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VITAMIN D RECEPTOR ACTIVATOR AND DIETARY SODIUM RESTRICTION TO REDUCE RESIDUAL URINARY ALBUMIN EXCRETION IN CHRONIC KIDNEY DISEASE (VIRTUE STUDY): RATIONALE AND STUDY PROTOCOL

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ABSTRACT

Background. Optimal albuminuria reduction is considered essential to halt chronic kidney disease (CKD) progression. Both vitamin D receptor activator (VDRA) treatment and dietary sodium restriction potentiate the efficacy of renin-angiotensin-aldosterone-system (RAAS)-blockade to reduce albuminuria. The ViRTUE study addresses whether a VDRA in combination with dietary sodium restriction provides further albuminuria reduction in non-diabetic CKD patients on top of RAAS-blockade.

Methods/design. The ViRTUE study is an investigator-initiated, prospective, multi-centre, randomized, double-blind (paricalcitol versus placebo), placebo-controlled trial targeting stage 1-3 CKD patients with residual albuminuria of >300 mg/day due to non-diabetic glomerular disease, despite angiotensin converting enzyme inhibitor or angiotensin receptor blocker use. During run-in, all subjects switched to standardized RAAS-blockade (ramipril 10 mg/day) and blood pressure titrated to <140/90 mmHg according to a standardized protocol. Eligible patients are subsequently enrolled and undergo four consecutive study periods in random order of 8 weeks each: (i) paricalcitol (2 µg/day) combined with a liberal sodium diet (~200 mmol Na+/day, i.e. mean sodium intake in the general population), (ii) paricalcitol (2 µg/day) combined with dietary sodium restriction (target: 50 mmol Na+/day), (iii) placebo combined with a liberal sodium diet, and (iv) placebo combined with dietary sodium restriction. Data are collected at the end of each study period. The primary outcome is 24-h urinary albumin excretion. Secondary study outcomes are blood pressure, renal function (estimated glomerular filtration rate), plasma renin activity and, in a sub-population (N=9), renal haemodynamics (measured glomerular filtration rate and effective renal plasma flow). A sample size of 50 patients provides 90% power to detect 23% reduction in albuminuria, assuming a 25% dropout rate.

Discussion. Further reduction of residual albuminuria by combination of VDRA treatment and sodium restriction during single-agent RAAS-blockade will justify long-term studies on cardiorenal outcomes and safety.

Clinical trial registration. NTR2898 (Dutch trial register).
RATIONALE

Albuminuria independently contributes to chronic kidney disease (CKD) progression towards end-stage renal disease (ESRD), and is also an independent predictor of cardiovascular outcome. Optimal lowering of albuminuria is therefore a cornerstone of current CKD treatment. Pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS) by angiotensin converting enzyme (ACE) inhibition or angiotensin receptor blockade (ARB) reduces albuminuria and blood pressure, retards renal disease progression and reduces cardiovascular risk in CKD patients. Despite optimally dosed single agent RAAS-blockade, however, considerable residual albuminuria remains in many CKD patients. The amount of residual albuminuria is closely related to long-term renal and cardiovascular prognosis. Consequently, further albuminuria reduction by means of adjunct pharmacological or dietary measures has been advocated to further improve cardiorenal outcomes. Recent studies have shown that dual RAAS-blockade using traditional RAAS-inhibitors did not result in increased renoprotection compared with single-agent RAAS-blockade. Rather, particularly in diabetic nephropathy patients, dual RAAS blockade was accompanied by an increased risk of acute kidney injury and hyperkalemia. Because dual RAAS-blockade is now considered insufficiently safe for a considerable part of the CKD population, it is necessary to find alternative treatment modalities with a more attractive efficacy/side effect ratio.

Dietary sodium restriction potentiates the antiproteinuric efficacy of RAAS-blockade. A modest reduction of dietary sodium intake to 2 g/day is associated with a 30% proteinuria reduction, which is in the same order of magnitude as the response to single RAAS-blockade. Combining RAAS-blockade with sodium restriction synergistically reduces proteinuria in non-diabetic CKD patients. Sodium restriction on top of RAAS-blockade is also associated with long-term renal and cardiovascular protective effects both in non-diabetes and diabetes. Conversely, sodium overload may even annihilate the antihypertensive and antiproteinuric effects of RAAS-blockade. Despite adequate sodium restriction during single-agent RAAS-blockade, however, residual proteinuria may still remain, requiring additional intervention.

