REVIEW

Diabetes Management

Role of sodium status in the clinical management of diabetic nephropathy: interaction with RAAS-blockade efficacy

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Practice points

- In patients with diabetes mellitus, the presence of diabetic nephropathy is associated with an increased risk of morbidity and mortality.
- Intensive glycemic control (Hba1c <6%) may retard the development and progression of diabetic nephropathy, but when chronic kidney disease (CKD) has ensued, intensive control is associated with an increased mortality risk; therefore in patients with CKD, recommended target Hba_{1c} is ~7%.
- Optimal reduction of albuminuria (aim for a urinary albumin excretion rate <30 mg/g, comparable with <30 mg/24 h) and blood pressure (aim for <140/90 mmHg, although guidelines disagree) are the cornerstone of diabetic nephropathy management. These treatment targets are preferably achieved by renin–angiotensin–aldosterone system (RAAS)-blockade, using an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.
- The efficacy of RAAS-blockade to reduce albuminuria and blood pressure is abolished by high dietary sodium intake; this was linked with adverse cardiovascular and renal outcomes. Conversely, dietary sodium restriction (aim for 5 g of NaCl per day) potentiates RAAS-blockade efficacy on blood pressure and albuminura. Moreover, it improves renal and cardiovascular outcome of RAAS-blockade, even independent of blood pressure.
- In patients with Type 2 diabetes and CKD, habitual sodium intake is (very) high and requires active intervention.
- The high-risk population of diabetic nephropathy patients requires a tailored approach to titrate sodium intake, monitored by 24-h urine sodium excretion, aiming for optimal reduction of volume overload, assessed by evaluating blood pressure and the presence of edema.

SUMMARY Diabetic nephropathy is the leading cause of chronic kidney disease worldwide. The expanding endemic of diabetes, the high risk of premature morbidity and mortality and the incapacity of current therapies to halt progression toward renal failure urges additional treatment modalities. We will review current evidence addressing dietary sodium intake as a key determinant of renin–angiotensin–aldosterone system (RAAS)-blockade efficacy, particularly in diabetic nephropathy. High sodium intake is very common in these patients, and blunts the protective effects of RAAS-blockade on cardiovascular and renal outcomes. Moderate dietary sodium restriction restores the protective effects of RAAS-blockade. The data warrant monitoring of sodium intake and practical implementation of sodium restriction as a lifestyle-related intervention, mandatory as an addition to RAAS-blockade in diabetic nephropathy.

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The worldwide incidence and prevalence of diabetes mellitus have substantially grown over the past decades, primarily as a consequence of a globally increased prevalence of obesity, contributing to Type 2 diabetes [1]. Diabetes is the leading cause of chronic kidney disease (CKD) worldwide. Diabetic nephropathy affects 20–25% of patients with diabetes mellitus within 20–25 years of disease onset. Diabetic nephropathy is defined as the presence of albuminuria (urinary albumin/creatinine ratio of >30 mg/g [>3.0 mg/mmol]) and/or impaired renal function (diabetic CKD without albuminuria is increasingly recognized) in a patient with diabetes mellitus. Diabetic nephropathy is associated with an increased risk of comorbidity including cardiovascular disease and mortality in diabetic patients [2,3]. For several reasons, terminology in the clinical guidelines are changing toward albuminuria rather than proteinuria (normal to mildly increased proteinuria defined as urinary protein/creatinine ratio <15 mg/mmol [<150 mg/g], moderately increased 15–50 mg/mmol [150–500 mg/g] and severely increased >50 mg/mmol [>500 mg/g]): albumin is the main component of urinary protein in most kidney diseases, recent global epidemiologic data show a strong-graded relationship between albuminuria and both kidney and cardiovascular disease risk, and finally, current KDIGO guidelines classify kidney disease by level of albuminuria [4]. In this paper, as in KDIGO guidelines, we will refer to proteinuria when discussing general concepts, and to albuminuria when discussing specific clinical associations and outcomes related to albuminuria, thereby as much as possible maintaining the term used in the respective original study or studies.

According to current guidelines, diabetic nephropathy requires a multifactorial intervention strategy addressing glycemic control, blood pressure control and cardiovascular risk management, promoting the use of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) treatment, statins and antiplatelet therapy where clinically indicated [4]. Despite renin–angiotensin–aldosterone system (RAAS)-blockade through ACEi or ARB treatment, however, many patients develop progressive renal function loss toward end-stage renal disease, when dialysis or kidney transplantation is required. It has been known for decades that dietary sodium restriction modulates the renoprotective efficacy of RAAS-blockade in terms of blood pressure and proteinuria reduction [5]. The first prospective trial confirming this effect in patients with diabetic nephropathy was published just recently [6]. Yet, the beneficial effect of sodium restriction in (diabetic and non-diabetic) CKD is still subject of debate, mainly fueled by the J-shaped curve in the association between sodium intake and mortality risk in large epidemiological studies.

In this paper, we will first discuss two controversial topics related to the management of diabetic nephropathy, namely which is optimal glucose control and how to achieve optimal RAAS-blockade. The majority of this review is dedicated to the role of dietary sodium restriction as a tool to optimize renal protection in patients with diabetic nephropathy, mostly against the background of RAAS-blockade since the majority of currently available data have been obtained in patients on RAAS-blockade.

Glucose control

Before 2008, intensive glucose management was recommended for all patients with diabetes mellitus. Publication of the primary results from two major randomized controlled trials (RCTs), ACCORD and ADVANCE, considerably changed this viewpoint [7,8]. Both ACCORD and ADVANCE compared intensive glucose control, defined as a target Hba1c of ≤6.0 or ≤6.5%, respectively, with more lenient control (7.0–7.9% or as defined by local guidelines, respectively). In ADVANCE, intensified glycemic control did in fact reduce the primary study end point, a composite of major macrovascular and major microvascular events, which was predominantly driven by an effect on incident diabetic nephropathy (and particularly albuminuria). On the other hand, no effect on cardiovascular or all-cause mortality was demonstrated. Participants of the ADVANCE study were recently followed up in a post-trial evaluation (ADVANCE-ON) [9]. This analysis showed that after the trial had ended, Hba_{1c} was no longer significantly different between the two original study arms, the protective effect of intensive glycemic control on macrovascular events was no longer evident and there was no effect on mortality. In the ACCORD trial, intensive glucose control was even accompanied by an increased risk of both all-cause and cardiovascular mortality. More recently, a re-analysis of the ACCORD data clearly demonstrated that

the excess mortality risk in the intensified glucose control arm was most prominent in patients with prevalent CKD [10]. Furthermore, the presence of CKD was a strong and independent risk factor for cardiovascular complications.

What are the implications of these findings for clinical practice? Current KDIGO guidelines recommend a target Hba1c of ~7.0% in order to prevent or delay progression of microvascular complications of diabetes including CKD [4]. This recommendation is in accordance with the implication from the ACCORD trial that Hba_{1c} should optimally be around 7%. It is however more difficultly reconciled with the finding that intensive control exerted a renoprotective effect in the ADVANCE trial. Glucose management seems to require a different approach in patients without CKD (lower Hba_{1c} target level) than in patients with CKD (higher Hba_{1c} target level).

RAAS-blockade

The presence of albuminuria and hypertension is associated with an increased risk of progressive renal function decline and cardiovascular complications in diabetic patients [2,11]. Reduction of albuminuria and blood pressure by ACEi or ARB treatment can attenuate these risks, and is therefore considered as the cornerstone of treatment in diabetic nephropathy [12]. Current KDIGO guidelines suggest blood pressure targets to be more strict in diabetic patients with CKD (<130/80 mmHg) than in those with normal renal function (<130/90 mmHg) [4]. Although successful reduction of albuminuria and blood pressure by RAAS-blockade contributes to renal and cardiovascular protection, this protection is far from complete, with an average postponement of renal and/or cardiovascular end points of just 3–6 months [13,14]. Based on the predictive effect of residual albuminuria during an optimally dosed ACEi or ARB for long-term renal and cardiovascular outcome, residual albuminuria has been put forward as an independent therapeutic target in diabetic nephropathy [15]. Thus, strategies have been proposed to enhance the efficacy of RAAS-blockade, targeting albuminuria. The initial finding that dual RAAS-blockade, combining an ACEi with an ARB, provides further reductions in blood pressure and albuminuria, in short-term studies [16–18], fueled RCTs on the effect of dual blockade hard end points. Disappointingly, these studies demonstrated no benefits in terms of cardiorenal outcomes, but rather clear safety concerns in terms of an increased risk of acute loss of renal function and hyperkalemia [19,20]. The combination of RAAS-blockade (i.e., ACEi or ARB) with a direct renin inhibitor, although lowering albuminuria more than ARB alone [21], did even increase the cardiorenal risk, along with a higher incidence of hyperkalemia and hypotension [22]. Alternatively, aldosterone antagonists have been evaluated as adjunct to single-agent ACEi or ARB therapy.

