Early post-transplantation hypophosphatemia and the risk of graft failure and cardiovascular mortality after kidney transplantation
Abstract (English)

Background and objectives
Post-transplantation hypophosphatemia, phosphate levels below 0.7 mmol/L, is common after kidney transplantation. Hypophosphatemia is probably the consequence of still elevated levels of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH). Long-term exposure to FGF23 and PTH, have been associated with adverse patient and graft outcomes, but may also reflect good graft function. We therefore investigated whether post-transplant hypophosphatemia is associated with graft failure or mortality.

Design, setting, participants & measurements
In a cohort of renal transplant recipients (n=957), the lowest serum phosphate during the first year post-transplantation was recorded. We analyzed the association between the lowest serum phosphate, either as a categorical (absent >0.7 mmol/L, mild 0.5-0.7 mmol/L, severe <0.5 mmol/L) or as a continuous variable (per halving), and the outcomes graft failure and mortality. This was done by multivariable Cox regression analyses adjusted for known risk factors for adverse patient and graft outcomes.

Results
821 patients (86%) developed hypophosphatemia during the first year post-transplantation, of which 446 patients (47% of the total cohort) had severe hypophosphatemia. Lowest levels of serum phosphate were reached at 33 [21-51] days after transplantation. During follow-up for 9 [5-12] (median [IQR]) years, 181 (19%) patients developed graft failure and 295 (31%) patients died. The development of hypophosphatemia was significantly associated with a lower risk of graft failure (full model HR, severe vs no hypophosphatemia: 0.41 [0.22-0.73], P<0.01 mild vs no hypophosphatemia 0.41 [0.24-0.72], P<0.01). Furthermore, hypophosphatemia was associated with a reduced risk of cardiovascular mortality (severe vs no hypophosphatemia: 0.29 [95% CI 0.13-0.67], P<0.01 mild vs no hypophosphatemia: 0.25 [0.11-0.58], P<0.01). Hypophosphatemia was not associated with non-cardiovascular mortality.

Conclusions
The development of post-transplantation hypophosphatemia in the first year after kidney transplantation is associated with a lower risk of both graft failure and cardiovascular mortality. This indicates that an optimal renal phosphate excretion capacity after transplantation is beneficial for graft and patient outcomes.

This abstract is accepted for an oral presentation for the Dutch Nephrology days on March 31th.
Abstract (Dutch)

Achtergrond
Hypofosfatemie, een serum fosfaat beneden 0.7 mmol/L, is een veel voorkomend fenomeen na niertransplantatie. Hypofosfatemie is waarschijnlijk de consequentie van resterende verhoogde levels van fibroblast groei factor 23 (FGF23) en bijschildklier hormoon (PTH). Langdurige blootstelling aan FGF23 en PTH, zijn geassocieerd met nadelige uitkomsten zoals transplantaatfalen en mortaliteit. Echter kunnen ze ook een goede transplantaatfunctie weerspiegelen. Wij hebben daarom gekeken of hypofosfatemie na transplantatie is geassocieerd met transplantaatfalen en sterfte.

Methode
Om het effect van het laagste serum fosfaat (hypofosfatemie) bereikt in het eerste jaar na transplantatie te analyseren op de lange termijn uitkomsten transplantaatfalen en mortaliteit, maakten wij gebruik van een cohort studie van niertransplantatiepatiënten (n=957). Het laagste serum fosfaat was geanalyseerd als een categorie (afwezig >0.7 mmol/L, mild 0.5-0.7 mmol/L, ernstig <0.5 mmol/L), of als een continue variabele. Voor de analyses werd een multivariabele cox regressie analyse gebruikt, die werd geadjusteerd voor bekende factoren voor transplantaatfalen en doodsoorzaken.

Resultaten
821 patiënten (86%) ontwikkelden een hypofosfatemie gedurende het eerste jaar na transplantatie, hiervan hadden 446 (47%) een ernstige hypofosfatemie. Het laagste serum fosfaat level was binnen 33 [21-51] dagen bereikt na transplantatie. Tijdens een follow-up van 9 [5-12] jaar, ontwikkelden 181 (19%) transplantaatfalen en overleden 295 (31%) patiënten. De ontwikkeling van hypofosfatemie was significant geassocieerd met een lager risico op transplantaatfalen (Hazard ratio ernstig versus geen hypofosfatemie 0.41 [0.22-0.73], P<0.01; mild versus geen hypofosfatemie 0.41 [0.24-0.72], P<0.01). Daarnaast was hypofosfatemie ook geassocieerd met een verlaagd risico op cardiovasculaire mortaliteit (ernstig versus geen hypofosfatemie 0.29 [95% CI 0.13-0.67], P<0.01; mild versus geen hypofosfatemie: 0.25 [0.11-0.58], P<0.01). Hypofosfatemia was niet geassocieerd met niet-cardiovasculaire mortaliteit.

Conclusie
De ontwikkeling van hypofosfatemie tijdens het eerste jaar na transplantatie is geassocieerd met een lager risico op transplantaatfalen en cardiovasculaire mortaliteit. Dit geeft aan dat een optimale renale fosfaat excretie capaciteit na transplantatie voordelig is voor de overleving van het transplantaat en de patiënten.
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**Introduction**

Chronic kidney disease (CKD) is a serious global health problem, affecting 10% of the world population (1). CKD is defined as a decreased kidney function (glomerular filtration rate (GFR) < 60 mL/min/1.73m²), or kidney damage (urinary albumin excretion ≥ 30 mg/day) for a period of three months or more, regardless of the underlying cause (2).

Over time, CKD may progress to end-stage renal disease (ESRD), outlined as a GFR below 15 mL/min/1.73 m². When patients reach ESRD, renal replacement therapy (dialysis or kidney transplantation) is needed.