Recent preclinical and clinical studies demonstrated that vitamin D receptor activators (VDRA, e.g. paricalcitol) may provide additional renoprotection by reducing residual albuminuria. The renoprotective effects of VDRA may at least partly be mediated by the RAAS. Vitamin D receptor activation directly suppresses renin gene transcription. Additionally active vitamin D has displayed anti-inflammatory and antifibrotic effects as well as specific beneficial effects on podocytes in models of CKD (reviewed by Mirkovic et al and Ito et al). Thus, the renoprotective effects of VDRA seem to be set forth partly beyond the RAAS, and because VDRAs are not accompanied by (major) effects on blood pressure or serum potassium, these agents are attractive adjuncts to RAAS-blockade. Indeed, renoprotective effects of VDRA treatment appear additive to RAAS-blockade effects, both in the clinical setting and in animal studies.

Whether the capacity of VDRA treatment to lower residual albuminuria depends on sodium intake is unclear. Surprisingly, a post-hoc analysis of the VITAL study suggested that patients with...
higher baseline dietary sodium intake displayed a stronger antiproteinuric effect upon VDRA treatment.\textsuperscript{24} This would be in contrast with a large number of reports demonstrating that sodium restriction potentiates the antiproteinuric efficacy of RAAS-blockade, but also other classes of drugs such as non-steroidal anti-inflammatory drugs\textsuperscript{25} and vasopeptidase inhibitors\textsuperscript{26}. Moreover, we recently demonstrated that dietary sodium restriction indeed potentiates the antiproteinuric effect of the VDRA paricalcitol in a rat model of proteinuric nephropathy\textsuperscript{27}.

To prospectively study the potentially interacting effects of dietary sodium intake and VDRA treatment on residual albuminuria during background RAAS-blockade in patients, we designed a double-blind randomized placebo-controlled crossover trial with a 2x2 factorial design. The trial consists of four study periods comparing residual albuminuria during treatment with the VDRA paricalcitol or placebo during a low or liberal sodium diet, respectively, all during background ACE inhibition in CKD patients with residual albuminuria due to non-diabetic glomerular disease. Diabetic CKD patients are not included because vitamin D may interfere with insulin secretion and insulin sensitivity (reviewed by De Boer et al\textsuperscript{28}) which could also influence residual albuminuria, and thus cause heterogeneity in the results. Furthermore, the ViRTUE focuses on patients with albuminuria from glomerular origin. Therefore, patients with secondary albuminuria due to disease such as amyloidosis, multiple myeloma or cancer are also excluded from participation in this trial. In a substudy, we will investigate the effect of paricalcitol and dietary sodium restriction on renal haemodynamics, \textit{i.e.} measured glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), given the previously documented effect of paricalcitol on estimated glomerular filtration rate (eGFR)\textsuperscript{17}. Successful reduction of residual albuminuria by VDRA treatment in combination with dietary sodium restriction during single RAAS-blockade may pave the way for a large-scale clinical trial providing evidence for long-term beneficial effects of this combination therapy on cardiorenal endpoints.

**STUDY PROTOCOL**

**Study design and organization**

The ViRTUE study is an investigator-initiated, prospective, multi-centre, randomized, double-blind, placebo-controlled trial targeting non-diabetic CKD patients with residual albuminuria despite single-agent RAAS-blockade. The ViRTUE study is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO, The Netherlands). The study has been approved by the Medical Ethical Committee of the University Medical Center Groningen, the Netherlands (METc 2009.272), and has been registered in the Dutch clinical trial register (NTR2898). Participation in the study is on voluntary basis. Patients will not receive any financial support or priority for treatment of other diseases during this study.
**Participants**

The ViRTUE study recruited stage 1-3 non-diabetic CKD patients with residual albuminuria >300 mg/day due to (non-diabetic) glomerular disease despite optimally dosed single-agent RAAS-blockade. Recruitment took place at five academic or non-academic hospitals in the Netherlands. Patients were required to have a stable renal function with a creatinine clearance >30 mL/min, the average of two parathyroid hormone (PTH) values should be <1.5 times the upper limit of normal (defined by the reference values of each participating centre) and the average of two corrected serum calcium values should be between 2.0 and 2.6 mmol/L. Furthermore, patients should not have received (within 3 months prior to screening) vitamin D (analogues). Circulating 25(OH)D was not used as specific criteria, because previous studies suggest that the albuminuria-lowering effect of vitamin D receptor activation is independent of the vitamin D status as reflected by 25(OH)D levels (VITAL study, unpublished data). This approach is similar to the previous clinical trials with paricalcitol among CKD patients. Patients who also met the other prespecified eligibility criteria (Table 1) and provided written informed consent were enrolled. Patient enrolment started March 2012 and was closed in May 2014.