Dietary sodium restriction potentiates RAAS-blockade efficacy

Modulation of dietary sodium intake increased the efficacy of RAAS-blockade in hypertension, and nondiabetic and diabetic CKD [23,24] with potentiation of the effects on blood pressure and proteinuria. Sodium restriction shifts the top of the dose-response curve for RAAS-blockade, for both blood pressure and proteinuria, thus increasing the maximum efficacy that could be achieved in the reduction of blood pressure and proteinuria in an experimental model of proteinuric nephropathy [25]. Dietary sodium restriction enhances the efficacy in terms of blood pressure and proteinuria reduction of all types of RAAS-blocking agents, including ACEi [5], ARB [26], their combination [16] and renin inhibition [27]. Interestingly, lowering of sodium intake also increases the antiproteinuric efficacy of non-RAAS blocking agents including neprilysin inhibitors [28] and vitamin D receptor agonists [29].

The effect size of the potentiation is more or less equivalent for moderate sodium restriction as compared with a thiazide diuretic for blood pressure and proteinuria/albuminuria, in nondiabetic [26] and diabetic CKD patients **(Figure 1)** [6]. Importantly, combination of dietary sodium restriction and hydrochlorothiazide during ARB treatment may have additive effects on blood pressure and albuminuria.

The potentiating effects of sodium restriction on RAAS-blockade efficacy have long been known [30], but in diabetic CKD the data on sodium restriction have only recently become available. This delay may have been due to concerns on the safety of sodium restriction in diabetic patients, based on the so-called sodium paradox, namely that GFR varies inversely with dietary sodium in patients with early Type 1 diabetes and in streptozotocin-diabetic rats [31]. In animal models of Type 1 diabetes, and in humans with uncomplicated

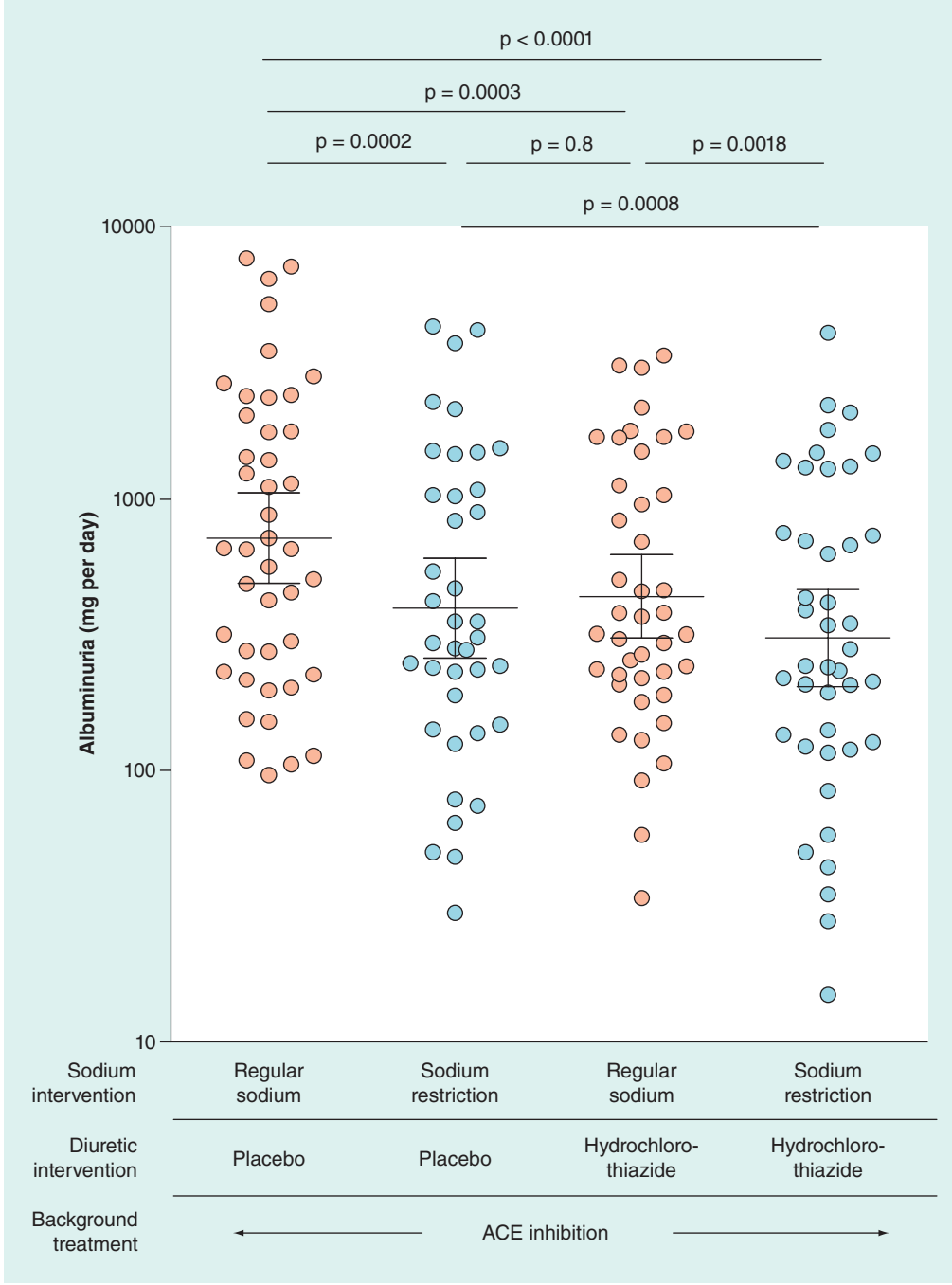

Figure 1. Albuminuria reduction by sodium restriction, hydrochlorothiazide and their combination, added to angiotensin-converting enzyme inhibition in patients with diabetic nephropathy. In a randomized controlled trial in 45 patients with diabetic nephropathy on standardized background ACE inhibition, dietary sodium restriction strongly reduced albuminuria, to a similar extent as hydrochlorothiazide. The strongest lowering of albuminuria occurred when dietary sodium restriction and hydrochlorothiazide were combined. Data are shown as geometric mean (95% CI). p-value shows treatment effect by linear mixed modeling.
ACE: Angiotensin-converting enzyme.
Reproduced with permission from [6].

Type I diabetes [32,33], dietary sodium restriction increases glomerular pressure, which could theoretically exert adverse effects on the development of glomerular damage, e.g., glomerulosclerosis. This effect, however, has never been demonstrated in patients with overt nephropathy, neither in the untreated condition nor on RAAS-blockade. The current data, demonstrating a mild decrease in glomerular filtration rate during sodium restriction in diabetic CKD patients on RAAS-blockade, indicate that the sodium paradox is not likely to be of relevance to patients with diabetic nephropathy on RAAS-blockade.

Of note, the proteinuria- and blood pressure-lowering effects of sodium restriction were achieved by a relatively moderate reduction in sodium intake. This moderate sodium intake reduction was achieved by limited dietary counseling in an outpatient clinic setting, supporting the feasibility of such a regimen in daily clinical practice. Importantly, during sodium restriction the average urinary sodium excretion was ~150 mmol/day (equal to ~8.5 g of salt [sodium chloride] per day) as compared with >200 mmol/day (>11.3 g NaCl per day) on habitual sodium intake. Thus, only a moderate reduction of dietary sodium, even well above the daily salt intake as recommended by WHO and KDIGO guidelines for management of CKD [4] (both recommending salt intake <5 g/day), as well as the Dietary Guidelines for Americans (recommending sodium intake <1.5 g/day equaling <3.8 g/day of salt intake for CKD patients) [34] allows significant benefits on blood pressure and albuminuria during standard therapy by RAAS-blockade.

