamin D use in the two study arms of the study may explain our failure to observe an interaction of vitamin D and phosphate binder exposure impacting survival. Nonetheless, vitamin D use is associated with FGF23 secretion[29] and different actions of vitamin D and cinacalcet can be hypothesized.

The current analyses suffer from a few limitations worth noting. This is a *post hoc* analyses of a RCT designed to test the impact of sevelamer vs calcium carbonate on outcome in patients starting dialysis. As such, the current findings should be regarded as hypothesis generating and future efforts will be required to confirm the potential synergistic effect of sevelamer and cinacalcet on survival. Of importance, cinacalcet and vitamin D were administered as part of the routine care and were not protocolized or randomized. Attending physicians were free to adjust uses and doses according to attainment of mineral metabolism serological targets[4]. Our analyses do not account for the time on prescribed medication. However, the use of medications was substantially similar throughout follow-up between the 2 study arms[4]. Furthermore, one may speculate that although some cross-over between study arms and/or discontinuation of prescribed drugs may have occurred during follow-up, this would have likely resulted in a statistical signal attenuation rather than amplification of the observed effect. In spite of our best effort to control for factors associated with all-cause mortality in patients new to dialysis, some unmeasured residual confounding cannot

be excluded. However, progressive model adjustments for numerous factors as well as the consistency of the results across different sensitivity analyses reduce the probability of bias in our data including bias by indication and support the likely validity of the conclusion of a significant interaction between phosphate binders and cinacalcet on reducing mortality. The lack of FGF23 measurement, as well as, the absence of a reliable marker of calcium balance in CKD patients does not permit us to test whether our pathophysiological hypothesis explain the current findings.

In conclusion, we showed a robust and independent effect modification of cinacalcet on the survival benefit associated with sevelamer use in a large cohort of incident to dialysis patients[4]. Although this effect was independent of numerous potential confounders, future endeavors should prospectively test the hypothesis generated by current results.

Methods

The INDEPENDENT Study protocol has been reported previously[30]. Briefly, adult (>18 years), CKD-5 patients new to hemodialysis (requiring dialysis for less than 120 days) were enrolled at 18 dialysis center in Italy and allocated randomly in a 1:1 fashion to receive either open label sevelamer or calcium carbonate (Fig 1). Patients older than 75 years, or with congenital prolongation of QT segment syndrome, corrected QT (QTc) longer than 440 ms, increased QT dispersion (QTd), with history of cardiac arrhythmia, coronary artery bypass (CABG), liver dysfunction, hypothyroidism, or prescribed medications that may prolong the QT interval were excluded.

Study investigators were free to adjust the assigned phosphate binder dose and other medications to achieve the targets for bone mineral metabolism, blood pressure, anemia, iron status, dyslipidemia as suggested by guidelines available at the time of the study design.[31]

Study protocol was approved by each institutional Ethical Review Board. Participants provided written informed consent at study entry. Study procedures were conducted in adherence to the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects. The INDEPENDENT study was registered on ClinicalTrials.Gov (NCT00710788) and the primary results of the INDEPENDENT Study have been published previously.[4]

Laboratory measurements and cardiovascular disease assessment.

Biochemistry and imaging measurements considered in current analyses were obtained at baseline. Blood samples were drawn before the mid-week dialysis session in a fasting condition. Biochemistry and dialysis adequacy variables were assessed at the facilities usual laboratories as part of the standard patient care. Intact PTH and high sensitivity CRP levels were determined using the Nichols second-generation immunoradiometric and an immunoturbidimetric assay (normal<5 mg/L). Coronary Artery Calcium Score (CACS) was assessed as previously described.[32]

Definition of cinacalcet, vitamin D and binder use:

Patients were classified as having been treated with cinacalcet or vitamin D if they were prescribed cinacalcet or any forms of vitamin D at study entry, concurrently with the study assigned phosphate binder (*intention-to-treat*). All analyses were carried out as per *intention-to-treat* and no adjustments for time on concurrent drugs was exploited.

