The issue of optimal intake of salt—sodium chloride—is longstanding and has led to numerous animated controversies. Defining the optimal sodium chloride intake is relevant both from a public health perspective and, importantly, with respect to its role in the genesis of renal and cardiovascular disease. For sodium chloride–dependent health problems, two aspects deserve consideration: (1) the effects of sodium chloride on BP and (2) BP-independent target-organ damage. Today, it is well documented that the effect of salt on these two measures goes beyond the concept of Guyton. According to recent studies, sodium chloride also causes—independently of BP and volume—adverse cardiovascular and renal malfunction through sodium chloride–dependent activation of Rac I guanosine triphosphatase; plasma and extracellular volume-independent effects mediated, among others, by vascular endothelial growth factor-C; and activation of the Na⁺-K⁺-adenosine triphosphatase signalosome through the sodium-dependent steroid, ouabain, which mediates cardiovascular and renal damage.

Denton and colleagues documented that salt intake reversibly modulates BP in chimpanzees, the species closest to Homo sapiens. On the basis of observational data, there is no doubt that salt plays a major role in the genesis of hypertension in humans as well. Does reduction of salt intake in humans decrease BP, thereby reducing cardiovascular and renal events, possibly in concert with BP-independent direct effects of sodium chloride? The long-term, 10- to 15-year Trials of Hypertension Prevention (TOHP) I and II show that, apart from lowering BP, net sodium reduction by 44 mmol/24 hours (TOHP I) and 33 mmol/24 hours (TOPH II) leads to significant reduction in cardiovascular events by 25%, even after adjustment for several confounding factors. Given the complexity of such studies and the need for long-term observations, TOPH I and II will presumably remain the best evidence for a beneficial effect of moderate reduction of salt intake in the general population; the effect in specific populations, such as diabetic patients or patients with CKD, remains unknown.

Given the absence of controlled long-term evidence, the second best approach is to have a look at post hoc analyses of controlled intervention trials in patients with hypertension, diabetes, and renal or cardiovascular disease. What does such information tell us?

The analysis of such post hoc evidence must address several questions. First, is lower intake of sodium chloride better? Or is there an optimal sodium chloride intake that results in a U-shaped relationship, as is known for BP, hemoglobin A1c, and other measures? Second, are all renal diseases created equally, or is there a difference, for example, between proteinuric and nonproteinuric kidney diseases? Third, does restriction of dietary sodium chloride modify, or even amplify, the response to established treatments? Finally, is the sodium chloride intake that is optimal for health and survival in the general population also optimal for individuals with renal or cardiovascular disease?

Because cardiovascular events are the major cause of death in renal patients, it is still useful to assess the effect of sodium chloride intake on the risk for cardiovascular events in individuals with no renal disease. O’Donnell et al. provided

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a post hoc analysis of two cohorts of patients with cardiovascular disease in the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) trials (Figure 1). The authors analyzed cardiovascular events and death and their relationship to estimated 24-hour urinary sodium excretion at baseline. Sodium excretion was extrapolated from first morning urine samples based on the Kawasaki formula (which was established in Japanese cohorts and may somewhat overestimate daily sodium chloride consumption in Europeans). Higher baseline sodium excretion was associated with an increased risk for cardiovascular death (9.7% for an estimated sodium intake of 7–8 g/d [hazard ratio, 1.53]; 11.2% for >8 g/d [hazard ratio, 1.66] compared with an estimated baseline sodium excretion of 4–6 g/d; note that this refers to sodium intake and not sodium chloride intake). Of interest is the finding that not only higher but also lower sodium excretion was associated with an increase in cardiovascular death (hazard ratio, 1.19) and hospitalization for congestive heart failure (hazard ratio, 1.23). In other words, the association between estimated sodium excretion and cardiovascular events was J-shaped, with a nadir at sodium excretions of 4–6 g/d (10–15 g sodium chloride per day). Because of the above-mentioned uncertainty of the estimation of 24-hour sodium chloride excretion, this important study should be replicated with measurement of 24-hour sodium chloride.

What is the relation of salt intake to indicators of renal malfunction and progression of established renal disease? In a cross-sectional analysis of the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, Verhave et al. documented a continuous positive relation between 24-hour urinary sodium excretion and albuminuria. Furthermore, in the Nurses’ Health Study, Lin et al. found that in more than 3000 women observed for more than 14 years, lower sodium intake was associated with a lower risk (odds ratio, 1.52) for decline in estimated GFR compared with women in the highest quartile of sodium intake. No specific studies have assessed the effect of dietary salt on the evolution of diabetic nephropathy, but two recent studies in type 2 diabetes and type 1 diabetes raise important issues that cannot be definitively resolved today. In type 2 diabetes, a relationship was seen between 24-hour sodium excretion and all-cause mortality: For every 100-mmol increase in 24-hour urinary sodium, all-cause mortality was decreased by 28%. Does this finding suggest that high sodium was beneficial? Thorough inspection of this study reveals some caveats: Low sodium intake was associated with more advanced disease (lower baseline estimated GFR), longer duration of diabetes, more macrovascular disease, older age, lower body mass index (possibly indicating malnourishment), less use of angiotensin-converting enzyme (ACE) inhibitors, and more use of insulin. Furthermore, the general question arises: Can findings in diabetes be extrapolated to nondiabetic conditions?