Dietary sodium & RAAS-blockade: effects on renal & cardiovascular outcomes

As outlined above, the potentiating effect of dietary sodium restriction on RAAS-blockade efficacy in terms of proteinuria and blood pressure reduction is consistent and may have a sufficient effect size to impact hard outcomes. Recently, two *post-hoc* analyses from landmark studies, one in diabetic and one in nondiabetic patients, demonstrated that sodium intake indeed substantially modifies the effects of RAAS-blockade on renal and cardiovascular outcomes in CKD.

The study in nondiabetic CKD patients analyzed the outcome of the RAAS-blockade arm of the REIN study, an RCT in CKD patients with nephrotic range proteinuria addressing the long-term renoprotective effects of RAAS-blockade versus conventional antihypertensive therapy [35]. As part of the trial protocol, patients received a general advice to limit their dietary sodium intake, however without specific counseling. By design, blood pressure was titrated toward <140/90 mmHg. In the *post-hoc* study in the RAAS-blockade arm, data were analyzed per tertile of baseline sodium intake, i.e., 7, 10 or 14 g salt per day calculated from 24-h urine collections throughout the study, respectively [36]. Patients in the tertile of higher sodium intake required more antihypertensives, with diuretics as the first titration step, than those in the lower tertiles. Despite similar blood pressure across tertiles of baseline sodium intake, proteinuria remained higher in the two highest tertiles of sodium intake. After 4 years of follow-up, a renal end point (start of dialysis or doubling of serum creatinine) was reached by 60% of the patients in the highest tertile as compared with 20% in the lowest tertile [36]. Thus, dietary sodium considerably modulated the renoprotective response to RAAS-blockade; remarkably, this effect was independent of blood pressure or antihypertensive comedication, but rather related to proteinuria, which persisted in subjects with high dietary sodium intake.

More recently, similar analyses were performed in patients with diabetic nephropathy. Here, a combined analysis of the RENAAL and IDNT trials extended the above results to cardiovascular outcome. These trials assessed the effects of RAAS-blockade versus non-RAAS-blockade-based antihypertensive treatment in patients with Type 2 diabetes and nephropathy on renal and cardiovascular outcome [13,14], again, with titration of blood pressure toward target in all patients. In the *post-hoc* analysis analyzing the pooled two study cohorts, salt intake across the population was on average 10 g/day, and when considered per tertile: 12, 10 or 8 g/day, respectively [37]. In the highest salt intake tertile, the numbers of both renal and cardiovascular events were approximately twofold higher than in the lowest tertile. Sensitivity analyses adjusting the relative treatment effects for estimated glomerular filtration rate (eGFR) or urinary urea excretion provided essentially similar results. Findings were similar irrespective of sodium intake measure (24-h urinary sodium/creatinine ratio or 24-h urinary sodium excretion measured on multiple occasions). Interestingly, the effects of sodium

intake on renal and cardiovascular outcomes were only observed in patients on RAAS-blockade (Figure 2), indicating a specific interaction of excess sodium intake with the efficacy of RAAS-blockade.

Again, the effect of dietary sodium intake on renal and cardiovascular outcomes was only weakly related to changes in blood pressure (blood pressure decline [95% CI] in RENAAL/IDNT at 6 months, comparison ARB vs non-RAAS-blockade-based therapy according to tertiles of sodium intake: lowest sodium tertile -5.0 [-8.8 to -1.1] mmHg, intermediate tertile -4.6 [-8.3 to -1.0] mmHg, highest tertile -3.5 [-7.4 to +0.4] mmHg), but rather strongly associated with differences in albuminuria (albuminuria decline [95% CI] in RENAAL/IDNT at 6 months, comparison ARB vs non-RAAS-blockade-based therapy according to tertiles of sodium intake: lowest tertile -44% [-55 to -30%], intermediate tertile -16% [-32 to +3%], highest tertile -21% [-35 to +2%]). The minor changes in blood pressure can be explained by the design of the original study: patients were titrated to reach a blood pressure target during the trial [13,14].

In summary, the two *post-hoc* analyses reviewed above strongly suggest that limiting sodium

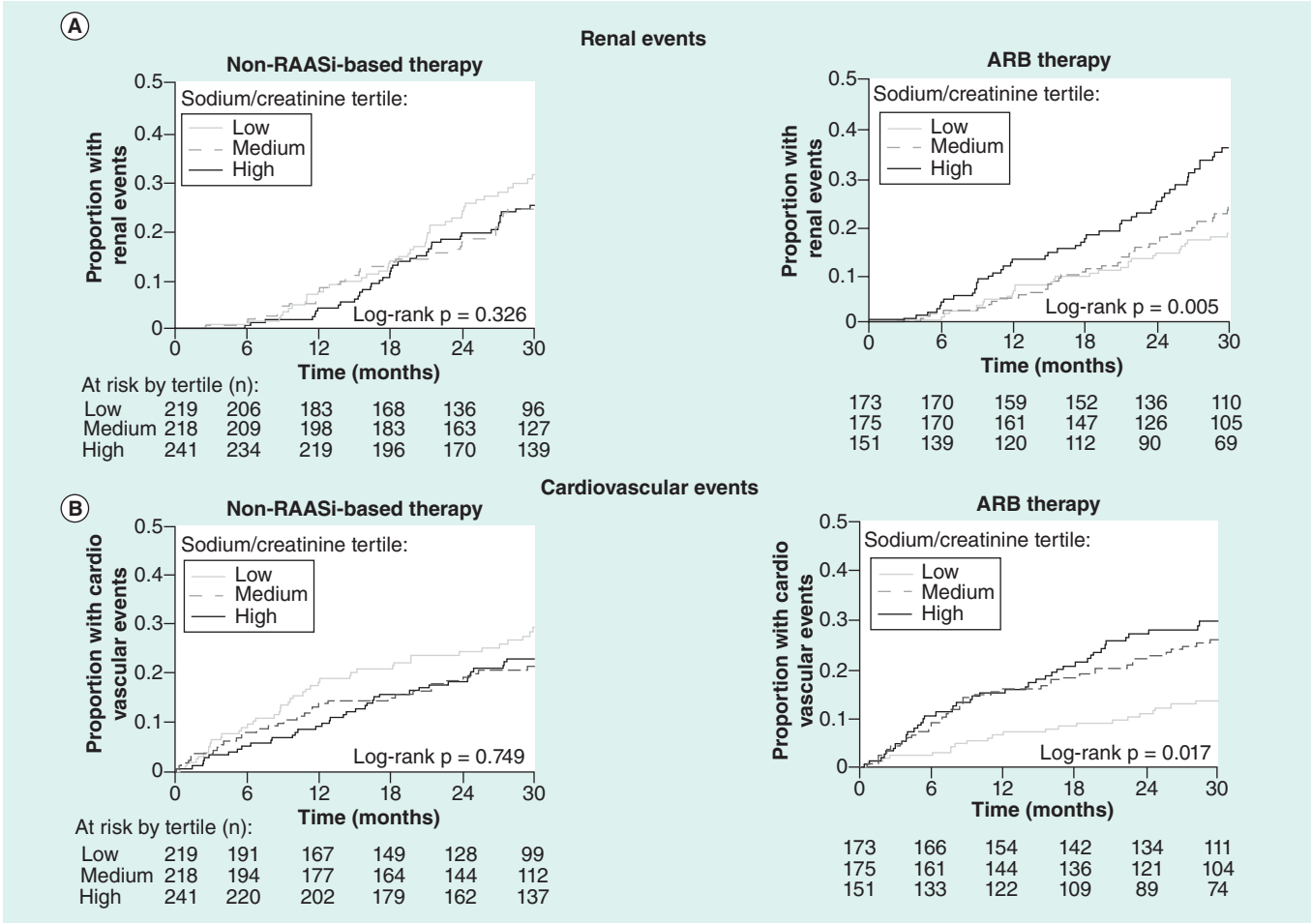

Figure 2. Kaplan–Meier curves according to tertiles of 24-h urinary sodium/creatinine ratio in a *post-hoc* analysis of the RENAAL and IDNT trials. Kaplan–Meier curves for **(A)** renal and **(B)** cardiovascular events in subjects who received angiotensin receptor blocker (ARB, right panels) – and non-renin–angiotensin–aldosterone system (non-RAASi, left panels)-based therapy stratified by tertiles of 24-h sodium/creatinine ratio: <121 mmol/g; 121–153 mmol/g; greater than or equal to 153 mmol/g. Renal events were defined as a composite of a confirmed doubling of serum creatinine or end-stage renal disease. Note that sodium intake modulates the response to RAASi-based, but not non-RAASi-based therapy, both for **(A)** renal and **(B)** cardiovascular outcomes.
ARB: Angiotensin receptor blocker; RAASi: Renin–angiotensin–aldosterone system inhibitor.
Reproduced with permission from [56].

intake potentiates the renal and cardiovascular protective efficacy of RAAS-blockade. The effect is independent of blood pressure, and relates to an effect on proteinuria. Conversely, excessive sodium intake blunts the renal and cardiovascular protective effects of RAAS-blockade.