Definition of study endpoint

Mortality status was prospectively collected throughout study follow-up from September 2006 until July 2011. Study participants were followed from study inception until the occurrence of any lethal event or study completion (36 months follow-up or early study termination). Fatal clinical events were documented and adjudicated before statistical analyses were carried out.

Statistical Methods

The impact of cinacalcet and vitamin D use as well as the interaction effect on all-cause survival of either cinacalcet or vitamin D and phosphate binder use was tested in the overall study cohort. Due to a lack of association between Vitamin D and mortality as well as a significant interaction between vitamin D and phosphate binder use on survival(***data not shown***), we focus on the interaction between cinacalcet and phosphate binders use.

Study participants were divided in four groups according to the use of cinacalcet in each study arms (i.e. Sevelamer vs Calcium salts treatment arm). Demographic, clinical and laboratory characteristics were collected at study inception. Continuous variables are presented as mean ± standard deviation or median (interquartile range) when appropriate. Categorical variables are presented as proportion.

Cumulative event rates were calculated across study groups via the Kaplan-Meier method and compared by the use of the product-limit method. The association between cinacalcet as well as the interaction of cinacalcet and types of phosphate binder use was estimated via the Cox proportional-hazards models to calculate hazard ratios (HR) and 95% Confidence Intervals (CI). To test for statistically significant effect modification, a term for interaction of cinacalcet and phosphate binder use was included in the Cox Models.

The robustness of the association was tested by progressive adjustment of the Cox models with variables known to be associated with survival based on existing literature or imbalanced among study groups. **Model 1** was adjusted for demographic characteristics (age, sex, body weight); **model 2**: adjusted for model 1 and comorbidities as well as markers of cardiovascular disease (diabetes mellitus, coronary artery calcification, systolic and diastolic blood pressure, ejection fraction and pulse wave velocity); **model 3**: adjusted for model 2 and laboratory characteristics (serum sodium, calcium, phosphate, parathyroid hormone, C-reactive protein, triglycerides); **model 4**: adjusted for model 3 and medications (angiotensin receptor blockers, ace inhibitors, vitamin D). The most parsimonious model was then selected via a stepwise approach. Analyses were repeated in each arm of the study. However, models were only adjusted for demographic, clinical and laboratory characteristics (model 2), due to the limited number of events recorded in the Sevelamer arm at study completion (28 events).

Further sub-categorization of the study cohort according to the use of sevelamer or calcium carbonate and cinacalcet was carried out to gauge the additive effect on survival of the different binders. The robustness of the association was also tested in a propensity-matched subsample of the study cohort. Patients receiving and not receiving cinacalcet were matched via the nearest method on a 1:1 ratio based on predictors of death and factor that might influence cinacalcet administration (age, sex, diabetes, pulse wave velocity, coronary artery calcification, body weight, systolic blood pressure, serum sodium, serum calcium, serum phosphate, serum parathyroid hormone as well as ACE-I , ARB, vitamin D and phosphate binder use). After matching, a total of 223 cinacalcet treated and 223 controls were identified while 18 cinacalcet treated patients did not receive a match. Thus, the association between the combined use of cinacalcet and phosphate binder was tested in a final database of 446 individuals.

All analyses were conducted as *intention-to-treat*. Two-tailed probability values ≤ 0.05 were considered statistically significant. Analyses were completed using R version 3.1.3 (2015-03-09) (The R Foundation for Statistical Computing).

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Table 1: Demographic, clinical and laboratory characteristics of study cohort at baseline and according to phosphate binder and cinacalcet prescription.