On January 2015, almost 16,000 chronic kidney disease patients in the Netherlands are in need of renal replacement therapy (3). This number has increased by fifty percent over the last ten years (3). The preferred treatment for patients with ESRD is kidney transplantation, having better patient outcomes compared to dialysis. Kidney transplantation considerably improves the prognosis of chronic kidney disease, by reducing the risk of mortality and by substantially improving quality of life (4). Pre-emptive transplantation (i.e. transplantation before ESRD has been reached) increases patient and graft survival and is only possible with a living donor. Furthermore, living donor kidney transplantation is characterized by shorter ischemia times, well-controlled perioperative conditions, and optimal donor organ quality. Therefore living kidney transplantation provides better graft survival than transplantation from a deceased donor and is therefore considered the best treatment for patients with ESRD (5).

While short-term graft survival after kidney transplantation has improved over the last decade due to new available immunosuppressive drugs (6). Long-term graft survival after the first year showed a slight improvement (7). Therefore, most patients will end up in need of a new renal transplant after 10 to 15 years. Besides that, although kidney transplantation reduces the excessive cardiovascular risk of ESRD patients, kidney transplant recipients still remain at higher risk of cardiovascular disease compared with the general population (8). Cardiovascular disease remains the most common cause of death among kidney transplantation recipients (9). Furthermore, interventions targeting classical cardiovascular risk factors appear less effective in renal transplant recipients. To improve renal transplant outcome, cardiovascular risk management after renal transplantation needs to improve.

Recent studies have pointed out that phosphate metabolism and its regulatory hormones may influence patient and graft outcomes after kidney transplantation (10,11), but the underlying mechanisms and implications for clinical practice remain unknown.

**Phosphate metabolism**

Phosphate is an important mineral of the human body. It plays a critical role in bone metabolism, mineral metabolism and has several cellular functions. For example, phosphate is an important mineral for cell membrane structure, cellular metabolism (formation of adenosine triphosphate (ATP)), cell signaling through protein phosphorylation of key enzymes and cell signaling through phosphorylation of enzymes.

In bone metabolism, phosphate is important for the mineralization of extracellular matrix, mostly being connected to calcium to form hydroxyapatite crystals (12), essential parts of the extracellular matrix in the bones (13). Therefore, hypophosphatemia (serum phosphate levels below 0.7 mmol/L) may induce osteomalacia, which is characterized by unmineralized soft bones.
In humans, most of the phosphate is found in bones and teeth (85 %). The remaining part is found in the soft tissues (14%) and a small portion is present in the extracellular fluid. Phosphate is obtained by dietary intake of 800 to 1500 mg a day (14). Phosphate is mostly found in foods such as meat, grains and dairy products. As a result, a dietary deficiency is rare with the western diet. Approximately 65 % of the phosphate is absorbed in the small intestines either by transcellular or paracellular routes. Phosphate is actively transported transcellularly by the natrium-phosphate co-transporter 2b (NaPi-2b), see figure 1 (15). NaPi-2b is partly regulated and influenced by 1,25 (OH)D3 (16). The paracellular route is a diffusion driven process, mostly regulated by dietary phosphate intake (17). The remaining phosphate, from daily intake, which is not absorbed by the intestine is excreted into the stools. When phosphate has entered the blood after intestinal uptake, it can be absorbed by bones or excreted by the kidneys. In the kidney, almost all phosphate is filtered through the glomerulus. Phosphate is partially reabsorbed by sodium-phosphate co transporter 2a or 2c (NaPi-2a/2c) in the first segment of the proximal tubules (18).

The recently discovered Fibroblast Growth Factor 23 (FGF23) is a major hormone regulating phosphate metabolism. In osteocytes, FGF23 is produced and excreted in response to high levels of phosphate. After excretion, FGF23 needs the membrane protein Klotho to bind to the FGFR3ceptor (19). FGF23 decreases the reabsorption of phosphate in the kidneys by reducing the presence of NaPi2a/NaPi2c in the proximal tubules (20). As a result, phosphate is excreted from the body and serum phosphate levels will decrease. FGF23 also inhibits 1a-hydroxylase activity, limiting the production of 1,25(OH)2D3 (calcitriol), the hormonally active form of vitamin D.

Parathyroid hormone (PTH) is another key regulator of phosphate metabolism. PTH inhibits tubular phosphate reabsorption by endocytosis of the NaPi2a (21).

Figure 1. An overview of the phosphate metabolism.
Chronic kidney disease-mineral and bone disorder
Chronic kidney disease and mineral and bone disorder (CKD-MBD) is a common disorder in CKD, and involves disturbed phosphate metabolism (22). CKD-MBD usually occurs when GFR decreases below 40 mL/min/1.73m², but subclinical changes are observed earlier on. CKD-MBD refers to alterations in mineral metabolism, abnormalities of bone remodeling and extra-skeletal calcifications (23,24). The most important alterations of mineral metabolism are abnormalities of phosphorus, calcium, parathyroid hormone (PTH), FGF23 and vitamin D metabolism.

The first measurable alteration of CKD-MBD is an elevation of FGF23 levels (24). As GFR declines in CKD, renal phosphate excretion is impaired resulting in higher serum phosphate levels (25). In response to this rise in serum phosphate levels, FGF23 levels will increase further, in an effort to prevent the development of hyperphosphatemia. As a result, FGF23 concentrations can be >1000 times higher in patients with ESRD compared with healthy individuals (25,26). Also levels of PTH will rise in response to the high serum phosphate levels, resulting in a secondary hyperparathyroidism. Once GFR declines below a critical threshold (<25 mL/min), urinary phosphate excretion is no longer able to keep up with phosphate intake. From this moment on, hyperphosphatemia occurs.

Both hyperphosphatemia and an elevated FGF23 level are risk factors for the development of vascular calcifications in patients with CKD (27),(28). Vascular calcifications are associated with a greater risk of developing cardiovascular diseases (29), and, in turn, hyperphosphatemia is correlated with a higher risk of mortality (30).