**Table 1. Eligibility criteria of the ViRTUE study**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>1 Male and female patients</td>
<td>1 Diabetes Mellitus</td>
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<tr>
<td>2 Non-diabetic glomerular disease as established by history, serum biochemistry tests and/or renal biopsy</td>
<td>2 Uncontrolled hypertension</td>
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<td>3 Age ≥ 18 years</td>
<td>3 Hyperkalemia (potassium &gt;6.0 mmol/L)</td>
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<td>4 Residual albuminuria &gt;300 mg/day and &lt;10 g/day during conventional treatment of at least 8 weeks with ACEi or ARB at the maximum recommended dose</td>
<td>4 Cardiovascular disease (myocardial infarction, unstable angina, percutanous transluminal coronary angioplasty, coronary artery bypass grafting, or stroke within last 6 months, heart failure NYHA III-V)</td>
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<tr>
<td>5 Stable renal function (creatinine clearance of &gt;30 ml/min; with &lt;6 ml/min per year decline)</td>
<td>5 Epilepsy</td>
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<tr>
<td>6 Average of 2 consecutive PTH values of &lt;1.5 times the upper limit of normal (defined by the reference values of each participating center), 2 consecutive serum calcium levels between 2.0 and 2.6 mmol/L (corrected for albumin levels), 2 consecutive serum phosphorus levels of ≤ 1.5 mmol/L within 4 weeks prior to treatment</td>
<td>6 Liver disease resulting in aberrations of liver function tests</td>
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<tr>
<td>7 Self-written informed consent (no incapacitated adults)</td>
<td>7 Previously treated (within 3 months of screening) with paricalcitol or vitamin D (analogue)</td>
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<tr>
<td>8 Contraindication to ACEi, high/low-sodium diet or paricalcitol</td>
<td>8 Contraindication to ACEi, high/low-sodium diet or paricalcitol</td>
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<tr>
<td>9 Medication interacting with ACEi or paricalcitol</td>
<td>9 Medication interacting with ACEi or paricalcitol</td>
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<tr>
<td>10 Frequent NSAID use (&gt; 2 doses/week), use of immunosuppressive drugs or use of digoxin</td>
<td>10 Frequent NSAID use (&gt; 2 doses/week), use of immunosuppressive drugs or use of digoxin</td>
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<tr>
<td>11 Active malignancy</td>
<td>11 Active malignancy</td>
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<tr>
<td>12 Any bowel disorder resulting in fat malabsorption</td>
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<td>13 Pregnant or nursing (lactating) women, where pregnancy is defined as a state of a female after conception and until the termination of gestation, confirmed by a positive ß-hCG laboratory test (&gt;5 mIU/ml)</td>
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</tr>
<tr>
<td>14 Incompliance with diet or study medication</td>
<td>14 Incompliance with diet or study medication</td>
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<tr>
<td>15 Any psychiatric condition or psychiatric medication use</td>
<td>15 Any psychiatric condition or psychiatric medication use</td>
</tr>
<tr>
<td>16 Drug or alcohol abuse</td>
<td>16 Drug or alcohol abuse</td>
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Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ß-hCG, beta human chorionic gonadotropin; NSAID, non-steroidal anti-inflammatory drug; NYHA, New York Heart Association; PTH, parathyroid hormone.
Run-in period

Before study entry, patients start with a wash-out/wash-in period in which RAAS-blocking agents and diuretics (except for furosemide) are discontinued, and standardized RAAS-blockade (10 mg ramipril/day) is started to titrate blood pressure to a value of <140/90 mmHg. If necessary, pharmacological antihypertensive therapy is optimized during the run-in period. Blood pressure is evaluated during every outpatient clinic visit under constant conditions, at 1-min intervals for 15 min by an automatic device (Dinamap; DE Medical systems, Milwaukee, WI), with the patient in a semi-supine position. If the target blood pressure of <140/90 mmHg is not reached within 6 weeks after the initiation of ramipril, additional antihypertensive medication (metoprolol, doxazosin and/or amlodipine) is added to the treatment regimen with 4-week intervals. Blood pressure is evaluated every fourth week, and patients with adequate blood pressure values enrol in the study. After a maximum wash-in/wash-out period of 18 weeks, patients with a blood pressure value < 180/100 mmHg will be able to enrol in the study. Patients with a blood pressure value of >180/100 mmHg, despite optimal antihypertensive treatment as indicated above, are not included in the study.

