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Sodium, Blood Pressure, and Cardiovascular Disease Further Evidence Supporting the American Heart Association Sodium Reduction Recommendations

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Abstract—Recent reports of selected observational studies and a meta-analysis have stirred controversy and have become the impetus for calls to abandon recommendations for reduced sodium intake by the US general population. A detailed review of these studies documents substantial methodological concerns that limit the usefulness of these studies in setting, much less reversing, dietary recommendations. Indeed, the evidence base supporting recommendations for reduced sodium intake in the general population remains robust and persuasive. The American Heart Association is committed to improving the health of all Americans through implementation of national goals for health promotion and disease prevention, including its recommendation to reduce dietary sodium intake to <1500 mg/d. (*Circulation*. 2012;126:00-00.)

Key Words: AHA Scientific Statements ■ sodium ■ diet ■ prevention

In almost every country that has established guidelines for the prevention and treatment of cardiovascular disease (CVD) and stroke, national health agencies and professional societies recommend a reduction in dietary sodium as a means to lower blood pressure (BP) and to prevent CVD and stroke. The American Heart Association (AHA) currently recommends a sodium intake <1500 mg/d for the entire US population.¹ The US Department of Agriculture and US Department of Health and Human Services joint 2010 *Dietary Guidelines for Americans* calls for no more than 1500 mg/d in African-Americans, people >51 years of age, and people with hypertension, diabetes mellitus, or chronic kidney disease, and no more than 2300 mg/d in all others.² Guideline recommendations far exceed adequate intake for sodium in some age groups, especially in children; the adequate intake

for children aged 1 to 3 years is 1000 mg/d, and for children aged 4 to 8 years is 1200 mg/d.³

The scientific rationale for the AHA recommendation was documented in an AHA presidential advisory published in 2011.⁴ The principal basis for the recommendation was the strength of the evidence relating excess sodium intake to high BP, CVD, and stroke and the capacity of reduced intake of sodium to prevent and treat hypertension and to reduce the risk of adverse CVD and stroke events. High BP, both prehypertension and hypertension, is a leading cause of preventable morbidity and mortality worldwide.⁵ Excess sodium intake has also been linked to kidney stones, asthma, osteoporosis, and gastric cancer.^{3,6} Various local, state, federal, and global initiatives are focused on efforts to meet sodium reduction guidelines.⁷ Even a modest reduction in sodium intake is likely to result in substan-

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tial health benefits, especially when it is achieved in the general population.^{8,9} The World Economic Forum and World Health Organization have identified a reduction in dietary sodium as a “best buy” for lessening the increasing costs of noncommunicable diseases.¹⁰

Since the 2011 AHA presidential advisory on sodium reduction⁴ was issued, additional studies dealing with this topic have been published. Reports of paradoxical inverse or J-shaped associations between sodium intake and CVD and stroke risk and a meta-analysis have been widely misinterpreted as disproving the relationship between sodium and CVD and stroke risk and have received considerable media attention.^{11–13} These publications have stirred controversy and confusion in the popular press and the general population. In addition, they have been the impetus for calls to abandon current guidelines and recommendations promoting sodium reduction in the general population.^{14–19}

In this article, we review recent scientific reports related to dietary sodium, especially those that described the relationship between dietary sodium and CVD and stroke risk. The new publications were grouped into the following 5 categories: experimental and laboratory studies, survey data, risk association, clinical trials, and nutritional adequacy.

Experimental and Clinical Laboratory Studies

Excess sodium intake has been shown to increase BP and to cause adverse cardiovascular effects in humans and several species of experimental animals, including mice, rats, rabbits, dogs, pigs, green monkeys, baboons, and chimpanzees.^{4,20} These observations have been made under carefully controlled conditions using a wide range of sodium intakes, and in some cases, excess sodium consumption has been maintained for a significant part of the animal’s lifespan. Recent publications have added to prior knowledge in this area.

Although many deleterious effects of high sodium intake on the blood vessels, heart, and kidneys are related to increased BP, excess sodium intake also produces adverse effects through BP-independent mechanisms. For example, high sodium intake results in massive albumin excretion, oxidative stress, severe renal arteriolar damage, interstitial fibrosis, increased glomerular hydrostatic pressure, glomerular hyalinization, fibrosis, and end-stage renal disease independently of increased BP.^{21–24} Moreover, excess sodium intake attenuates the beneficial effects of many antihypertensive drugs, including blockers of the renin-angiotensin-aldosterone system, whereas reducing sodium intake enhances these effects.²⁵ Excess sodium intake in experimental animals also promotes left and right ventricular hypertrophy and fibrosis, perivascular fibrosis of the coronary arteries, and diastolic dysfunction.^{24,26} These findings in animal studies are strikingly similar to those seen in patients with similarly impaired left ventricular function, the most common basis for cardiac and renal failure and hospitalization in Medicare patients.²⁷ Even in young healthy adults with clinically normal BP, those who consume more sodium and less potassium are more likely to have increased left ventricular mass; this is especially prominent when BP is elevated, suggesting that excess dietary sodium sensitizes the heart, large arteries, and kidneys to hypertrophic and fibrotic stimuli.^{25,26}

A challenge in studying the impact of excess sodium intake in humans is that target-organ damage often develops slowly, likely over many years. Moreover, these target-organ effects, especially kidney injuries, can make BP more salt sensitive over time. This makes characterization of cause and effect more difficult. Aging, hypertension, diabetes mellitus, and other adverse health indicators that cause renal injury, with progressive loss of functional nephrons, make BP increasingly salt sensitive.²⁸ Thus, individuals whose BP was initially only modestly salt sensitive may later become more sensitive to the BP effects of sodium because of gradual injury to their kidneys and other target organs. The long-term effects of excess sodium intake on BP and target-organ injury may therefore be much greater than predicted from relatively short-term studies in animals or humans that last for only a few weeks or months.