Phosphate metabolism after kidney transplantation
After successful transplantation, kidney function is partly restored. However, CKD-MBD may still persist. A new kind of CKD-MBD will occur consisting of an “old” persisting CKD-MBD from before transplantation in combination with a de novo CKD-MBD as a result of the effects of transplantation (31). In this new situation, CKD-MBD occurs as a result of the effects of immunosuppressive drugs, a persistent hyperparathyroidism and possibly a still reduced renal function, around 40 mL/min/1.73m² (32). Following kidney transplantation, even when successful, levels of FGF23 and PTH may remain elevated for up to one year or even longer (33,34)(35). Because renal function is mostly restored after transplantation, the transplanted kidney is able to respond to the high levels of FGF23 and PTH by decreasing the NaPi2a/2c activity. In response to high FGF23 and PTH levels, through the decreased NaPi2a/2c activity, less phosphate is reabsorbed in the proximal tubules. Consequently, phosphate excretion is enhanced and phosphate wasting occurs. Phosphate wasting contributes to a further rise in PTH, resulting in hyperparathyroidism. In turn, serum calcium will rise as well, resulting in hypercalcemia. Because of the phosphate wasting, low serum levels of phosphate will occur and can decline below 0.7 mmol/L i.e. hypophosphatemia. Approximately 90% of patients develop hypophosphatemia after kidney transplantation (31). The effects of hypophosphatemia on renal recipient outcomes are unknown.

Deregulated phosphate metabolism
In recent years it has become clear that a deregulated phosphate metabolism is associated with adverse outcomes. In 2011, Faul et al, showed a strong association between high levels of FGF23 and the effect on graft failure and cardiovascular mortality after kidney transplantation. Elevated levels of FGF23 play a causal role in the pathogenesis of left ventricular hypertrophy, by inducing pathological hypertrophy of cardiomyocytes (11). After kidney transplantation high serum phosphate levels seems to be associated with graft loss after kidney transplantation (10).
However, Egbuna et al. only saw a trend in which high calcium/phosphate products showed a
toward trend of a higher risk on graft failure after kidney transplantation, no significance
difference was found (36). Therefore literature is contradictive: not all studies show a strong
association between high levels of phosphate and adverse outcomes after transplantation
(36,37). It remains unclear which role serum phosphate levels have on long-term outcomes of
kidney transplantation.

**Graft outcomes after kidney transplantation**

Graft failure is a common problem after transplantation. During the first year
approximately 6.1% of the grafts of living kidney donors and 12.2% of the grafts from
deceased donors will fail due to acute rejection, see figure 2 (6). These
percentages have decreases dramatically since the release of the new
immunosuppressive agent cyclosporine in 1980. Cyclosporine decreased the rate of
acute rejection in the first year, therefore the graft survival during the first year after
transplantation increased (38). Later on, new immunosuppressive drugs mycophenolate
mofetile and tacrolimus led to a further reduction in acute rejection episodes (39).
Harihan et al. also found important factors that influence acute rejection, such as cold
ischemia time, delayed graft function and HLA mismatching which lead to higher
serum panel reactive antibodies. Also kidneys from living donors have a higher
survival rate than deceased donors, as shown before.

In the recent years significant progression has been made on the improvement of graft
survival. The average half life of a transplanted graft improved from 16.9 [15.1-
18.7] to 35.9 [19.3-52.2] years for grafts from living donors and from 11.0 [10.5-
11.5] years to 19.5 [15.1-23.8] years for graft from deceased donors, all data
censored for patient who died with a functional graft. However, as shown in
figure 2 most of this improvement was achieved in the first four months after transplantation (6). This emphasizes that the outcomes on long-term graft survival after kidney transplantation are still in need of improvement.

Chronic rejection is the main cause of graft failure in the long-term follow-up. The new
immunosuppressive drugs are known for their nephrotoxicity effect which can lead to higher
incidence of chronic rejection (40). Because long-term graft survival is still in need of further
improvement, it is necessary to identify risk factors that influence late graft failure.

Figure 2 - Kaplan–Meier Estimates of Graft Survival during the First Year after Transplantation for Grafts from Living Donors (Panel A) and Cadaveric Donors (Panel B) from 1988 to 1996.

Phosphate metabolism and CKD-MBD are important risk factors in chronic kidney disease, therefore they may also play a role in graft outcomes after transplantation. Evenepoel et al. showed an independent significant association between hypophosphatemia and hypercalcemia with calcium-phosphate depositions in renal allografts (41). They did however not find a strong association with graft function.

A previous study focused on the association between hypophosphatemia at fixed time points after transplantation (3 and 6 months) and graft outcomes (42). The authors found that hypophosphatemia was associated with superior graft survival, but when adjusting for kidney function, significance was lost. Therefore they conclude that hypophosphatemia was only associated with a better allograft function instead of an independent factor for graft survival. However, in clinical practice hypophosphatemia occurs mostly before 3 months after transplantation. Whether the lowest serum phosphate at any time point during the first year after transplantation is associated with graft outcomes has not been studied before.

Another group did find an association between calcium-phosphate products and the risk on long-term death-censored graft loss (36). This suggests that high serum phosphate levels in combination with high calcium levels in the first year after transplantation can damage the graft. Low serum phosphate may therefore be an important protecting factor in long-term follow up of graft failure.

Patient outcomes after kidney transplantation
Deregulations in phosphate metabolism are associated with patient outcomes after kidney transplantation. Kidney transplant recipients have a higher mortality rate compared to the normal age-matched population (43). As mentioned previously, cardiovascular mortality is the most common cause of death after transplantation. Traditionally the Framingham risk factors (recipient age and sex, systolic blood pressure, the use of antihypertensive treatment, smoking, diabetes mellitus, total and HDL cholesterol) are the best known predictors for cardiovascular mortality. Recently, factors related to CKD-MBD, such as FGF23, PTH and phosphate have been identified as independent risk factors for mortality and cardiovascular disease.

Baia et al. found an association between high levels of FGF23 and adverse patient outcomes after kidney transplantation. Plasma FGF23 levels were independently associated with all-cause and cardiovascular mortality after kidney transplantation (44). Both FGF23 and CKD-MBD have been associated with cardiovascular mortality after transplantation, but no study has looked for an association between early hypophosphatemia and mortality after transplantation.

The prognostic significance of post-transplant hypophosphatemia in terms of graft failure and patient survival is unclear. We hypothesize that on the one hand, hypophosphatemia may reflect good renal function, because the kidney is able to respond to the high levels of FGF23 and PTH by excreting large amounts of phosphate. Which in turn exerts beneficial effects in terms of protection against vascular calcification. Therefore hypophosphatemia may be associated with a reduced risk of both graft failure and cardiovascular mortality.