Mechanisms of interaction between sodium intake & pharmacological effects of RAAS-blockade

The mechanism of the interaction between sodium status and the pharmacological effects of RAAS-blockade is likely to be multifactorial, as demonstrated by preclinical and clinical studies. First, animal studies indicate that vascular conversion of angiotensin I, measured after 3 weeks of treatment with ACEi, was only reduced in rats treated with ACEi accompanied by low sodium, but not high-sodium diet [38]. This suggests that sodium intake influences RAAS-blockade efficacy at the level of the vasculature. Second, sodium restriction potentiates the rise in angiotensin I that normally occurs during RAAS-blockade. Besides being a precursor for angiotensin II, angiotensin I is also a precursor of angiotensins with vasodilator and antifibrotic properties, such as angiotensin (1–7). During RAAS-blockade, sodium restriction further shifts the balance between vasoconstrictor and vasodilator angiotensins toward an antifibrotic, vasodilator profile, as shown in patient studies [39]. Third, sodium restriction potentiates the rise in the anti-inflammatory, anti-fibrotic compound AcSDKP in CKD patients [40]. This might well be relevant to the renal protective effects of RAAS-blockade, as data from animal studies have shown that intrarenal inflammation blunts or annihilates the renal protective effects of RAAS-blockade [41], whereas both dietary sodium restriction [42] and anti-inflammatory treatment [43] can restore the susceptibility to the protective effects of RAAS-blockade.

These findings from animal studies have at least in part been confirmed in the clinical setting, although clearly not all studies performed in the experimental setting allow replication in humans. First, several lines of evidence indicate that high sodium intake is associated with increased activity of the RAAS at the tissue level, with increased ACE activity and hence conversion of angiotensin I into II [44,45]. Furthermore, the anti-inflammatory properties of low sodium diet as such have become apparent from a reduction in urinary CTGF in CKD patients during sodium restriction [46].

Effects of dietary sodium irrespective of concurrent RAAS-blockade

In contrast with the clear findings during RAAS-blockade, the association between sodium status and (renal and cardiovascular) outcomes in subjects without RAAS-blockade is currently subject of debate. The above findings highlighting the impact of dietary sodium on RAAS-blockade efficacy raise the question whether sodium excess in itself is a risk factor for cardiovascular disease, and whether these findings may be extrapolated to (diabetic or nondiabetic) individuals without CKD, and without RAAS-blockade. As the study populations of the REIN and the RENAAL/IDNT trials consisted of patients with advanced CKD, which is frequently accompanied by sodium retention, these populations might be particularly susceptible to the effects of excess sodium intake. The generalizability of the link between high sodium intake and adverse cardiovascular and renal outcomes to populations with earlier stages of CKD, or with normal renal function, requires confirmation.

Data from a Finnish prospective study in the general population demonstrated that a high sodium intake, as determined by urinary sodium excretion, increased the risk of cardiovascular disease and mortality in obese but not in nonobese individuals [47]. A subsequent analysis in the third National Health and Nutrition Examination Survey confirmed this observation and revealed that each gram per day increment in sodium was associated with a 20% increased risk for all-cause mortality [48]. Furthermore, according to long-term follow-up data from the Trials of Hypertension Prevention (TOHP), dietary sodium restriction was associated with a 25% lower risk of cardiovascular events [49]. These findings were extended to renal outcomes by a study reporting retarded renal function loss in subjects on a low, as compared with a high dietary sodium intake [50]. Recently, another globally performed analysis linked high dietary sodium intake with an increased cardiovascular mortality risk, particularly in low- or middle-income countries and in two out of five cases prematurely, i.e., before 70 years of age [51]. A very recent analysis in 1588 Japanese diabetic patients demonstrated an association between

high sodium intake and an increased risk of incident cardiovascular disease, particularly in subjects with Hba_{1c} >9% [52]. These data, although appearing equivocal, are however contrasted by observational data suggesting that lower sodium intake is associated with a higher risk of cardiovascular mortality [53]. Another global cohort study demonstrated that both a low and a high sodium intake, as compared with a moderate sodium intake of 3–6 g/day, are associated with an increased risk of cardiovascular events and mortality [54]. Clearly, these observational data require further prospective trials to clarify whether the observations in subjects with the lowest sodium intake were driven by confounding, for example, related to co-morbidity, as outlined in more detail below.

J-shaped relationship between sodium intake & outcome?

Although, as shown in the previous paragraphs that avoiding sodium excess substantially improves outcome of RAAS-blockade in CKD, nevertheless epidemiological and experimental data suggest that overzealous sodium restriction is not warranted. *Post-hoc* analyses from large clinical trials in diabetic patients indicate a J-shaped curve for the association between sodium intake and all-cause mortality or renal outcome, with an excess risk when salt intake is below 3 g/day [55,56]. These studies suggest that urinary sodium should ideally be between 100 and 150 mmol/day, representing sodium intake of 6–9 g NaCl per day. Going above, but also below, this range has been associated with adverse outcomes. A similar conclusion can be drawn from a very large analysis of the ONTARGET and TRANSCEND trials, performed in diabetic patients at high cardiovascular risk. In this analysis not only higher but also lower sodium excretion was associated with an increase of cardiovascular death hospitalization for congestive heart failure [54]. Another note of caution on strict dietary sodium restriction comes from another study in Type 2 diabetes that reveals an inverse association between salt intake and outcome, i.e., a higher sodium intake was associated with a lower all-cause mortality risk [57]. It is noteworthy, however, that patients with low sodium intake also had more advanced disease as evidenced by a lower baseline eGFR, longer diabetes duration, more abundant macrovascular disease, higher age and lower BMI. Moreover, ACE inhibitors were less often used and insulin was more intensively used by these patients. It is therefore likely to presume that these characteristics of a worse clinical condition, all linked with adverse outcome, may have confounded the relation between sodium intake and mortality in this study [58].

Another reason for worse outcome in subjects with the lowest sodium intake could be that this association indicates increased susceptibility to hypotension-related complications such as stroke or acute kidney injury. In fact, experimental studies suggest the concept of the J-shaped curve. Severe sodium restriction combined with ACEi, although it may strongly reduce or even annihilate proteinuria in animal models, has been shown to induce severe tubulo-interstitial damage [59]. Further data from animal studies have predominantly been performed in the setting of dual RAAS-blockade, and confirming that too aggressive sodium restriction may have adverse renal [60] and cardiac [61] effects. A recent meta-analysis, summarizing data from observational studies in the healthy population, confirmed the presence of a J-shaped association between sodium intake and all-cause mortality [62].

Other lines of evidence support the principle that aggressive targeting of a single factor could have deleterious effects in diabetic nephropathy. As summarized above, recent data from the ACCORD trial now indicate that, particularly in the setting of diabetic CKD, lowering glucose levels to an Hba_{1c} below 6% is not favorable. Another example is related to anemia management in CKD patients. According to the TREAT study results in patients with diabetes and CKD, erythropoiesis-stimulating agent (ESA) treatment did not reduce the risk of death or a cardiovascular event, but was rather associated with an increased risk of stroke [63]. Moreover, in the same study, correction of anemia with high doses of ESA was associated with an increased risk of death or cardiovascular events [64]. Finally, the unfavorable outcomes of dual RAAS-blockade – also representing aggressive management of a single target (i.e., excess RAAS-activity) might also be ranked among these lines of evidence. The common denominator of these unrelated lines of evidence seems to be that aggressive targeting of a single factor in multifactorial conditions is associated with a risk–benefit balance that

can easily turn unfavorable. This reinforces the case for multifactorial interventions, with interventions of moderate intensity.