Survey Data

Bernstein and Willett²⁹ estimated temporal trends in 24-hour urinary sodium excretion in the US population by analyzing the experience in 38 research studies conducted between 1957 and 2003. They identified a mean (SE) sodium excretion of 3526 mg/d (SE, 75 mg/d) with a low-order nonsignificant trend for increased per capita sodium intake over time. These data complement an earlier report based on 24-hour recall experience in 4 National Health and Nutrition Examination Surveys (NHANES) conducted between 1971 to 1974 and 1999 to 2000.³⁰ The NHANES results showed a 48% and 69% increase in daily sodium intake in men and women, respectively, between 1971 to 1974 and 1988 to 1994. There was little change between 1988 to 1994 and 1999 to 2000, with average sodium intakes in adult men and women of 4127 and 3002 mg/d, respectively, in 1999 to 2000. The NHANES report benefits from the use of a representative national sample but is limited by changes in survey methodology over time and by its dependence on 24-hour dietary recalls. As discussed in the next section, dietary recalls underestimate sodium intake and are prone to errors because of underreporting of food intake and changes in manufacturing and food composition databases.^{30,31} The Bernstein and Willett²⁹ report has the advantage of using the gold standard approach to estimate sodium intake (24-hour urinary sodium collection, often measured on multiple occasions) but is limited by its dependence on nonrepresentative samples of volunteers who are likely to provide a lower estimate of sodium consumption compared with their counterparts in the general population. Taken together, the 2 reports provide complementary information indicating that the average intake of sodium by US adults greatly exceeds guideline recommendations, with only a small percentage achieving the recommended goal. The data are insufficient to provide a definitive conclusion on time trends in sodium intake.

Neither data set suggests that current approaches to sodium reduction in the United States have been effective in reducing the average intake of dietary sodium over recent decades. In an analysis of 24-hour dietary recalls from the 2003 to 2008 NHANES, 99.4% of US adults consumed more sodium than recommended by the AHA, 97% exceeded the corresponding 2010 *Dietary Guidelines for Americans* recommendations

(60.4% consuming more than twice their recommended intake), and 90.7% consumed more than the Institute of Medicine tolerable upper intake level of 2300 mg/d.³² Further evidence for high sodium intake in the general population (3739 mg/d based on a mean of two 24-hour urinary sodium excretions and 3660 mg/d based on a mean of four 24-hour dietary recalls) comes from a recent report of experience in the 2195 US adult International Study of Macro- and Micro-Nutrients and Blood Pressure (INTERMAP) participants.³³ Corresponding estimates were marginally lower for the United Kingdom and much higher for China and Japan. Commercially processed foods such as breads, grains, cereals, soups, sauces, and cured meats accounted for the vast majority of sodium consumed in the United States, the United Kingdom, and Japan.

The Centers for Disease Control and Prevention, the US Food and Drug Administration, the US Department of Agriculture, and the National Heart, Lung, and Blood Institute are collaborating to strengthen US national surveillance of sodium content in processed foods, personal food choices, and urinary sodium excretion. This includes development of a list of sentinel foods to be monitored for changes in sodium content; evaluation of urine samples for population trends in sodium excretion; and measures of salt taste preference, knowledge, attitudes, and behavior related to sodium (R.K. Merritt, MSPH, chief, Epidemiology and Surveillance Branch, Division for Heart Disease and Stroke Prevention, Centers for Disease Control and Prevention; personal communication to Darwin R. Labarthe, MD, MPH, PhD, July 2012).

Risk Association

Nutritional epidemiology has the potential to generate information on sodium-risk relationships, but participant characteristics, accuracy of study variable measurements (including dietary sodium), and appropriateness of the analytic techniques must be carefully considered before clinical or public policy conclusions are reached. The challenge of recognizing and interpreting risk relationships identified through the application of nutritional epidemiologic methods is well recognized.³⁴ The 3 most important pitfalls in these studies are measurement error, confounding, and reverse causality. Accurate measurement of sodium is difficult. Part of the problem is large within-person day-to-day variability in sodium consumption. This makes it necessary to average sodium intake obtained from >7 to >10 days to determine an individual's intake.^{35,36} In addition to random error, many approaches used to measure dietary sodium provide systematically inaccurate results. The gold standard for measurement of sodium intake is estimation from 24-hour urine collection, preferably based on an average of multiple collections. Careful instructions and quality control oversight are essential to ensure the accuracy of 24-hour urine collections. Even then, undercollection and, to a lesser extent, overcollection of urine can result in systematic underestimation or overestimation of sodium excretion. Overnight and spot urines are much less burdensome for study participants and research staff, so they are often used as surrogates for 24-hour urine collections. However, these measures are a weak substitute for 24-hour urine collections, especially when estimating excretion in an individual, and the validation