On the other hand, (deep) post-transplant hypophosphatemia may reflect long-term exposure to high circulating FGF23 and PTH levels before transplantation, and therefore be associated with an increased cardiovascular risk (31). Also, since phosphaturia accompanying hypophosphatemia may contribute to nephrocalcinosis, the development of hypophosphatemia may also predispose to long-term graft failure.

Because it is unknown what the role is of post-transplant hypophosphatemia, we will study whether hypophosphatemia is either beneficial or deleterious for graft and patient outcomes.
Hypothesis

In this research project we investigated whether post-transplant hypophosphatemia, defined as the lowest serum phosphate level below 0.7 mmol/L, reached at any moment during the first year after transplantation, is associated with graft failure, all-cause and cardiovascular mortality in a cohort of renal transplant recipients.

Therefore the primary research question is defined as:

- Is the lowest serum phosphate during the first year after transplantation associated with graft failure, cardiovascular mortality and non-cardiovascular mortality?

Our secondary aim of this research is to investigate if serum phosphate levels below 0.3 mmol/L are associated with graft failure.

Therefore our secondary research question is defined as:

- Are serum phosphate levels below 0.3 mmol/L in the first year after transplantation associated with graft failure?
Materials and Methods

Study population
To look for an association between the lowest serum phosphate during the first year and our hard point outcomes, a single-center retrospective cohort study was performed in kidney transplant recipients. A total of 957 patients were evaluated from whom serum phosphate levels were available. All transplantations took place between 1993 and 2008 in the University Medical Center Groningen, the Netherlands, or in a collaborating center in The Netherlands on behalf of the Dutch donor exchange program for donor kidneys. The study was approved by the institutional ethical review board (METc 2014/077). All procedures were conducted in accordance with the declaration of Helsinki.

Transplantation and follow-up
Upon transplantation, standard immunosuppression was given to avoid rejection of the donor kidney. In our hospital immunosuppression consisted of triple therapy with tacrolimus, a calcineurin inhibitor (Prograf®, Avagraf®, Astellas Pharma b.v. Leiden, the Netherlands; initial trough level 8-12 ng/mL) or cyclosporine microemulsion (Neoral®, Novartis Pharma b.v. Arnhem, the Netherlands; 2 times 4 mg/kg daily; initial trough level 200-500 ug/L), in a combination with mycophenolate mofetil (Cellcept®, Roche b.v. Woerden, the Netherlands; 2g daily or Myfortic®, Novartis Pharma, b.v. Arnhem, the Netherlands; 1440 mg daily) and prednisolone.
As described in the introduction, cyclosporine was released in 1980. In 1994, tacrolimus was approved and showed a better graft survival, less acute rejection and a reduction of steroid-induced rejection compared to cyclosporine (45). Therefore tacrolimus has since become the preferred immunosuppressive drug in many cases.
Patients with contra-indications for standard immunosuppression received personalized alternative therapy (e.g. azathioprine). Upon suspicion of allograft rejection, a renal biopsy was performed.
Patients were followed up in our center, initially weekly, and later once per year. Follow-up was started directly after transplantation and was recorded until November 2014. Lost of follow-up was recorded if patients stopped visiting our center, developed graft failure or died.

Study outcomes
The primary outcomes of this study were death-censored graft failure, all-cause mortality and cardiovascular mortality. Death censored graft failure was defined as end stage renal disease requiring dialysis or re-transplantation censored for death. The cause of death was obtained from death certificates coded by a physician, according to the International Classification of Diseases, Ninth Revision (ICD-9). Cardiovascular mortality was defined as death from a cardiovascular event such as myocardial infarction, transient ischemic attack, ischemic cerebrovascular accident and heart failure.
The diagnosis post-transplantation diabetes mellitus (PTDM) was defined according to the American Diabetes Association guidelines: causal plasma glucose ≥ 200 mg/dL or fasting plasma ≥126 mg/dl or use of anti diabetic medication (46).
Clinical and biochemical data
For all biochemical analyses, data from routinely determined biochemical measurements were used. Data on the recipients’ type of kidney disease, pre-emptive character of the transplantation, and ischemia times were collected from our central hospital registry. Blood samples were taken after an 8 to 12 hour overnight fasting period. Serum phosphate was determined by routine laboratory measurements. Plasma creatinine concentration was determined using a modified version of the Jaffe method (MEGA AU 510, Merck Diagnostic, Darmstadt, Germany).
The lowest serum phosphate level within the first year after kidney transplantation, was collected by selecting the lowest measurement of phosphate from all recorded measurements in our clinical laboratory during the first year post-transplantation. If patients developed graft failure, died or lost of follow-up was recorded, no more phosphate levels were collected after that point.
Post-Tx hypophosphatemia was categorized as severe (lowest serum phosphate <0.5 mmol/L), mild hypophosphatemia (lowest serum phosphate 0.5-0.7 mmol/L), or absent (>0.7 mmol/L). These cut off points were made on the clinical experience in our hospital. In our hospital a serum phosphate level below 0.7 mmol/L is indicated as a hypophosphatemia. Serum phosphate levels below 0.3 mmol/L is indicated as a severe hypophosphatemia, patients will experience complaints at this point.
Renal function was estimated using the creatinine-based CKD-EPI formula (see figure 3 below), using the serum creatinine level obtained at the same date as the lowest serum phosphate (47).

\[
GFR = 141 \times \min(\text{Scr/\kappa}, 1)^{\alpha} \times \max(\text{Scr/\kappa}, 1)^{\lambda} \times 0.993^{\text{Age}} \times 1.018[\text{if female}] \times 1.159[\text{if black}]
\]
\[
\kappa = 0.7 \text{ if female}
\]
\[
\kappa = 0.9 \text{ if male}
\]
\[
\alpha = -0.329 \text{ if female}
\]
\[
\alpha = -0.411 \text{ if male}
\]
\[
\min = \text{The minimum of Scr/\kappa or 1}
\]
\[
\max = \text{The maximum of Scr/\kappa or 1}
\]
\[
\text{Scr} = \text{serum creatinine (mg/dL)}
\]

