Urinary Sodium and Cardiovascular Disease Risk

Informing Guidelines for Sodium Consumption

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ALMOST EVERY NATIONAL HEALTH AGENCY[1-4] AND professional society[5] recommends a reduction in dietary sodium intake as a means to lower blood pressure (BP) and prevent cardiovascular disease (CVD). For US adults in the general population, goals for sodium intake have generally ranged from no more than 1500 mg/d[5] to no more than 2300 mg/d.[2] In the latter context, guidelines have typically suggested sodium intake of no more than 1500 mg/d in black individuals, middle-aged and older persons, and individuals with hypertension, diabetes mellitus, or chronic kidney disease.[2] In part because these groups constitute nearly 70% of US adults,[6] the most recent Dietary Guidelines for Americans recommended a sodium intake of no more than 1500 mg/d for the general population.[7] Most US adults consume a diet that exceeds even the 2300-mg/d goal, with an estimated sodium intake of nearly 5 g/d, excluding table salt, in 30- to 39-year-old men.[8]

Evidence supporting sodium guideline recommendations comes from animal studies, knowledge of physiologic requirements, scrutiny of isolated populations who eat a natural diet, migration studies, observational analysis in populations who consume processed foods, and randomized controlled trials. Although there is general agreement that sodium reduction is appropriate for persons with hypertension, there are some questions about applying this recommendation to the remainder of the population.[9] Part of the hesitation appears to be based on reports of metabolic disturbance, inconsistency in the results of observational studies, and a paucity of clinical trials that document the efficacy of sodium reduction as a means to reduce CVD risk. Evidence regarding metabolic disturbance is sparse, inconsistent, and of limited relevance in clinical practice. Most observational studies have identified a positive association between sodium intake and CVD risk, whereas some studies have failed to identify a significant relationship, and a few others have shown an inverse association.[7,8] One explanation for this inconsistency is a J-shaped relationship between sodium intake and CVD risk.[10]

The report by O'Donnell and colleagues[11] in this issue of *JAMA* provides the best evidence in support of the hypothesis of a J-shaped relationship. In this observational study of 2 cohorts included in the ONTARGET and TRANSCEND trials, the authors assessed the relationship of urinary excretion of sodium and potassium (estimated from a single urine sample obtained at baseline) with the composite clinical outcome of CVD death, myocardial infarction, and hospitalization for congestive heart failure (CHF) over a follow-up of 56 months. Based on the composite outcome event occurring in 4729 (16.4%) participants (including 2057 with CVD death, 1412 with myocardial infarction, 1282 with stroke, and 1213 with hospitalization for CHF), the authors report that compared with a baseline estimated urinary sodium excretion of 4 to 5.99 g/d, sodium excretion greater than 7 g/d was associated with an increased risk of all CV events, whereas a sodium excretion of less than 3 g/d was associated with increased risk of CV mortality and hospitalization for CHF. These findings are consistent with a J-shaped relationship between sodium excretion and CVD risk. Increased potassium excretion was associated with a reduced risk of stroke.

Despite the strengths of this investigation (eg, large sample size, long-term follow-up, careful ascertainment of outcome events), it has, like other observational studies, methodological limitations that may undermine the ability to arrive at a valid, definitive conclusion. None of the observational studies were designed to address the relationship between daily sodium intake and CVD risk, and most are limited by shortcomings in measurement of key variables, especially sodium intake. Few had the advantage of 24-hour urine collections, undermining the opportunity to recognize a relationship and its magnitude. Even among studies in which an association has been identified, appropriate interpretation is challenging. Dietary sodium is interrelated with other

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food nutrients, decreasing the ability to determine the primacy of sodium intake in the association. The relationship between dietary intake and CVD outcome events is further complicated in the context of a J-shaped relationship. For instance, underlying illness may lead a patient to secondary changes in diet as a result of the disease or a desire to improve health. This is a particular concern in high-risk cohorts like the ones studied by O'Donnell et al.[11] Regardless of the level of sophistication of the analysis, the intrinsic weakness of observational studies in this area limits the strength of the inferences that can be drawn.

Randomized controlled trials have the greatest capacity to enlighten guideline recommendations for sodium intake. More than 60 trials and 10 meta-analyses have reported the effects of sodium reduction on blood pressure.[12-14] The trials have varied in quality, duration, and intervention success. Some studies have failed to demonstrate a treatment effect, but most have shown a relatively consistent dose-dependent decrease in BP following the reduction in sodium intake, with the greatest BP declines observed in those with the highest BP and the most successful interventions.[7,8]