Implications for clinical practice

Despite recommendations by WHO, the Dietary Guidelines for Americans and KDIGO, the vast majority of individuals in the general population consume more than the recommended amount on a usual daily basis [65]. We recently documented that patients with diabetic nephropathy in The Netherlands consume over 200 mmol/day (>11.3 g NaCl per day) [6]. On the other hand, the observed J curve for the association between sodium intake and adverse outcomes, as for other exposures relevant to the CKD patient, confronts the clinician with the challenge to maintain sodium status within an optimal range, rather than below a certain level. In daily practice, however, this will merely be a matter of (moderate) sodium restriction, given the massive abundance of sodium in the majority of populations world-wide **(Figure 3)** [66].

Based on the above, dietary sodium restriction to 100 mmol/day, equal to 5–6 g of sodium chloride per day, in line with guidelines for the general population and CKD, is warranted. As an important tool to monitor and guide optimization of sodium status, 24-h urine collection is essential, since it is notoriously difficult to estimate salt intake from dietary questionnaires. The collection of 24-h urine, moreover, allows to additionally assess the intake of other relevant nutrients, such as phosphate, and proteins [67], also relevant to outcome.

Furthermore, volume status should be monitored from blood pressure and by evaluating the presence of edema. It should be kept in mind that volume status, rather than sodium intake, actually modifies the response to RAAS-blockade, since diuretics may provide a similar effect [68]. Yet, prescription of a diuretic does not eliminate the need to adhere to dietary sodium restriction, as this further contributes to control of volume status, and consequently, RAAS-blockade efficacy [6], and, moreover, it should be remembered that improving the response by a diuretic on short term, did not abolish the long-term adverse effects of high sodium intake [36,37].

Volume status is partly determined by sodium intake, and sodium-induced changes in volume status are influenced by other genetic and environmental factors including specific renal conditions, proteinuria [69], heart failure [70] and obesity **(Figure 4)** [71]. Recent genetic analyses have identified variants in several genes including genes related to the endothelial system [72], epithelial sodium transporters [73], sex hormones [74], the kallikrein-kinin system [75] and the RAAS (particularly the ACE I/D polymorphism) [76,77] as genetic determinants of changes in volume status in response to sodium [78]. The fact that genome-wide screening tools and whole genome sequencing information become increasingly available [79] is likely to provide further insight into the mechanisms and pathways involved in sodium-modulated volume regulation.

Integrating the above findings, it is crucial to adapt an individualized approach when titrating toward optimal renoprotection, as genetic factors including the ACE I/D polymorphism may also specifically influence the impact of sodium intake on the response to RAAS-blockade [80,81]. Of relevance for clinical practice, during RAAS-blockade blood pressure becomes more dependent on volume status [30], rendering blood pressure into a reasonable indicator of volume status under this condition, which can be used to guide sodium restriction. In other words, when blood pressure and proteinuria are insufficiently responsive to single-agent RAAS-blockade, volume overload is the most likely cause of therapy resistance. This is supported by Slagman *et al.*, showing that in CKD subjects on RAAS-blockade, where blood pressure is suboptimal, a mild elevation of the volume marker NT-proBNP predicts a favorable response of blood pressure and proteinuria to volume correction by sodium restriction, diuretic or the combination [82]. As a consequence, dietary sodium restriction, which may be accompanied by diuretic use, is needed to overcome this situation.

Several eating plans have been proposed to reduce dietary sodium intake and, more generally, to promote a healthy lifestyle. The DASH (Dietary Approaches to Stop Hypertension) eating plans are rich in vegetables, fruits and low-fat dairy products, and have a maximum sodium intake limit of 2300 mg/day, according to the recommendation by the Dietary Guidelines for Americans. The DASH diet as such can reduce blood pressure [83], and the effect can be enhanced by concomitant focusing on sodium restriction, as demonstrated by the DASH-sodium trial [84]. Furthermore,

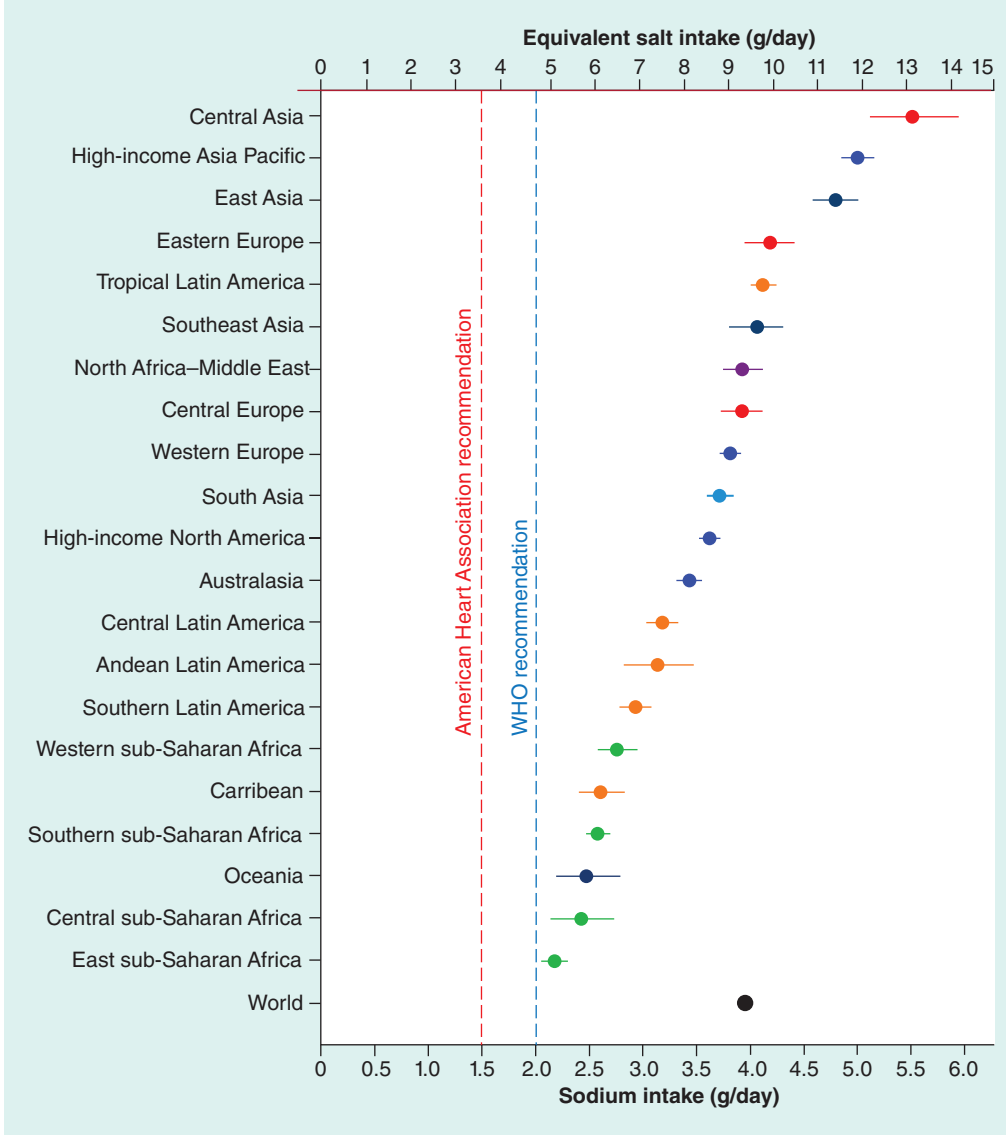

Figure 3. Sodium intake in 21 global burden of diseases regions. Mean (95% uncertainty interval) sodium intake (g/day) in 2010 in 21 Global Burden of Diseases regions. Note: regions are ranked by levels in both sexes combined, ages 20+ years. Intakes are not age-standardized. Reproduced with permission from [6].

a subgroup analysis from the Nurses' Health Study indicated that the DASH-style dietary pattern was associated with a lower risk of rapid renal function decline [85]. It remained unclear whether this association was driven by sodium intake, since an earlier study found no correlation between DASH scores and 24-h urinary sodium excretion in a subgroup of the Nurses' Health Study [86].