Figure 3 – Formula CKD-EPI

Statistical analyses
Variable distribution was tested using histograms and probability plots. Normally distributed variables are presented as mean ± standard deviation, and non-normally distributed variables as median [first-third quartile], unless indicated otherwise. To see if there was a significant association between the serum phosphate in groups and the variables, the non parametric test Kruskal Wallis (all pair wise multiple comparisons) was performed, when variables were continue. In an all pair wise multiple comparison, the null hypothesis assumes that the variable is the same across all groups, a significant level below 0.05 indicates that the variable differs between the groups. If the variable was determined in categories, Chi Square test was used.
To investigate the association between hypophosphatemia severity and clinical outcomes, multivariable Cox regression analysis was used. Model 1 was adjusted for recipient age and gender. Model 2 was additionally adjusted for eGFR and proteinuria, which are known markers for progression of kidney function. Model 3a, used for analysis of graft failure outcome, was additionally adjusted for determinants of transplantation-related factors (dialysis vintage, donor type, warm and cold ischemia times, acute rejection, total mismatches, delayed graft function, cyclosporine use, donor age and gender). Model 3b, used for cardiovascular mortality outcomes, was additionally adjusted for smoking status, diabetes mellitus, and history of cardiovascular events. Cox regression analyses were performed for serum phosphate as a category (absent, mild, severe), and as a continuous (log-transformed) variable. In the continuous analysis we calculated the hazard ratio per halving of the lowest serum phosphate (for example, 0.4 mmol/L vs 0.8 mmol/L). The association between hypophosphatemia and graft failure was analyzed in model 1,2 and 3a. Because the most important determinants for graft failure are those who influence progression of kidney function and transplant related factors. The association between hypophosphatemia and cardiovascular or non cardiovascular mortality was analyzed in model 1,2 and 3b. Here we replaced model 3a which was mostly adjusted for transplantation-related factors by model 3b, mainly consisting of cardiovascular risk factors related to mortality risk. As a secondary analysis, we also addressed the association with graft and patient outcomes in patients with a lowest serum phosphate < 0.3 mmol/L. We performed sensitivity analyses after exclusion of patients with an eGFR < 30 and > 90 mL/min/1.73m². We investigated these patients in model 1 for graft failure. P values below 0.05 were considered significant. All statistical analyses were performed with SPSS software, version 22.0 for Windows (IBM, Armonk, NY) and Graphpad Prism 6 for Windows (Graphpad, San Diego, CA).
Results

Patient characteristics
Patient characteristics and laboratory values are shown in Table 1. Patients were transplanted between March 1993 and February 2008. Patients were at median 49 [IQR 39-59] years old, 58% were men, and 23.9% were transplanted with a kidney from a living kidney donor. As shown in Figure 4, 446 (47%) of the patients had a serum phosphate lower than 0.5 mmol/L (severe hypophosphatemia), 375 (39%) had a serum phosphate between 0.5 - 0.7 mmol/L (mild hypophosphatemia) and 136 (14%) had a serum phosphate higher than 0.7 mmol/L (no hypophosphatemia or absent).

Overall, median [interquartile range] lowest serum phosphate in the first year post-transplantation was 0.52 mmol/L [0.41-0.63]; which was reached at 33 [21-51] days after transplantation. The number of serum phosphate levels that were available in the first year after transplantation was 27 [23-34]. In figure 5 the days between transplantation and the lowest serum phosphate measurement is shown.

Figure 4: Pie chart of the categories (absent, mild or severe) of the lowest serum phosphate in the first year after transplantation.

Figure 5: Days between transplantation (Tx) and serum phosphate
Clinical characteristics of the cohort per hypophosphatemia category are presented in Table 1. Median eGFR at the time of lowest serum phosphate was 52 [39-66] mL/min/1.73m². There was a significant difference in eGFR between the hypophosphatemia groups in eGFR (P < 0.001), as shown in Figure 6.

Figure 6: Boxplot lowest serum phosphate in categories and CKD-EPI
Data as median [first-third interquartile range] and minimum-maximum

Patients who developed severe hypophosphatemia (< 0.5 mmol/L) were more likely to be man; were more likely to have been transplanted with a kidney from a living donor; had a shorter cold ischemia time, and used less frequently tacrolimus as an immunosuppressive, compared with patients who did not develop hypophosphatemia.

Incomplete data was recorded for the variables proteinuria (40% missing of the total study population) and total mismatches in graft matching (18% missing of the total study population). The variable proteinuria was used in model 2,3a and 3b and the variable total mismatches was used in model 3a. Therefore 572 out of the 957 patients were analyzed in model 2 and 449 patients were analyzed for model 3a and model 3b.

Post-transplant hypophosphatemia and graft failure
During follow up of 9 [5-12] years, 181 (19%) patients developed graft failure. The association between the three categories of hypophosphatemia and the risk of graft failure [model 1] is shown in figure 7.
In the fully adjusted model 3b, compared with no hypophosphatemia, both mild (Hazard ratio: 0.41; 95% Confidence Interval (CI) [0.24-0.72], P<0.01) and severe (Hazard ratio 0.41 95% CI [0.22-0.73], P<0.01) hypophosphatemia was significantly associated with a lower risk of death censored graft failure, independent of adjustment for potential confounders (Table 3). The higher a hazard ratio the more likely an event will happen. Here both hazard ratio’s are below 1, this means that the risk on graft failure is lower for patients with hypophosphatemia compared to those who did not develop hypophosphatemia. An important condition for the Cox regression is that the hazards between the different groups are proportional relative to each other. In figure 7 it is clear that the three groups do not cross each other and overall decline in the same proportion, hereby the condition is made.

After the adjustment for kidney function (eGFR) in model 2 the hazard ratio increased, the risk on graft failure increased, but the association remained significant compared to model 1. In analyses with the lowest level of phosphate achieved as a continuous variable, for each halving of the lowest serum phosphate the risk of graft failure was 70 percent lower (full model hazard ratio 0.30 [95% CI 0.16-0.52], P<0.001). So, for every decrease in serum phosphate by 50 % the risk on graft failure decreased with 70 percent.