Study period

Patients are subjected to four consecutive study periods in random order with duration of 8 weeks each. These study periods (Figure 1) consist of: (i) the VDRA paricalcitol (19-nor-1,25[OH]2-vitamin D2, 2 µg/day24,30) combined with a liberal sodium diet (~200 mmol Na+/d [~4.8 g], i.e. corresponding to the mean sodium intake in the general population), (ii) paricalcitol (2 µg/day) combined with dietary sodium restriction (target 50 mmol Na+/day, ~1.2 g), (iii) placebo combined with a liberal sodium diet, and (iv) placebo combined with dietary sodium restriction. The duration of each treatment period is based on previous studies with paricalcitol demonstrating maximum albuminuria reduction at 4-6 weeks after treatment initiation.24,31 Since our 8-week study periods are considerably longer than the wash-out of the interventions (paricalcitol < 2 weeks31 and re-establishment of steady state after a change in sodium diet < 2 weeks11,12), the protocol does not include wash-out periods.

Patients are instructed to take the study medication once daily, in the morning, except for study days, when the study drug will be taken after data have been collected at the study centre. Every 8 weeks, patients collect 24-h urine, and after an overnight fast blood pressure is measured and blood and spot urine samples are taken (see Figure 1). Collected data at the end of each 8-week treatment period are used for analysis. At 4 weeks from start of the treatment period, serum albumin, calcium, phosphorus and PTH are measured for safety analyses.

During the course of the study, patients will receive a thorough monitoring of compliance to the sodium diet by measuring 24-h urinary sodium excretion every 4 weeks. Patients will be motivated to ensure a stable protein intake (1.1 g/kg body weight per day) during the periods of different sodium intake. Between inclusion and start of the study, patients will be asked to keep a dietary diary for a period of 3 days and to collect 24-h urine on the third day. The results of the dietary diary and the 24-h urine collection will be used during a dietary consult in which
the patient will receive personal dietary advice to be compliant to the sodium-restricted diet. Differences in sodium intake between the study periods will be achieved by replacing sodium-rich products with a low-sodium product of the same product group to maintain isocaloric intake with a similar balance among protein, carbohydrate and fat. When subjects report symptomatic hypotension during the study period, especially while on dietary sodium restriction, the dose or the number of antihypertensives will be reduced. If blood pressure afterwards rises to >140/90 mmHg, the dose or number of antihypertensives will be restored.

Renal haemodynamics substudy
In a substudy consisting of male patients, we will evaluate the effect of paricalcitol and dietary sodium restriction on renal haemodynamics (GFR and ERPF). All male patients participating at the University Medical Center Groningen or Martini Hospital Groningen were asked informed consent for this sub-study. At the end of each study period, subjects undergo GFR/ERPF measurements remaining in a semi-supine position except during voiding as previously described in more detail32. In short, to ensure sufficient urine output, subjects will be provided with 250 ml of oral fluids every hour. After a 1.5-h stabilization period, GFR and ERPF are measured as the clearances of constantly infused $^{125}$I-iothalamate and $^{131}$I-hippuran, respectively. After the stabilization period, blood is drawn every hour and urine is collected every two hours. In this set-up, GFR is measured as the urinary clearance of $^{125}$I-iothalamate using the formula $(U \times V)/P$ (where $U$ is concentration per mL urine, $V$ is urinary flow rate in ml/min and $P$ is plasma concentration) and corrected for voiding errors by the ratio of plasma to urinary clearance of $^{131}$I-hippuran. Furthermore, 24-h
Ambulatory blood pressure is measured in the week prior to the GFR/ERPF measurement using a Spacelabs 90217 (Spacelabs Medical Products, Sydney, Australia) device with blood pressure and heart rate recorded three times per hour throughout awake periods and once every hour during sleeping periods.

**Randomization and blinding**

To prevent systematic errors resulting from the crossover design, the different periods, treatment (placebo or paricalcitol) as well as diet (low or liberal sodium diet), will be randomized for each patient. We defined four different treatment sequences (see Figure 2). Randomization of these sequences was performed externally by the pharmaceutical company that delivered the study medication (AbbVie).

Administration of study medication (placebo or paricalcitol) takes place in a double-blinded fashion, while the diet (low or liberal sodium) will be open label. Unblinding is only acceptable when severe deterioration of renal function (defined as ≥25% renal function decline between two visits) is recorded or when a serious adverse event occurs that requires information regarding the study medication use (paricalcitol or placebo).