	Total (n=466)	Calcium (n=108)	Calcium and cinacalcet (n=126)	Sevelamer (n=116)	Sevelamer and cinacalcet (n=116)	p-trend
Demographic characteristics						
Age (years)	65.61 (14.79)	65.33 (14.96)	63.99 (15.82)	66.25 (13.8)	66.99 (14.46)	0.452
Female (%)	50.86%	54.63%	48.41%	50%	50.86%	0.813
Body Weight (Kg)	69.22 (14.09)	67.66 (12.72)	67.61 (12.71)	72.15 (15.92)	69.51 (14.46)	0.065
Clinical Characteristics						
Diabetes (%)	30.90%	25.93%	31.75%	32.76%	32.76%	0.644
Systolic Blood Pressure (mmHg)	137.13 (17.7)	137.44 (16.19)	136.86 (18.28)	137.46 (16.93)	136.82 (19.3)	0.987
Diastolic Blood Pressure (mmHg)	76.04 (9.37)	76.72 (9.59)	76.02 (9.58)	76.16 (10.03)	75.3 (8.25)	0.692
Baseline Coronary Artery Calcification	**256.95 (715.61)**	**434.12 (940.18)**	**446.74 (959.6)**	**72.23 (235.1)**	**70.55 (231.65)**	**<0.0001**
Left Ventriculat Mass Index (g/cm2)	150.41 (46.96)	151.46 (36.64)	153.9 (34.03)	147.41 (55.72)	148.65 (57.25)	0.676
Ejection fraction (%)	**56.64 (10.43)**	**55.71 (11.8)**	**54.52 (11.84)**	**58.84 (8.33)**	**57.59 (8.77)**	**0.006**
Pulse Wave Velocity (m/sec)	8.78 (2.7)	8.48 (2.4)	8.66 (3.33)	8.96 (2.73)	9 (2.11)	0.303
QTc (msec)	407.1 (33.04)	408.42 (28.23)	406.17 (27.72)	409.06 (38.94)	404.93 (36.18)	0.781
QTd (msec)	26.77 (11.5)	26.53 (11.99)	25.84 (10.14)	27.53 (12.11)	27.23 (11.85)	0.638
Laboratory characteristics						
Creatinine (mg/dl)	7.78 (2.54)	7.64 (2.71)	7.77 (2.76)	7.78 (2.35)	7.95 (2.34)	0.828
Albumin (g/dl)	3.8 (0.44)	3.78 (0.45)	3.73 (0.46)	3.86 (0.4)	3.83 (0.43)	0.089
Hemoglobin (g/dl)	11.05 (1.49)	10.9 (1.54)	11.1 (1.46)	11.17 (1.47)	11.01 (1.51)	0.59
Sodium (mEq/l)	**139 (3.36)**	**139.49 (2.94)**	**139.33 (3.58)**	**138.6 (3.14)**	**138.57 (3.61)**	**0.058**
Potassium (mEq/l)	5.18 (0.84)	5.25 (0.82)	5.17 (0.73)	5.02 (0.99)	5.27 (0.78)	0.15
Total cholesterol (mg/dl)	160.03 (47.31)	153.76 (47.61)	162.83 (51.65)	162.03 (42.15)	160.84 (47.07)	0.472
LDL cholesterol (mg/dl)	99.3 (29.31)	101.68 (29.12)	98.68 (27.3)	97.38 (29.69)	99.66 (31.35)	0.735
Triglicerides (mg/dl)	**180.92 (119.8)**	**159.39 (97.05)**	**168.01 (112.21)**	**187.68 (124.62)**	**208.23 (136.51)**	**0.012**
CRP (mg/dl)	**7.37 (10.72)**	**5.08 (3.45)**	**6.62 (8.68)**	**8.92 (14.99)**	**8.77 (11.71)**	**0.001**
Calcium (mg/dl)	**8.88 (0.78)**	**8.72 (0.66)**	**8.88 (0.76)**	**8.96 (0.68)**	**8.96 (0.95)**	**0.035**
Phosphorous (mg/dl)	**5.18 (1.59)**	**4.66 (1.45)**	**4.93 (1.3)**	**5.19 (1.55)**	**5.93 (1.79)**	**<0.0001**
PTH (pg/ml)	**274.33 (207.73)**	**288.67 (248)**	**278.21 (207.35)**	**294.8 (210.28)**	**236.29 (155.62)**	**0.055**
Medication use						
ACE Inhibitors use (%)	**79.40%**	**83.33%**	**73.81%**	**86.21%**	**75%**	**0.044**
ARB use (%)	**84.12%**	**75.93%**	**91.27%**	**76.72%**	**91.38%**	**<0.001**
Beta Blockers use (%)	50.43%	50.93%	50.79%	50.86%	49.14%	0.991
Calcium Channel Blockers (%)	31.76%	35.19%	34.13%	28.45%	29.31%	0.611
Other antihypertensives use (%)	46.57%	51.85%	46.83%	44.83%	43.10%	0.59
Vitamin D use (%)	**42.06%**	**54.63%**	**28.57%**	**54.31%**	**32.76%**	**<0.0001**