Post-transplant hypophosphatemia and mortality

During follow up of 9 [5-12] years; 295 (31%) patients died, of which 93 (32 %) died from cardiovascular disease and 141 (48%) of non-cardiovascular cause. The cause of death was unknown in 113 (38%) of patients. The development of hypophosphatemia after transplantation was not associated with the risk of all-cause mortality. However, when assessing cause-specific mortality as an outcome, we found that the development of hypophosphatemia after transplantation was associated with a reduced risk of cardiovascular mortality.

In figure 8, model 1 of cardiovascular mortality is shown in a survival function. The category with a lowest serum phosphate < 0.5 mmol/L has a lower risk of cardiovascular death compared to the other two categories.
In a fully adjusted model (model 3b), severe hypophosphatemia was strongly associated with the risk of cardiovascular mortality (hazard ratio 0.29, 95% confidence interval 0.13-0.67, P value of <0.001) compared with no hypophosphatemia. For mild hypophosphatemia versus no hypophosphatemia the hazard ratio was 0.29 with a 95% confidence interval of 0.11-0.58 and a P value lower than 0.01. In the analysis of continuous per halving of lowest serum phosphate the risk of graft failure was 70 percent lower with a hazard ratio of 0.30, a 95% confidence interval of [0.14-0.63] and a P value of 0.001. All together, the risk for cardiovascular mortality is lower for a patient that developed hypophosphatemia compared to a patient that did not developed hypophosphatemia, analyzed as a category and a continuous variable.

We found no association between serum phosphate and all cause mortality. For severe vs no hypophosphatemia in the fully adjusted model 3b hazard ratio was 1.23 with a confidence interval of 0.69-2.22 and a P value of 0.486. Mild vs no hypophosphatemia had a hazard ratio of 1.20 with a confidence interval of 0.67-2.15 and P value of 0.54. In the analysis of continuous per halving of the lowest serum phosphate the risk of graft failure was 16% higher with a hazard ratio of 1.16, a confidence interval of [0.78-1.72] and a P value of 0.47.

No significant association was found between the lowest serum phosphate and non-cardiovascular mortality. For severe vs no hypophosphatemia in the fully adjusted model 3b hazard ratio was 0.94 with a confidence interval of 0.47-1.89 and a P value of 0.86. Mild vs no hypophosphatemia had a hazard ratio of 0.54 with a confidence interval of 0.27-1.10 and P value of 0.091. In the analysis of continuous per halving of the lowest serum phosphate the risk of graft failure was 3% lower with a hazard ratio of 0.97, a confidence interval of [0.56-1.72] and a P value of 0.93.

Analysis for graft failure
As a secondary analysis we investigated if there is an association between patients with a serum phosphate level below 0.3 mmol/L and graft failure. We only included patients with a kidney function (eGFR) between 30-90 mL/min/1.73m². 51 out of the 976 patients remained, with 9 cases of graft failure. In this subgroup the lowest serum phosphate was associated with a reduced risk on graft failure with a hazard ratio of <0.000 with a 95% confidence interval of [0.000 – 0.040] and a significance level of P = 0.021.
Discussion

CKD is a global health problem affecting an increasing number of patients each year (1,3). When patients reach ESRD, living donor kidney transplantation is the best treatment (4,5,48). After transplantation graft failure and cardiovascular mortality are still major problems (7,8). The prospects regarding these outcomes are therefore still in need of improvement.

Hypophosphatemia is a commonly observed phenomenon in the first year after kidney transplantation (31). Previous research shows that hypophosphatemia in combination with hypercalciemia is associated with a higher risk on graft failure (31,36). Our results do not support this previous study in that we found that hypophosphatemia as such is associated with a lower risk of graft failure. Analyzing the lowest serum phosphate level reached within the first year after transplantation, we found that the absence of hypophosphatemia is associated with a higher risk of graft failure as compared to those with a hypophosphatemia. Furthermore, post-transplant hypophosphatemia was associated with a lower risk of cardiovascular mortality. Hypophosphatemia was not associated with non-cardiovascular mortality. In our analysis the lowest serum phosphate (lower than 0.3 mmol/L) was still significant associated with a decreased risk on graft failure. These results should be interpret with caution, only 51 patients were analyzed in this sensitivity analysis, whereby only 9 patients developed graft failure. This is a relatively small group, but we still found a significance association. With the sensitivity analysis we do show that patients with a good kidney function and a very low serum phosphate are still at a lower risk on graft failure. Further research with a larger population of patient with phosphate levels below 0.3 mmol/L is needed to fully draw this conclusion.

Our findings are in line with a previous study of Huber et al. showing an association between post-transplant hypophosphatemia and superior graft survival (42).

In the study population of Huber et al. only 1% of the patients developed a severe hypophosphatemia below of serum phosphate levels below 0.5 mmol/L. In our study 47% of the patients developed a severe hypophosphatemia. In the study of Huber et al, serum phosphate levels were analyzed at 6 months after transplantation in all patients, which could have been relatively late given our finding that 50% of patients develop their lowest serum phosphate level at approximately one month after transplantation. We chose a different approach, namely to consider all serum phosphate measurements performed in our cohort within the first year after transplantation, and to consider the lowest serum phosphate value at any given moment in the first year. Using this approach, we found that the incidence of severe hypophosphatemia is more common than previously reported (42). We are the first to identify an association between the lowest serum phosphate during the first year after transplantation and graft and patient outcomes.

To check if our results are fully in line with the research of Huber et al. an analyses of the serum phosphate levels at 6 and 12 months after transplantation are needed. We are currently performing these analyses as sensitivity analyses.