Conclusion & future perspective

With the expanding epidemic of obesity, driving the rapidly increasing prevalence of Type 2 diabetes, novel tools are required to avoid the development of diabetic nephropathy on the one hand, and to halt progressive renal function loss after diabetic nephropathy has ensued on the other hand. Classically, intensive glucose control has been advocated as an important strategy to avoid micro- and macrovascular complications of diabetes, but this approach may not be beneficial, or rather result in excess mortality, in the setting of established CKD. Single-agent RAAS-blockade to reduce albuminuria and blood pressure is the current cornerstone therapy to improve renal and cardiovascular risk

in patients with diabetic nephropathy, however, this therapy is insufficiently effective in many patients. Sodium restriction is required to optimize RAAS-blockade efficacy in terms of albuminuria and blood pressure reduction, but this may very well also impact clinical outcomes. Importantly, the reduction in dietary sodium intake needed to elicit a significant effect is relatively modest [6]. On the other hand, the renal and cardiovascular protective effects of RAAS-blockade-based therapy disappear when combined with excessive sodium intake in diabetic nephropathy [37]. Thus, lifestyle-related factors including sodium intake should be considered as important additional targets in diabetic patients with nephropathy. Dietary counseling regarding sodium intake should be part of a more general package of lifestyle-related interventions. Recent data also highlight the importance of managing obesity in Type 2 diabetes, which may result in fewer hospitalizations, reduced medication use and lower healthcare costs compared with standard care [87]. Although an effect on cardiovascular outcomes could not be demonstrated in a large trial in diabetic patients without overt kidney disease [88], this has not been explored extensively in diabetic nephropathy. Short-term data however suggest beneficial effects of intensive exercise on renal outcomes including renal function [89]. Moreover, obesity-associated sodium-sensitivity of blood pressure is reversible by weight loss, illustrating that obesity is a main determinant of sodium-sensitivity of blood pressure [90]. An integrated approach targeting both obesity and sodium intake may thus be even more effective than each action individually [71]. In addition, dietary sodium restriction is under investigation as an intervention that may potentiate novel renoprotective therapies, such as vitamin D receptor activators. The vitamin D receptor activator paricalcitol provides reduction of albuminuria in addition to single-agents RAAS-blockade, as documented in diabetic nephropathy [91]. Surprisingly, paricalcitol appeared to more effectively reduces albuminuria in patients with high sodium intake at baseline. Whether this paradoxical effect is true or rather a consequence of bias will presumably be determined by ongoing prospective studies in both nondiabetic (ViRTUE trial, Dutch trial register NTR2898) [92] and diabetic (PROCEED trial, Clinical Trials identifier: NCT01393808 [93]) populations.

The beneficial effects of dietary sodium restriction on clinical renal and cardiovascular endpoints in diabetic nephropathy still require

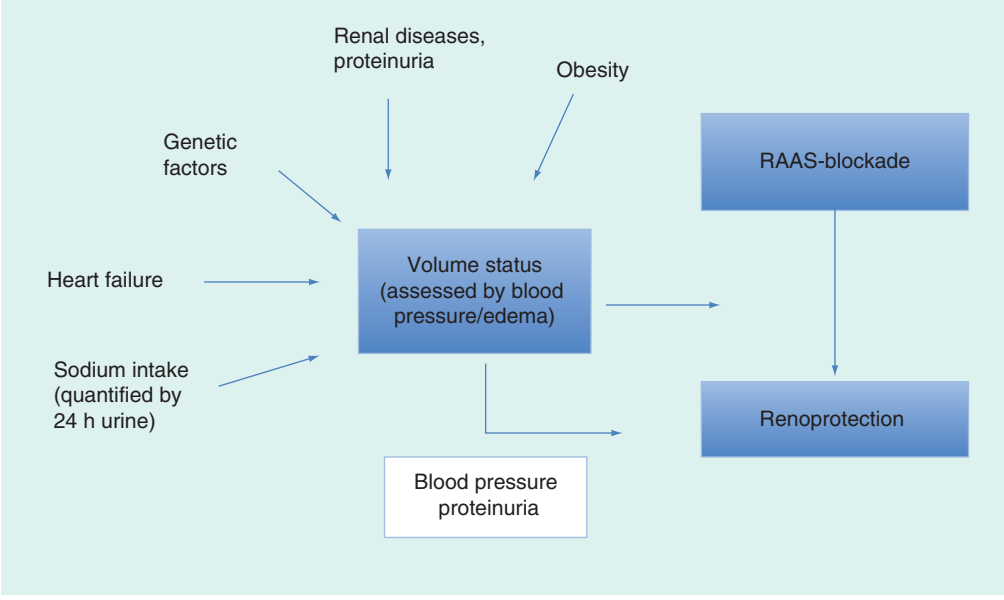

Figure 4. The effect of sodium intake and other factors on changes in volume status as a determinant of therapy response and a direct mediator of renoprotection. Volume status is determined by sodium intake as well as other genetic and environmental factors, either directly or through modulation of the response to sodium intake.
RAAS: Renin–angiotensin–aldosterone system.

prospective confirmation. Nevertheless, currently available data strongly support implementation of a moderate reduction in sodium intake combined with single RAAS-blockade as a potent and feasible strategy to mitigate the burden of renal and cardiovascular disease in the highly vulnerable population of diabetic nephropathy patients.

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References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 414(6865), 782–787 (2001).

2 Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N. Engl. J. Med.* 310(6), 356–360 (1984).

3 So WY, Kong AP, Ma RC *et al.* Glomerular filtration rate, cardiorenal end points, and all-cause mortality in Type 2 diabetic patients. *Diabetes Care* 29(9), 2046–2052 (2006).

4 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.* 3(1), 1–150 (2013).

5 Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. *Kidney Int.* 36(2), 272–279 (1989).

6 Kwakernaak AJ, Krikken JA, Binnenmars SH *et al.* Effects of sodium restriction and hydrochlorothiazide on RAAS blockade efficacy in diabetic nephropathy: a randomised clinical trial. *Lancet Diabetes Endocrinol.* 2(5), 385–395 (2014).

•• **First intervention trial showing the effects of sodium restriction, diuretic and their combination in patients with diabetes and nephropathy on renin–angiotensin–aldosterone system (RAAS)-blockade. Moderate dietary sodium restriction considerably increased the efficacy of RAAS-blockade. This article also reports on sodium excretion in the unselected recruitment population, showing that sodium intake in this outpatient population of patients with diabetes and nephropathy was considerably above the population average in The Netherlands.**

7 Patel A, MacMahon S *et al.* Intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2560–2572 (2008).

8 Gerstein HC, Miller ME *et al.* Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2545–2559 (2008).

9 Zoungas S, Chalmers J, Neal B *et al.* Follow-up of blood-pressure lowering and glucose control in Type 2 diabetes. *N. Engl. J. Med.* 371(15), 1392–1406 (2014).

10 Papademetriou V, Lovato L, Doumas M *et al.* Chronic kidney disease and intensive glycemic control increase cardiovascular risk in patients with Type 2 diabetes. *Kidney Int.* 87(3), 649–659 (2014).

• **Re-analysis of the ACCORD randomized trial demonstrating that patients with diabetes and chronic kidney disease are at increased risk of mortality when on intensive glycemic control as compared with more lenient control.**

11 Molitch ME, Steffes M, Sun W *et al.* Development and progression of renal insufficiency with and without albuminuria in adults with Type 1 diabetes in the diabetes control and complications trial and the epidemiology of diabetes interventions and complications study. *Diabetes Care* 33(7), 1536–1543 (2010).

12 Parving HH, Lehnert H, Brochner-Mortensen J *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with Type 2 diabetes. *N. Engl. J. Med.* 345(12), 870–878 (2001).

13 Brenner BM, Cooper ME, de Zeeuw D *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with Type 2 diabetes and nephropathy. *N. Engl. J. Med.* 345(12), 861–869 (2001).

14 Lewis EJ, Hunsicker LG, Clarke WR *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to Type 2 diabetes. *N. Engl. J. Med.* 345(12), 851–860 (2001).

15 Holtkamp FA, de Zeeuw D, de Graeff PA *et al.* Albuminuria and blood pressure, independent targets for cardioprotective therapy in patients with diabetes and nephropathy: a post hoc analysis of the combined RENAAL and IDNT trials. *Eur. Heart J.* 32(12), 1493–1499 (2011).

16 Slagman MC, Waanders F, Hemmelder MH *et al.* Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 343, d4366 (2011).

17 Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann. Intern. Med.* 148(1), 30–48 (2008).

18 Jennings DL, Kalus JS, Coleman CI, Manierski C, Yee J. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. *Diabet. Med.* 24(5), 486–493 (2007).

19 Mann JF, Schmieder RE, McQueen M *et al.* Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet* 372(9638), 547–553 (2008).