Table legend: CAC: Coronary Artery Calcification; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blockers

Table 2: Independent predictors of all-cause survival in the Independent study. Variables selected by the use of a stepwise approach.

	HR	lower .95	upper .95	Pr(>|z|)
Sevelamer Use	**0.3743**	**0.2045**	**0.6853**	**0.001448**
Cinacalcet use	1.3698	0.8966	2.093	0.14565
Body weight	**0.9677**	**0.9532**	**0.9823**	**1.80E-05**
Diabetes	**8.8953**	**5.9246**	**13.3556**	**< 2e-16**
Coronary artery calcium score	**1.1219**	**1.048**	**1.201**	**0.000938**
Pulse Wave velocity	**1.1437**	**1.0866**	**1.2038**	**2.79E-07**
Systolic Blood pressure	**1.0118**	**1.002**	**1.0217**	**0.018474**
Serum Sodium	**1.1117**	**1.0481**	**1.1793**	**0.000432**
Serum phosphate	0.8825	0.7648	1.0184	0.087169
Serum Triglicerides	**0.997**	**0.9949**	**0.999**	**0.003444**
ACE inhibitor use	**0.5067**	**0.3223**	**0.7967**	**0.003235**
ARB use	**0.291**	**0.1748**	**0.4847**	**2.10E-06**
Sevelamer:cinacalcet interaction	**0.2937**	**0.1189**	**0.7255**	**0.007919**

Table legend: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker

Table 3: combined effect of phosphate binder type and cinacalcet in the Independent study Cohort

Unadjusted	**HR**	**lower .95**	**upper .95**	**Pr(>|z|)**
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.27	0.85	1.89	0.23
Sevelamer use	0.38	0.2	0.67	<0.001
Sevelamer+cinacalcet use	0.14	0.06	0.29	<0.001

Model 1: adjusetd for clinical characteristics

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.19	0.77	1.83	0.42
Sevelamer use	0.34	0.18	0.62	<0.001
Sevelamer+cinacalcet use	0.11	0.05	0.24	<0.001

Model 2: model 1 + comorbities and markers of CV risk

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.18	0.77	1.82	0.43
Sevelamer use	0.36	0.2	0.66	0.001
Sevelamer+cinacalcet use	0.1	0.05	0.23	<0.001

Model 3: model 2 + laboratory characteristics

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.38	0.89	2.1	0.14
Sevelamer use	0.44	0.23	0.82	0.001
Sevelamer+cinacalcet use	0.16	0.07	0.36	<0.001

Model 4: model 3 + medications

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.39	0.9	2.15	0.13
Sevelamer use	0.37	0.2	0.71	0.002
Sevelamer+cinacalcet use	0.14	0.06	0.32	<0.001

Table legend: 95% CI: 95% confidence Interval; Model 1: Demographic characteristics (age, sex, body weight); Model 2: Model 1 and comorbities and markers of CV risk (diabetes, coronary artery calcium, systolic blood pressure, diastolic blood pressure, ejection fraction, pulse wave velocity);

Model 3: Model 2 and laboratory characteristics (serum sodium, calcium, phosphate, CRP, triglicerides, PTH); Model 4: Model 3 and medications (use of ARBs, ACEi and vitamin D)

Supplemental Table 1: Cinacalcet effect on all-cause survival in both arms of the Independent study (within study arm comparison)