The development of hypophosphatemia was associated with a higher eGFR, in line with the concept that good renal function reflects an increased renal capacity to excrete phosphate. In the study by Huber et al., significance was lost after adjusting the analysis for the association between hypophosphatemia and graft failure for kidney function. As described in the results our hazard ratio increased when we corrected for the kidney function, but remained significant. This may be explained by a difference in sample size (and thus statistical power) between our studies. It is still important to address this finding, kidney function remains a very important factor in the prognosis of graft function outcomes after kidney transplantation, and eGFR is not the only estimate of renal function.
That is, although eGFR may be a well-established marker of glomerular function, there is no established equivalent to measure tubular function. Tubular function clearly plays an important role in renal phosphate handling and might therefore be considered an important determinant of long-term graft outcome (49-51).

Our findings are in contrast with a previously postulated hypothesis that hypophosphatemia, due to persistently elevated PTH and FGF23 levels, would contribute to nephrocalcinosis and graft failure after transplantation (41). Other research have shown that elevated levels of PTH and FGF23 are associated with vascular calcifications and a higher risk of cardiovascular mortality (11,44,52,53). Rather, our data support the sequence of events that hypophosphatemia results in more efficient lowering of FGF23 and PTH after transplantation, contributing to improved mineral metabolism after transplantation.

Hypophosphatemia was also more commonly observed in patients receiving from a living kidney donor, in line with a previous study on FGF23 in renal transplant recipients (44). Living kidney donation provides better graft survival and graft outcomes compared to a kidney from a deceased donor (48). Even after adjustment for the type of donation, hypophosphatemia was still associated with a better graft survival.

A major finding of our study thus was that improved renal phosphate handling was associated with beneficial graft outcomes in renal transplant recipients. During my internship I have worked at another research project as well. In this other project we investigated whether in healthy kidney donors, assessed before donation, the maximum renal phosphate reabsorption capacity would be associated with outcome after transplantation. The maximum capacity to reabsorb phosphate was defined by the maximum rate of tubular phosphate reabsorption to the glomerular filtration rate (TmP-GFR). Our main finding was that a higher TmP-GFR predonation, reflecting a better renal capacity to reabsorb phosphate, is associated with a better kidney function (mGFR) in recipients one year after kidney transplantation. This shows that even healthy living kidney donors with an excellent GFR, may have some tubular damage that can influence the outcomes in renal replacement recipients.

The association between hypophosphatemia and lower cardiovascular mortality can be reconciled with previous studies by our group and others, showing that a higher plasma FGF23 is independently associated with an increased risk of cardiovascular and all-cause mortality (24,44). Early after successful kidney transplantation, when renal function is rapidly restored but FGF23 and PTH remain high, the resulting renal phosphate leak will lead to a subsequent decline in circulating FGF23 and PTH. This decline will be more efficient in those with hypophosphatemia than in those with no hypophosphatemia.

As FGF23 has been implicated in cardiovascular disease (11,53,54), more efficient lowering of FGF23 could well contribute to the reduced risk of cardiovascular mortality in renal transplant recipients who developed hypophosphatemia in the first year after transplantation. For a full complete model to adjustments for cardiovascular mortality more Framingham risk factors are needed such as blood pressure, cholesterol levels and body mass index. However, so far we have had too extensive missing data that preclude inclusion of these covariates in the analyses.

Also it is known that high levels of phosphate before transplantation are associated with vascular calcifications and a higher risk on mortality (29,30). This can also be the case after transplantation, whereby lower levels of phosphate will protect against vascular calcification and are therefore associated with a reduced risk of cardiovascular mortality. This hypothesis is in line with our findings, but further research needs to be done. It can be a possibility to compare the amount of vascular calcifications between the three categories of phosphate levels.
A limitation of our study is that we could not take phosphate supplementation into account, the timing and dosing of which must have influenced the course of serum phosphate after kidney transplantation. Yet, despite this limitation, our positive findings suggest that we were apparently able to discriminate patients developing no, mild or severe hypophosphatemia independently of the timing and dose of supplementation. It is actually conceivable that the intervention resulted in an underestimation of the effect reported in our study, as supplementation is aimed at stopping the decrease of phosphate in patients with severe hypophosphatemia. Also we do not know if phosphate supplementation is necessary.

Furthermore, for a considerable proportion of patients the cause of death was unknown. Only 30% of the patients in our cohort died of cardiovascular causes, which is lower than commonly observed (9). In over 100 patients, no cause of death could be identified; this group probably represents a relatively high percentage of patients who died from a cardiovascular cause, being a source of selection bias.

Also, in model 2 and model 3a/3b not all data was available for the variables. Therefore there is a bias, because of only selecting the patients of whom all data for the variables is available. Further, our patient population had a low incidence of diabetes mellitus, potentially limiting the generalizability of our findings.

Also the percentage of tacrolimus use is very low compared with today’s clinical practice. Nowadays most patients receive tacrolimus, a newer immunosuppressiva than cyclosporine. Tacrolimus has the same mechanism of action as cyclosporine, but tacrolimus is accompanied by a reduced risk of acute rejection over cyclosporine (45).

However, in this study we have adopted a unique approach: to consider all serum phosphate measurements in all patients during the first year after transplantation. Also the follow-up of our study was extensive, making long-term predictions of graft failure possible.
Conclusion

In conclusion, we found that patients who develop hypophosphatemia after kidney transplantation compared:

- at reduced risk of graft failure with patients who do not develop hypophosphatemia are
- at reduced risk of cardiovascular mortality with patients who do not develop hypophosphatemia are
- have the same risk of all-cause mortality with patients who do not develop hypophosphatemia are