Salt-sensitive individuals and groups are especially responsive to sodium reduction, but it is difficult to identify salt sensitivity in clinical practice. Four trials have reported on the relationship between sodium reduction and CVD events. The one trial specifically designed to address this question was conducted in a high-risk group of 1981 Taiwanese veterans.[15] The kitchens of their retirement homes were randomly assigned to use regular salt or a potassium-enriched salt with approximately 50% less sodium content. Participants in the low-sodium/high-potassium group experienced a significant 41% reduction in CVD mortality, an increase in life expectancy, and a reduction in inpatient care costs. The other 3 trials were US-based behavioral intervention studies primarily designed to assess the effect of sodium reduction on BP. Two trials were conducted in normotensive study participants enrolled in phases 1 and 2 of the Trials of Hypertension Prevention (TOPH). The interventions were administered over 18 months (phase 1) or 3 to 4 years (phase 2) and the participants were followed up for up to 15 (phase 1) or 10 years (phase 2) after cessation of the intervention. In a pooled analysis of 3126 phase 1 and phase 2 TOHP participants, those assigned to sodium reduction experienced a significant 25% to 30% reduction in CVD events, with a similar pattern being noted in both trials.[16] The fourth analysis, conducted in the Trial of Nonpharmacologic Intervention in the Elderly (TONE), reported a nonsignificant 23% reduction in CVD events during a median follow-up of 29 months in the 487 TONE participants assigned to sodium reduction.[17]

Conduct of additional trials specifically designed and powered to provide more definitive results would be ideal. As is the case for studies involving weight loss, physical activity, and other lifestyle interventions, considerations of cost and complexity make the possibility of a traditional design in which individuals are randomized to a behavioral intervention to lower dietary sodium an unlikely possibility. A more realistic option would be to use an approach similar to that used by Chang et al[15] in which clusters (eg, communities) are randomized to diets that differ in sodium content.

Despite the potential value of having longitudinal data on the relationship between urinary sodium excretion and CVD events, the findings reported by O'Donnell et al[11] should be interpreted with caution. To be convincing, these findings would first have to be replicated in high-quality studies. For instance, an important consideration is the accuracy of their values for urinary sodium excretion. As the authors acknowledge, there are several caveats related to their methods for estimating urinary sodium excretion based on a single morning sample, and extrapolating from these estimates to daily sodium intake is fraught with risk.

Furthermore, although the inverse relationship between urinary potassium excretion and stroke is consistent with many previous reports and meta-analyses,[18] the possible causal relationship between urinary sodium excretion and CVD events would have to be probed more carefully, especially at the lower end of the J curve. Prior experience, such as in the context of body mass index, cholesterol levels, BP, alcohol intake, or other factors, suggests that preexisting disease is an important potential confounding factor that must be considered in the uptick in risk observed at the bottom end of a J-shaped curve. Moreover, the curve reported by O'Donnell et al is J-shaped rather than U-shaped, and as such, a relatively small proportion of study participants were in the sodium intake categories at the lower end of the curve (ie, only 3% in the group identified with urinary sodium excretion of <2 g/d and 29% in the 2-3.99 g/d group). The CVD risk among this group was far less than that among the groups in the longer end of the J-shaped curve with higher levels of urinary sodium excretion.

Most US adults consume levels of sodium far in excess of physiologic need,[19] and the vast majority of that excess is added during the processing of foods.[20] A progressive reduction in the addition of sodium to food products could represent one of the "lifestyle" changes with the greatest potential for intervention success. This shift to a more natural diet would concurrently lead to an absolute increase in dietary potassium content[21] and also lead to an improved sodium-potassium ratio, which may be more desirable than change of either electrolyte on its own.[22] The scientific underpinning for the health benefits from sodium reduction is strong, and the available evidence does not support deviating from the stated goal[7] of reducing the exposure to dietary sodium in the general population.

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ONLINE FIRST

Is Severe Sepsis Associated With New-Onset Atrial Fibrillation and Stroke?

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Severe sepsis is a major health problem in the United States and around the world, with hospital mortality rates ranging from 18% to 50%.[1,2] Patients with severe sepsis are defined as a subset of patients with sepsis who have acute organ dysfunction in the setting of a systemic inflammatory response due to an infection.[3] Severe sepsis has an estimated incidence between 50 and 300 cases per 100 000 individuals annually, depending on the study.[4-7] The prevalence of severe sepsis increases with age and with the number of comorbidities (eg, liver disease and diabetes).[8,9] Arrhythmias are common in the intensive care unit, occurring in 12% of all patients (with supraventricular arrhythmias occurring in 8% of all patients).[10] Arrhythmias are more likely to occur in older patients and those with severe sepsis or septic shock.

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Despite the prevalence of arrhythmia, controversy persists regarding the effect of atrial fibrillation on clinical outcome, with studies showing both increased mortality associated with atrial fibrillation[11,12] and no association with mortality.[10,13,14] When treating a patient with severe sepsis and new-onset atrial fibrillation, the goals of the intensive care unit clinician are likely short-term—controlling heart rate or performing cardioversion if the patient is hemodynamically unstable. Initiating anticoagulation to prevent long-term sequelae in a patient who may already be coagulopathic poses a challenging risk-benefit assessment. Better data are needed to refine the understanding of the implication of this common complication in the setting of sepsis.

In this issue of *JAMA*, Walkey and colleagues[15] address this important question. The authors used administrative claims data from California in 2007 to address the clinical

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