20 Fried LF, Emanuele N, Zhang JH *et al.* Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N. Engl. J. Med.* 369(20), 1892–1903 (2013).

21 Persson F, Lewis JB, Lewis EJ, Rossing P, Hollenberg NK, Parving HH. Aliskiren in combination with losartan reduces albuminuria independent of baseline blood pressure in patients with Type 2 diabetes and nephropathy. *Clin. J. Am. Soc. Nephrol.* 6(5), 1025–1031 (2011).

22 Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in Type 2 diabetes and nephropathy. *N. Engl. J. Med.* 358(23), 2433–2446 (2008).

23 Houlihan CA, Allen TJ, Baxter AL *et al.* A low-sodium diet potentiates the effects of losartan in Type 2 diabetes. *Diabetes Care* 25(4), 663–671 (2002).

24 Ekinci EI, Thomas G, Thomas D *et al.* Effects of salt supplementation on the albuminuric response to telmisartan with or without hydrochlorothiazide therapy in hypertensive patients with Type 2 diabetes are modulated by habitual dietary salt intake. *Diabetes Care* 32(8), 1398–1403 (2009).

25 Wapstra FH, Van Goor H, Navis G, De Jong PE, De Zeeuw D. Antiproteinuric effect predicts renal protection by angiotensin-converting enzyme inhibition in rats with established adriamycin nephrosis. *Clin. Sci.* 90(5), 393–401 (1996).

26 Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J. Am. Soc. Nephrol.* 19(5), 999–1007 (2008).

27 Weir MR, Yadao AM, Purkayastha D, Charney AN. Effects of high- and low-sodium diets on ambulatory blood pressure in patients with hypertension receiving aliskiren. *J. Cardiovasc. Pharmacol. Ther.* 15(4), 356–363 (2010).

28 Laverman GD, Van Goor H, Henning RH, De Jong PE, De Zeeuw D, Navis G. Renoprotective effects of VPI versus ACEI in normotensive nephrotic rats on different sodium intakes. *Kidney Int.* 63(1), 64–71 (2003).

29 Mirkovic K, Frenay AR, van den Born J, van Goor H, Navis G, De Borst MH. Renoprotective effects of vitamin D receptor agonist during low but not high dietary sodium in adriamycin nephrosis. *J. Am. Soc. Nephrol.* 23, 809A (2012).

30 Navis G, de Jong P, Donker AJ, van der Hem GK, de Zeeuw D. Diuretic effects of angiotensin-converting enzyme inhibition: comparison of low and liberal sodium diet in hypertensive patients. *J. Cardiovasc. Pharmacol.* 9(6), 743–748 (1987).

31 Vallon V, Huang DY, Deng A, Richter K, Blantz RC, Thomson S. Salt-sensitivity of proximal reabsorption alters macula densa salt and explains the paradoxical effect of dietary salt on glomerular filtration rate in diabetes mellitus. *J. Am. Soc. Nephrol.* 13(7), 1865–1871 (2002).

32 Miller JA. Renal responses to sodium restriction in patients with early diabetes mellitus. *J. Am. Soc. Nephrol.* 8(5), 749–755 (1997).

33 Luik PT, Hoogenberg K, Van Der Kleij FG *et al.* Short-term moderate sodium restriction induces relative hyperfiltration in normotensive normoalbuminuric type I diabetes mellitus. *Diabetologia* 45(4), 535–541 (2002).

34 US Department of Agriculture, US Department of Health and Human Services. *Dietary Guidelines for Americans, 7th Edition*. US Government Printing Office, Washington, DC, USA (2010).

35 Ruggenenti P, Perna A, Gherardi G *et al.* Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 354(9176), 359–364 (1999).

36 Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. *J. Am. Soc. Nephrol.* 23(1), 165–173 (2012).

37 Heerspink HJ, Holtkamp FA, Parving HH *et al.* Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int.* 82(3), 330–337 (2012).

•• **Study showing for the first time in diabetic patients that high sodium intake is associated with a blunted response to RAASi-based therapy on renal and cardiovascular end points.**

38 Kocks MJ, Buikema H, Gschwend S, Boomsma F, de Zeeuw D, Navis G. High dietary sodium blunts affects of angiotensin-converting enzyme inhibition on vascular angiotensin I-to-angiotensin II conversion in rats. *J. Cardiovasc. Pharmacol.* 42(5), 601–606 (2003).

39 Kocks MJ, Lely AT, Boomsma F, de Jong PE, Navis G. Sodium status and angiotensin-converting enzyme inhibition: effects on plasma angiotensin-(1–7) in healthy man. *J. Hypertens.* 23(3), 597–602 (2005).

40 Kwakernaak AJ, Waanders F, Slagman MC *et al.* Sodium restriction on top of renin–angiotensin–aldosterone system blockade increases circulating levels of N-acetyl-seryl-aspartyl-lysyl-proline in chronic kidney disease patients. *J. Hypertens.* 31(12), 2425–2432 (2013).

41 Kramer AB, Laverman GD, van Goor H, Navis G. Inter-individual differences in anti-proteinuric response to ACEi in established adriamycin nephrotic rats are predicted by pretreatment renal damage. *J. Pathol.* 201(1), 160–167 (2003).

42 Kramer AB, Bos H, van Goor H, Navis GJ. Sodium intake modifies the negative prognostic value of renal damage prior to treatment with ACE inhibitors on proteinuria induced by adriamycin. *Nephron Physiol.* 103(1), 43–52 (2006).

43 Remuzzi G, Zoja C, Gagliardini E, Corna D, Abbate M, Benigni A. Combining an antiproteinuric approach with mycophenolate mofetil fully suppresses progressive nephropathy of experimental animals. *J. Am. Soc. Nephrol.* 10(7), 1542–1549 (1999).

44 van der Kleij FG, de Jong PE, Henning RH, de Zeeuw D, Navis G. Enhanced responses of blood pressure, renal function, and aldosterone to angiotensin I in the DD genotype are blunted by low sodium intake. *J. Am. Soc. Nephrol.* 13(4), 1025–1033 (2002).

45 Boddi M, Poggesi L, Coppo M *et al.* Human vascular renin–angiotensin system and its functional changes in relation to different sodium intakes. *Hypertension* 31(3), 836–842 (1998).

46 Slagman MC, Nguyen TQ, Waanders F *et al.* Effects of antiproteinuric intervention on elevated connective tissue growth factor (CTGF/CCN-2) plasma and urine levels in nondiabetic nephropathy. *Clin. J. Am. Soc. Nephrol.* 6(8), 1845–1850 (2011).

47 Tuomilehto J, Jousilahti P, Rastenyte D *et al.* Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet* 357(9259), 848–851 (2001).

48 Yang Q, Liu T, Kuklina EV *et al.* Sodium and potassium intake and mortality among US adults: prospective data from the Third National Health and Nutrition Examination Survey. *Arch. Intern. Med.* 171(13), 1183–1191 (2011).

49 Cook NR, Cutler JA, Obarzanek E *et al.* Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 334(7599), 885–888 (2007).

50 Lin J, Hu FB, Curhan GC. Associations of diet with albuminuria and kidney function decline. *Clin. J. Am. Soc. Nephrol.* 5(5), 836–843 (2010).

51 Mozaffarian D, Fahimi S, Singh GM *et al.* Global sodium consumption and death from cardiovascular causes. *N. Engl. J. Med.* 371(7), 624–634 (2014).

•• **Recent modeling study showing the impact of sodium consumption on cardiovascular mortality on a global scale.**

52 Horikawa C, Yoshimura Y, Kamada C *et al.* Dietary sodium intake and incidence of diabetes complications in Japanese patients with Type 2 diabetes: analysis of the Japan Diabetes Complications Study. *J. Clin.*

Endocrinol. Metab. 99(10), 3635–3643 (2014).

53 Stolarz-Skrzypek K, Kuznetsova T, Thijs L *et al.* Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA* 305(17), 1777–1785 (2011).

54 O'Donnell M, Mente A, Rangarajan S *et al.* Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N. Engl. J. Med.* 371(7), 612–623 (2014).

55 Thomas MC, Moran J, Forsblom C *et al.* The association between dietary sodium intake, ESRD, and all-cause mortality in patients with Type 1 diabetes. *Diabetes Care* 34(4), 861–866 (2011).

56 Lambers Heerspink HJ, de Borst MH, Bakker SJ, Navis GJ. Improving the efficacy of RAAS blockade in patients with chronic kidney disease. *Nat. Rev. Nephrol.* 9(2), 112–121 (2013).