Patients developing hypophosphatemia can be reassured that this phenomenon is accompanied by a relative good prognosis on both graft and patient outcomes. Future studies should address whether patients who do not develop hypophosphatemia require more intense monitoring for accelerated renal function loss or cardiovascular disease.
<table>
<thead>
<tr>
<th>Table 1. Clinical characteristics of the cohort</th>
<th>All patients (n=957)</th>
<th>Severe hypophosphatemia (n=446)</th>
<th>Mild hypophosphatemia (n=375)</th>
<th>No hypophosphatemia (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%) male</td>
<td>557 (58%)</td>
<td>272 (61%)</td>
<td>221 (59%)</td>
<td>64 (47%)</td>
</tr>
<tr>
<td>Diabetes Mellitus before transplantation, n (%)</td>
<td>53 (5.5%)</td>
<td>25 (5.6%)</td>
<td>19 (5.1%)</td>
<td>9 (6.6%)</td>
</tr>
<tr>
<td>Post-Transplantation diabetes mellitus</td>
<td>18 %</td>
<td>19 %</td>
<td>17 %</td>
<td>17 %</td>
</tr>
<tr>
<td><strong>Etiology of kidney disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary glomerulonephritis</td>
<td>24.6 %</td>
<td>26.8%</td>
<td>24.9 %</td>
<td>20.9 %</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>5.5 %</td>
<td>4.6 %</td>
<td>6.8 %</td>
<td>6.2 %</td>
</tr>
<tr>
<td>Tubulo-interstitial nephritis / pyelonephritis</td>
<td>10.2 %</td>
<td>10.8%</td>
<td>9.0 %</td>
<td>14.0 %</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>18.4 %</td>
<td>20.2 %</td>
<td>18.4 %</td>
<td>16.3 %</td>
</tr>
<tr>
<td>Renovascular</td>
<td>8.5 %</td>
<td>9.2 %</td>
<td>8.8 %</td>
<td>7.0 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.1 %</td>
<td>3.7 %</td>
<td>4.7 %</td>
<td>4.7 %</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>1.8 %</td>
<td>1.4 %</td>
<td>2.5 %</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Other</td>
<td>24.1 %</td>
<td>23.4 %</td>
<td>24.9 %</td>
<td>29.5 %</td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>96.4 %</td>
<td>95.1 %</td>
<td>97.3 %</td>
<td>98.5%</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>72.3 %</td>
<td>73.5%</td>
<td>70.7 %</td>
<td>72.8%</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>87.9 %</td>
<td>86.3 %</td>
<td>87.7%</td>
<td>93.4%</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>4.8 %</td>
<td>2.2 %</td>
<td>6.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>7.4 %</td>
<td>8.7 %</td>
<td>7.5%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>3.8 %</td>
<td>4.0%</td>
<td>4.3%</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Laboratory results (at the time of the lowest serum phosphate)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest serum phosphate post-transplantation, mmol/L</td>
<td>0.52 [0.41-0.63]</td>
<td>0.40 [0.34-0.46]</td>
<td>0.58 [0.54-0.64]</td>
<td>0.79 [0.73-0.88]</td>
</tr>
<tr>
<td>Number of phosphate levels available, n</td>
<td>27 [23-34]</td>
<td>27 [23-34]</td>
<td>28 [24-34]</td>
<td>26 [22-34]</td>
</tr>
<tr>
<td>Proteinuria, g/24h</td>
<td>0.32 [0.18-0.50]</td>
<td>0.32 [0.18-0.50]</td>
<td>0.32 [0.20-0.53]</td>
<td>0.32 [0.18-0.46]</td>
</tr>
<tr>
<td>Estimated GFR (CKD-EPI), mL/min/1.73m²</td>
<td>52 [39-66]</td>
<td>58 [46-70]</td>
<td>49 [38-60]</td>
<td>41 [26-53]</td>
</tr>
<tr>
<td><strong>Transplant characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type transplantation, living/cadaveric, n</td>
<td>232/737</td>
<td>128/318</td>
<td>64/311</td>
<td>28/108</td>
</tr>
<tr>
<td>Cold ischaemia time, min</td>
<td>1068 [606-1380]</td>
<td>960 [180-1376]</td>
<td>1140 [796-1428]</td>
<td>1095 [700-1463]</td>
</tr>
<tr>
<td>Acute rejection, n (%)</td>
<td>342 (36%)</td>
<td>160 (36%)</td>
<td>135 (36%)</td>
<td>47 (35%)</td>
</tr>
<tr>
<td>Total mismatches, (n)</td>
<td>2 (0-6)</td>
<td>2 (0-6)</td>
<td>2 (0-6)</td>
<td>2 (0-6)</td>
</tr>
<tr>
<td><strong>Donor characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%) male</td>
<td>477 (49.1 %)</td>
<td>214 (48 %)</td>
<td>197 (52.5 %)</td>
<td>66 (48.5%)</td>
</tr>
</tbody>
</table>
## Table 2. Cox regression models

<table>
<thead>
<tr>
<th>Hypophosphatemia category</th>
<th>Continuous (per halving of lowest serum phosphate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Mild</td>
</tr>
<tr>
<td>Graft failure (181 events)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 2</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 3a</td>
<td>Ref</td>
</tr>
<tr>
<td>All-cause mortality (295 events)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 2</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 3b</td>
<td>Ref</td>
</tr>
<tr>
<td>CV mortality (97 events)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 2</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 3b</td>
<td>Ref</td>
</tr>
<tr>
<td>Non CV mortality (141 events)</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 2</td>
<td>Ref</td>
</tr>
<tr>
<td>Model 3b</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Model 1: adjusted for recipient age and gender
Model 2: model 1 + eGFR at time of lowest phosphate, log proteinuria
Model 3a: model 2 + adjusted for cold ischemia time, total mismatches, dialysis vintage, acute rejection, delayed graft function, cyclosporine use, donor age and donor gender
Model 3b: model 2 + adjusted for smoking status, pre- or post-transplant diabetes mellitus, and CV history
* P<0.05; ** P<0.01; *** P<0.001
Conclusions

The development of tools to improve patient outcomes. The poster focuses on the use of technology to monitor and manage patients with CKD-
MBD. The work presented includes the use of new technologies to improve patient care. The potential for these tools to improve patient outcomes is discussed. The poster concludes with a call for further research to explore the use of these technologies in clinical practice.

Methods

Aim

Results

Conclusion

POST-TRANSPLANTATION HYPOPHOSPHATEMIA AND OUTCOME AFTER KIDNEY TRANSPLANTATION
References


(3) RENINE. Aantal patienten 1 januari, 1990 t/m 2014. Dialysepatienten en patienten met een functionerende donornier. 2014; Available at: https://www.renine.nl/static?id=prev_years&var=dg&style=line&render=png. Accessed 07/03.