Sevelamer Arm (total lethal events: 28)					Calcium carbonate arm (total lethal events: 100)				
	HR	lower .95	upper .95	Pr(>|z|)		HR	lower .95	upper .95	Pr(>|z|)
Unadjusted					**Unadjusted**				
Cinacalcet use	0.43	0.19	0.95	0.037	Cinacalcet use	1.13	0.76	1.69	0.52
Model 1					**Model 1**				
Cinacalcet use	0.37	0.16	0.85	0.018	Cinacalcet use	1.35	0.9	2.03	0.13
Model 2					**Model 2**				
Cinacalcet use	0.34	0.14	0.81	0.015	Cinacalcet use	1.28	0.82	2.00	0.26

Table legend: 95% CI: 95% confidence Interval; Model 1: Demographic characteristics (age, sex, body weight); Model 2: Model 1 and comorbities and markers of CV risk (diabetes, coronary artery calcium, systolic blood pressure, diastolic blood pressure, ejection fraction, pulse wave velocity)

Supplemental Table 2: combined effect of phosphate binder type and cinacalcet in the propensity matched cohort derived from the Independent study cohort (N=446)

Adjusted for propensity score

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	0.88	0.56	1.39	0.6
Sevelamer use	0.36	0.21	0.62	<0.001
Sevelamer+cinacalcet use	0.12	0.05	0.27	<0.001

Model 1: adjusetd for clinical characteristics and propensity score

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.07	0.68	1.68	0.74
Sevelamer use	0.39	0.22	0.68	<0.001
Sevelamer+cinacalcet use	0.13	0.06	0.28	<0.001

Model 2: model 1 + comorbities and markers of CV risk and propensity score

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.09	0.68	1.72	0.71
Sevelamer use	0.32	0.18	0.6	<0.001
Sevelamer+cinacalcet use	0.1	0.04	0.24	<0.001

Model 3: model 2 + laboratory characteristics and propensity score

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.18	0.75	1.88	0.46
Sevelamer use	0.42	0.22	0.78	0.006
Sevelamer+cinacalcet use	0.14	0.06	0.34	<0.001

Model 4: model 3 + medications

	HR	lower .95	upper .95	Pr(>|z|)
Calcium salt use	Ref	-	-	-
Calcium salts+ cinacalcet use	1.2	0.75	1.91	0.46
Sevelamer use	0.43	0.2	0.93	0.03
Sevelamer+cinacalcet use	0.15	0.06	0.39	<0.001

Table legend: 95% CI: 95% confidence Interval; Model 1: Demographic characteristics and propensity socre (age, sex, body weight); Model 2: Model 1 and comorbities and markers of CV risk (diabetes, coronary artery calcium, systolic blood pressure, diastolic blood pressure, ejection fraction, pulse wave velocity); Model 3: Model 2 and laboratory characteristics (serum sodium, calcium, phosphate, CRP, triglicerides, PTH); Model 4: Model 3 and medications (use of ARBs, ACEi and vitamin D)

Figure 1: Kaplan-Meier CV all-cause survival according to phosphate binder and cinacalcet assignment