**Figure 2.** Four different sequences of treatment periods in the ViRTUE study

The interventions are a liberal sodium diet or dietary sodium restriction in combination with paricalcitol (2 µg/day) or placebo.

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**Safety**

In general, the risk for participation in this study is estimated to be low. Paricalcitol has been approved by the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA) and the Dutch Medicines Evaluation Board (MEB) and is widely prescribed in the clinical setting, mainly for the treatment of secondary hyperparathyroidism and renal osteodystrophy in patients with advanced CKD. No serious side effects are expected at the paricalcitol dosage used in this study, except for hypercalcaemia. Possible other side effects of paricalcitol include stomach complaints, skin rash, dizziness, taste abnormalities, constipation, dry mouth, itching, urticaria, muscle spasms, intolerance or liver abnormalities; these side effects are rare and mild. Four weeks after the start of a treatment period, serum albumin, calcium and PTH are measured for a safety analysis. In case of hypercalcaemia (corrected serum calcium >2.60 mmol/l) or hypoparathyroidism (PTH <1.5 pmol/L), the dose of the study medication (paricalcitol or placebo) is reduced from two capsules to one capsule per day for the remaining study period(s). If hypercalcaemia or hypoparathyroidism as defined above persists, the patient is withdrawn for the study. Study medication is also discontinued if the investigator determines that continuing the drug would result in a significant safety risk for the patient or if the study drug would be considered detrimental to the patient’s well-being.

Use of any (other) RAAS-blocking agent, diuretics (except for furosemide), ketoconazole and antacids is not allowed after the start of the study as these medications may interfere with the evaluation of safety, tolerability and/or efficacy of the study medication. Furosemide is tolerated during the study since comorbidity (e.g. oedema) may require diuretic therapy to be continued throughout the study.

All patient-reported or observed adverse events are recorded. There are no predefined criteria for premature termination of the study, excepted for hypercalcaemia or hypoparathyroidism as defined above. If, however, during the conductance of the study new information becomes available showing that continuation of the study would result in a significant safety risk for the patients, the principal investigator and project leader will decide to terminate the study.

**Study endpoints**

The primary study endpoint is albuminuria, measured in a 24-h urine portion collected at the end of each study period. Secondary study endpoints are blood pressure (systolic, diastolic and mean arterial pressure), renal function (creatinine clearance and eGFR by creatinine-based CKD-EPI formula), urinary sodium excretion (assessment of dietary sodium intake), plasma renin activity and in the substudy renal haemodynamics (measured GFR and ERPF). Other prespecified exploratory parameters may include body mass index, circulating levels of calcium, phosphate, sodium, potassium, urea, cholesterol, triglycerides, total protein and albumin, aldosterone, 25(OH) and 1,25(OH)2 vitamin D, vitamin D binding protein (DBP), fibroblast growth factor 23, soluble Klotho, sclerostin, copeptin, asymmetric dimethylarginine (ADMA) and urinary excretion of urea (as a measure of dietary protein intake).
The VIRTUE study offers the opportunity for post hoc studies investigating the effect of VDRA therapy in combination with dietary sodium restriction on various mineral-bone disease or cardiovascular parameters.

**Statistical analysis and sample size**

We will use standard descriptive statistics to assess baseline clinical and laboratory data at enrolment. Subsequently, we will compare albuminuria at the end of each study period by using mixed models repeated measures. Fixed factors will be sequence, period, medication (placebo or paricalcitol), diet (liberal or restricted sodium diet) and the interaction between medication and diet (medication x diet). The effect on blood pressure, renal function and other outcome parameters will be evaluated similarly. Patients who drop out during the study period will be analysed until the last hospital visit at which data has been collected, except for dropout due to screening failure.

Based upon data from a previous study11, we calculated a sample size of 39 patients to detect a change of 23% in albuminuria (log delta albuminuria -0.26) with a power of 90%. If 25% dropout is taken into account, we require 50 patients. Of note, the sample size is smaller compared with a parallel study design, as subjects serve as their own internal control and the within-patient variability is smaller than the variability between patients.

Since no preliminary data exist on the effect of paricalcitol on ERPF, this will be assessed in a substudy which can be considered hypothesis-generating. We have enrolled 9 patients into the GFR/ERPF substudy.

**Trial status**

Patient enrolment started March 2012 and was closed in May 2014. The study will end in March 2015. First results from this trial are expected in the third quartile of 2015. The results will be presented at national and international scientific meetings. Publications will be submitted to peer-reviewed journals.
ACKNOWLEDGMENTS

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Authors’ contributions

DISCLOSURES
None declared.
REFERENCES


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