57 Ekinci EI, Clarke S, Thomas MC *et al.* Dietary salt intake and mortality in patients with Type 2 diabetes. *Diabetes Care* 34(3), 703–709 (2011).

58 Lambers Heerspink HJ, Kwakernaak A, de Zeeuw D, Navis G. Comment on: Ekinci *et al.* Dietary salt intake and mortality in patients with Type 2 diabetes. Diabetes Care 2011;34:703–709. *Diabetes Care* 34(7), e124; author reply e125–0711 (2011).

59 Hamming I, Navis G, Kocks MJ, van Goor H. ACE inhibition has adverse renal effects during dietary sodium restriction in proteinuric and healthy rats. *J. Pathol.* 209(1), 129–139 (2006).

60 Richer-Giudicelli C, Domergue V, Gonzalez MF *et al.* Haemodynamic effects of dual blockade of the renin–angiotensin system in spontaneously hypertensive rats: influence of salt. *J. Hypertens.* 22(3), 619–627 (2004).

61 Trongtorsak P, Morgan TO, Delbridge LM. Combined renin–angiotensin system blockade and dietary sodium restriction impairs cardiomyocyte contractility. *J. Renin Angiotensin Aldosterone Syst.* 4(4), 213–219 (2003).

62 Graudal N, Jurgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. *Am. J. Hypertens.* 27(9), 1129–1137 (2014).

63 Pfeffer MA, Burdmann EA, Chen CY *et al.* A trial of darbepoetin alfa in Type 2 diabetes and chronic kidney disease. *N. Engl. J. Med.* 361(21), 2019–2032 (2009).

64 Solomon SD, Uno H, Lewis EF *et al.* Erythropoietic response and outcomes in kidney disease and Type 2 diabetes. *N. Engl. J. Med.* 363(12), 1146–1155 (2010).

65 Centers for Disease Control and Prevention (CDC). Usual sodium intakes compared with current dietary guidelines — United States, 2005–2008. *Morb. Mortal. Wkly Rep.* 60(41), 1413–1417 (2011).

66 Powles J, Fahimi S, Micha R *et al.* Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open* 3(12), e003733 (2013).

•• **Global overview of sodium intake, demonstrating that sodium intake exceeds the recommended levels in almost all countries with small differences by age and sex. Virtually all populations would benefit from sodium reduction, supported by enhanced surveillance.**

67 Mitch WE. Beneficial responses to modified diets in treating patients with chronic kidney disease. *Kidney Int. Suppl.* (94)(94), S133–S135 (2005).

68 Buter H, Hemmelder MH, Navis G, de Jong PE, de Zeeuw D. The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. *Nephrol. Dial. Transplant.* 13(7), 1682–1685 (1998).

69 Imanishi M, Yoshioka K, Okumura M *et al.* Sodium sensitivity related to albuminuria appearing before hypertension in Type 2 diabetic patients. *Diabetes Care* 24(1), 111–116 (2001).

70 Joosten MM, Gansevoort RT, Mukamal KJ *et al.* Sodium excretion and risk of developing coronary heart disease. *Circulation* 129(10), 1121–1128 (2014).

• **Study demonstrating that high sodium intake is linked with an increased risk of coronary heart disease in patients with elevated NT-proBNP, that is, those who are more susceptible to changes in volume status.**

71 Visser FW, Krikken JA, Muntinga JH, Dierckx RA, Navis GJ. Rise in extracellular fluid volume during high sodium depends on BMI in healthy men. *Obesity* 17(9), 1684–1688 (2009).

72 Defago MD, Gu D, Hixson JE *et al.* Common genetic variants in the endothelial system predict blood pressure response to sodium intake: the GenSalt study. *Am. J. Hypertens.* 26(5), 643–656 (2013).

73 Zhao Q, Gu D, Hixson JE *et al.* Common variants in epithelial sodium channel genes contribute to salt sensitivity of blood pressure: the GenSalt study. *Circ. Cardiovasc. Genet.* 4(4), 375–380 (2011).

74 Kelly TN, Rebholz CM, Gu D *et al.* Analysis of sex hormone genes reveals gender differences in the genetic etiology of blood pressure salt sensitivity: the GenSalt study. *Am. J. Hypertens.* 26(2), 191–200 (2013).

75 Gu D, Zhao Q, Kelly TN *et al.* The role of the kallikrein-kinin system genes in the salt sensitivity of blood pressure: the GenSalt Study. *Am. J. Epidemiol.* 176(Suppl. 7), S72–S80 (2012).

76 Hiraga H, Oshima T, Watanabe M *et al.* Angiotensin I-converting enzyme gene polymorphism and salt sensitivity in essential hypertension. *Hypertension* 27(3 Pt 2), 569–572 (1996).

77 Giner V, Poch E, Bragulat E *et al.* Renin–\ angiotensin system genetic polymorphisms and salt sensitivity in essential hypertension. *Hypertension* 35(1 Pt 2), 512–517 (2000).

78 Kelly TN, He J. Genomic epidemiology of blood pressure salt sensitivity. *J. Hypertens.* 30(5), 861–873 (2012).

79 de Borst MH, Benigni A, Remuzzi G. Primer: strategies for identifying genes involved in renal disease. *Nat. Clin. Pract. Nephrol.* 4(5), 265–276 (2008).

80 Van der Kleij FG, Schmidt A, Navis GJ *et al.* Angiotensin converting enzyme insertion/deletion polymorphism and short-term renal response to ACE inhibition: role of sodium status. *Kidney Int. Suppl.* 63, S23–S26 (1997).

81 Lely AT, Heerspink HJ, Zuurman M *et al.* Response to angiotensin-converting enzyme inhibition is selectively blunted by high sodium in angiotensin-converting enzyme DD genotype: evidence for gene-environment interaction in healthy volunteers. *J. Hypertens.* 28(12), 2414–2421 (2010).

82 Slagman MC, Waanders F, Vogt L *et al.* Elevated N-terminal pro-brain natriuretic peptide levels predict an enhanced anti-hypertensive and anti-proteinuric benefit of dietary sodium restriction and diuretics, but not angiotensin receptor blockade, in proteinuric renal patients. *Nephrol. Dial. Transplant.* 27(3), 983–990 (2012).

83 Appel LJ, Moore TJ, Obarzanek E *et al.* A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N. Engl. J. Med.* 336(16), 1117–1124 (1997).

84 Sacks FM, Svetkey LP, Vollmer WM *et al.* Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N. Engl. J. Med.* 344(1), 3–10 (2001).

85 Lin J, Fung TT, Hu FB, Curhan GC. Association of dietary patterns with albuminuria and kidney function decline in older white women: a subgroup analysis from the Nurses' Health Study. *Am. J. Kidney Dis.* 57(2), 245–254 (2011).

86 Taylor EN, Stampfer MJ, Mount DB, Curhan GC. DASH-style diet and 24-hour urine composition. *Clin. J. Am. Soc. Nephrol.* 5(12), 2315–2322 (2010).

87 Espeland MA, Glick HA, Bertoni A *et al.* Impact of an intensive lifestyle intervention on use and cost of medical services among overweight and obese adults with Type 2 diabetes: the action for health in diabetes. *Diabetes Care* 37(9), 2548–2556 (2014).

88 Wing RR, Bolin P, Brancati FL *et al.* Cardiovascular effects of intensive lifestyle intervention in Type 2 diabetes. *N. Engl. J. Med.* 369(2), 145–154 (2013).

89 Friedman AN, Chambers M, Kamendulis LM, Temmerman J. Short-term changes after a weight reduction intervention in advanced diabetic nephropathy. *Clin. J. Am. Soc. Nephrol.* 8(11), 1892–1898 (2013).

90 Rocchini AP, Key J, Bondie D *et al.* The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. *N. Engl. J. Med.* 321(9), 580–585 (1989).

91 de Zeeuw D, Agarwal R, Amdahl M *et al.* Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with Type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet* 376(9752), 1543–1551 (2010).

92 Keyzer CA, De Jong MA, Van Breda GF *et al.* Vitamin D receptor activator and dietary sodium restriction to reduce residual urinary albumin excretion in chronic kidney disease (ViRTUE study): rationale and study protocol. *Nephrol. Dial. Transplant.* doi:10.1093/ndt/gfv033 (2015) (Epub ahead of print).

93 Clinical Trials. www.clinicaltrials.gov