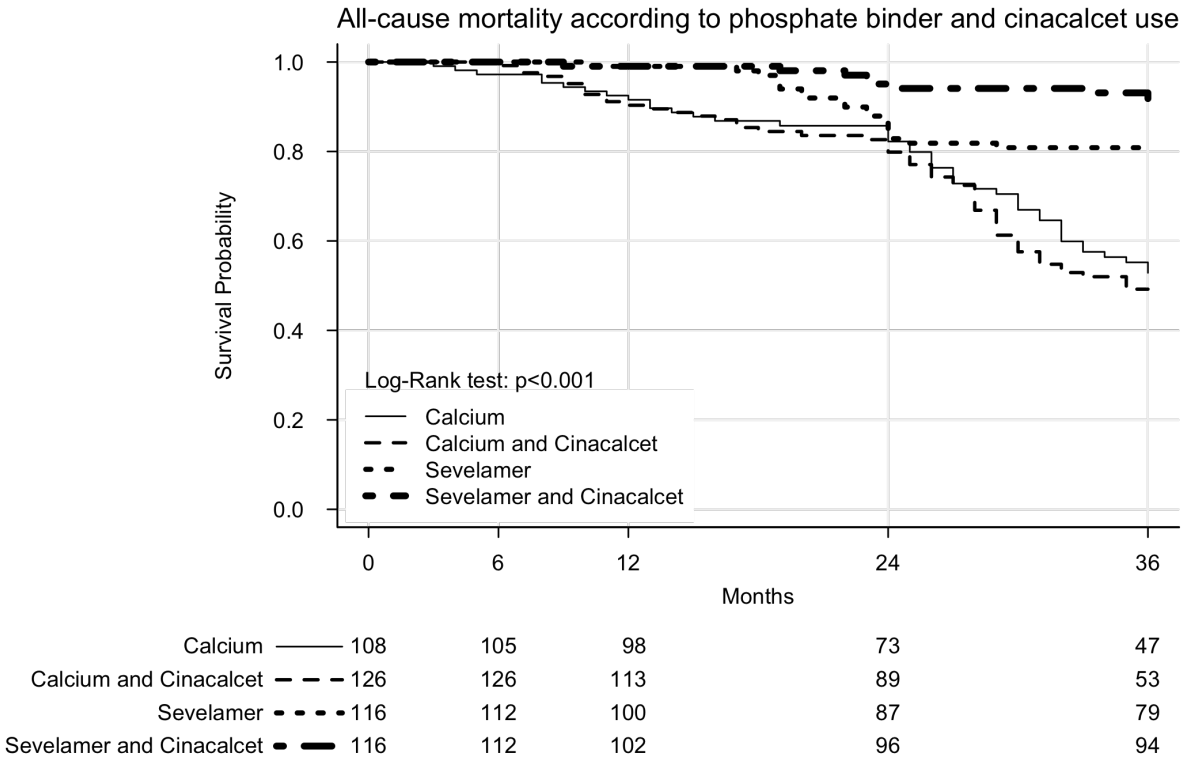
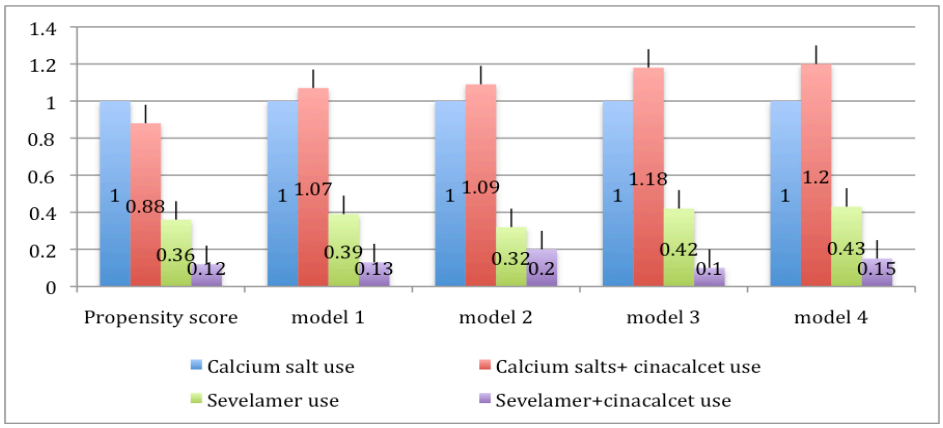
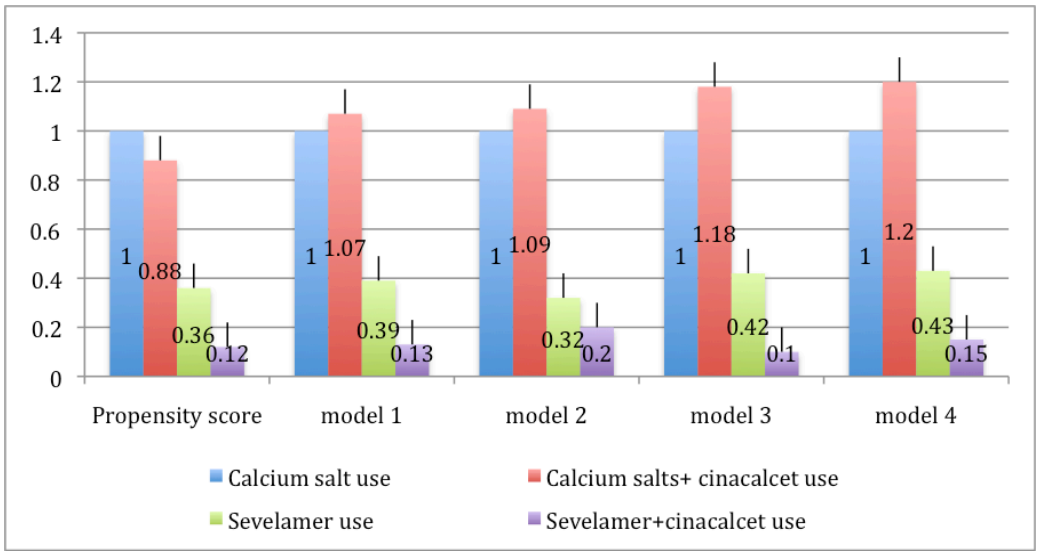