The carefully conducted FinnDiane study, comprising 2807 patients with type 1 diabetes, followed patients over a 10-year timeframe. The endpoints were all-cause mortality and ESRD. Mortality was highest in patients with both high and low-sodium excretion: that is, the association between 24-hour urinary sodium excretion and all-cause mortality was U-shaped, with a minimum hazard ratio at urinary sodium of 100–150 mmol/d (about 9 g of sodium chloride per day). This finding suggests that there is an optimal sodium intake between too-low and too-high intake. Low sodium intake was associated with increased incidence of ESRD, but again this reflected more severe disease and malnourishment in patients with low urinary sodium.

How about observations in primary kidney disease? Vegter et al. conducted a post hoc analysis of studies on ramipril in nondiabetic patients with CKD. The authors assessed the rate of progression to ESRD and the interaction between salt intake and proteinuria during ramipril treatment. They divided the population into low (<100 mEq/g creatinine), medium (100–200 mEq/g), and high (>200 mEq/g) sodium excretion. After a follow-up of >4.2 years, 18.4% of the patients developed ESRD; this was strongly related to sodium excretion (6.1, 7.9, and 18.2 cases of ESRD per 100 patient-years according to the three categories of sodium excretion, respectively; P<0.001). As a potential mechanism the authors proposed that high
sodium intake blunted the antiproteinuric effect of ACE inhibition. The risk for ESRD was increased by a factor of 1.61 per 100-mEq/g increase in the urinary sodium-to-creatinine ratio, but this relationship was lost after adjustment for changes in proteinuria. This finding raises the issue of whether the renoprotective effect of low sodium is explained by its antiproteinuric effect.

One study, however, argues against the hypothesis that reduction of proteinuria is the only mechanism by which low sodium reduces renal progression: Even in autosomal-dominant polycystic kidney disease with no major proteinuria, low sodium intake again turned out to be a factor predicting progression of this condition.15

A question remains: Is the benefit of low sodium intake caused only by low sodium per se, or does low dietary sodium also amplify the benefit of well established treatments, such as renin-angiotensin system blockade?

Slagman et al.16 examined the addition of a low-sodium diet to an ACE inhibitor; this combination reduced proteinuria and BP to a greater extent than did the combination of an ACE inhibitor plus angiotensin-receptor blocker in patients with nondiabetic kidney disease. The study clearly shows that compared with a regular-sodium diet, a low-sodium diet amplifies the antiproteinuric effect of an ACE inhibitor. This conclusion was confirmed in a recent post hoc analysis of two studies in type 2 diabetes and nephropathy, IDNT (Irbesartan Diabetic Nephropathy Trial) and RENAAAL (Reduction in End Points in NIDDM with the Angiotensin II Antagonist Losartan).17

What can one conclude from the preceding analysis? Reduction of dietary sodium intake is certainly a worthwhile goal in the care of renal patients. The results of the studies described here point to the existence of an optimum salt intake (which may differ between the general population and individuals with renal or cardiovascular disease). There is legitimate concern that targeting too low a sodium intake could cause cardiovascular and all-cause mortality in the general population. One level of sodium intake may not be optimal for everyone, whether among healthy persons or those with renal disease. We need specific documentation about whether the renal benefit from low sodium is achieved at the expense of increased cardiovascular mortality.

The antiproteinuric effect, as well as the retardation of GFR loss described in the above-mentioned studies, strongly points to the benefit of low sodium intake. Although direct data are not available, it is unlikely that diuretic treatment equals the benefit of low dietary sodium in patients without renin-angiotensin blockade, particularly considering the risks of hypokalemia and hyperuricemia. However, when proteinuric patients receiving losartan monotherapy were prescribed a low-sodium diet or hydrochlorothiazide as add-on therapy, the latter two alternatives were equally effective.18

In the more distant future, the mechanisms underlying the renal benefit from low sodium intake deserve further study, particularly in view of the effects of sodium on Rac guanosine triphosphatase, ouabain, and other pathogenic pathways. Interference with these downstream pathways might even amplify the beneficial effects of low dietary sodium.

DISCLOSURES
None.

REFERENCES