Figure 2: Hazard Ratio of all-cause mortality according to phosphate binder and cinacalcet assignment.



Supplemental Figure 1: Hazard Ratio of all-cause mortality according to phosphate binder and cinacalcet assignment in the propensity score matched cohort.



Model 1 adjusted for demographic characteristics (age, sex, body weight, propensity score); Model 2 adjusted for model 1 and comorbities and markers of CV risk (diabetes, coronary artery calcium, systolic blood pressure, diastolic blood pressure, ejection fraction, pulse wave velocity); Model 3 adjusted formodel 2 and laboratory characteristics (serum sodium, calcium, phosphate, CRP, triglicerides, PTH); Model 4 adjusted for model 3 and medications (use of ARBs, ACEi and vitamin D)

FUTURE PERSPECTIVES AND ONGOING PROJECTS

Ongoing projects (this project was accepted as poster at the meeting of the American Society of Nephrology- Philadelphia (PA), November 2014 and European Society of Nephrology – London 2015):

- **Bellasi A**, Cozzolino M, Russo D, Molony D, Di Iorio B. Predictive Value of Measures of Vascular Calcification for Risk of Death in Incident Dialysis Patients.

Aim of the project is to test what is the best Vascular Calcification scoring system to evaluate presence and extension of VC and to predict survival in CKD-5D patients. The publication is in preparation.

Study protocol

1. ***The Answer Study***. This study protocol aims at testing whether phosphate lowering by means of a calcium-free phosphate binder such as Sevelamer carbonate significantly reduces proteinuria on top of best available treatment. Indeed, proteinuria is both a marker and effector of renal failure. A large body of evidence suggests that the lower the proteinuria the better is the renal outcome. Nonetheless, a considerable number of patients fail to control it independently of the use of agents that inhibit the rennin-angiotensin system. New observational data support the notion that a phosphate metabolism imbalance maybe responsible of these findings. Thus, the ANSWER study aims at testing whether phosphate lowering significantly reduces proteinuria on top of best available treatment. This is a prospective, randomized, open, blinded endpoint (PROBE), clinical trial to assess the renal and humoral effects of sevelamer carbonate in patients with chronic kidney disease and residual proteinuria despite best available treatment (The Answer Study). The study has been approved by the local Ethical Committees and patient recruitment started in year 2013 and it is now completed. The study follow-up (last patient out) is scheduled for September 2015. The first study results are expected by January 2016.

2. ***Studio OPTIMAL ESRD TREATMENT***. This is a single-Center, open label, randomized study of

anemia management improvement in End-Stage-Renal Disease patients with secondary hyperparathyroidism- OPTIMAL ESRD TREATMENT. The study aims at testing whether PTH lowering by a therapeutic algorithm allows a Erythropoetin dose reduction in a cohort of patients on maintenance with secondary hyperparathyroidism. The study was approved by the local Ethical Committee and received approval for patient recruitment in March 2015. The recruitment process will continue until February 2016. The first study results are expected by May 2017.