methods supporting their use are often inadequate.³⁷ A 24-hour dietary recall or variants such as a 2- or 3-day recall can be used to measure dietary sodium, but they have many limitations. Not only do 24-hour recalls rely on databases that frequently do not include brand names or specific sodium content of processed foods that contribute most to daily intake, but this approach does not include sodium added in the kitchen and at the table, in supplements, or in drinking water. Underreporting of food and beverage intake and portion sizes also results in falsely low estimation, and those who exhibit this behavior may already be at increased risk for adverse outcomes. Finally, 24-hour recall estimates of sodium consumption are rendered inaccurate by changes in commercial food composition that are not reflected in the nutrient databases used to estimate sodium content.

In addition to measurement error, all the usual sources of confounding that are a challenge in other areas of epidemiology are equally problematic in nutritional epidemiology.³⁸ Even when the results can be statistically adjusted to account for presumed confounding variables, the potential for residual confounding can be substantial. A challenge of confounding that is especially common in nutritional epidemiology is collinearity.³⁴ Many nutritional variables are interrelated, some to a high degree. Dietary sodium is strongly related to energy intake and to consumption of potassium, calcium, magnesium, and many other nutrients. This collinearity makes it difficult to identify the causality of nutrition relationships in observational epidemiology and can result in unstable estimates or bias, resulting in paradoxical relationships when these factors are concurrently included in multivariate analyses.³⁹

A third important challenge in nutritional epidemiology that explores sodium-risk relationships is reverse causality. This is most likely to occur in studies that use cohorts with sick patients, such as those with heart failure, coronary heart disease, chronic kidney disease, or diabetes mellitus. Inclusion of such patients tends to result in many events being observed during follow-up, enhancing the statistical power of a study to recognize risk relationships. However, sick patients are likely to reduce their sodium intake either because they were advised to do so or because their appetite is poor. In either instance, a lower sodium intake is likely to be the result of rather than the cause of their illness (reverse causality). The situation is further compounded by the frequent use of diuretics and other medications that can distort estimates of sodium intake, especially overnight and spot urine collections. In many studies, the number of outcome events is relatively small. In this context, what might seem a trivial number of events owing to reverse causality can easily overwhelm a true relation and lead to a null or paradoxical relationship. Inverse and J-shaped risk relationships in cohorts with a high baseline prevalence of sick patients should be interpreted with great caution because reverse causality is common in this situation.

New Risk Association Studies

Six investigations of the relationship between dietary sodium and CVD and stroke risk or all-cause mortality have been reported since the 2011 AHA presidential advisory⁴ on sodium intake was published.⁴⁰⁻⁴⁵ Two identified a positive relationship,^{40,41} 2 identified a curved (J-shaped) relation-

ship,^{42,43} and the remaining 2 identified an inverse relationship.^{44,45}

The 2 studies^{40,41} that reported a positive relationship were conducted in general population samples. In an ecological analysis of regions in Japan, salt intake was identified as an independent risk factor for stroke mortality.⁴⁰ Even with the adjustment for mean arterial BP, the odds ratio for stroke mortality was 1.25 (95% confidence interval [CI], 1.23–1.27) for the 4 regions with the highest compared with the 4 regions with the lowest intake of salt. In a prospective analysis of 2657 US adults who were followed up for an average of 10 years, a strong, positive, statistically significant relationship was noted between dietary sodium, assessed by food frequency questionnaire, and stroke incidence.⁴¹ Compared with their counterparts who consumed ≤ 1500 mg/d sodium, participants who consumed ≥ 4000 mg/d sodium had a stroke hazard ratio of 2.59 (95% CI, 1.27–5.28), with an increased risk of 17% (95% CI, 1.07–1.27) for each 500-mg/d-higher level of sodium intake. A statistically significant increase in hazard ratio (1.68; 95% CI, 1.06–2.57) was also noted for the composite outcome of stroke, myocardial infarction, or vascular death in participants whose sodium consumption was ≥ 4000 mg/d compared with those with ≤ 1500 mg/d.

The 2 studies^{42,43} that reported a J-shaped relationship were conducted in patients at high risk for CVD and stroke and other morbidity and mortality. During a 10-year follow-up of 2807 Finnish adults with type 1 diabetes mellitus, a curved relationship was noted between urinary sodium, assessed by a single baseline 24-hour urine collection, and all-cause mortality.⁴² Across most of the sample ($\approx 75\%$), the relationship between urinary sodium and all-cause mortality was direct and dose dependent. However, a paradoxical inverse relationship between sodium and mortality was noted for those with the lowest level of baseline sodium excretion. Extrapolation from the authors' graphic results suggests that this uptick in risk was noted at a sodium excretion between 1156 and 1725 mg/d (50–75 mmol/d),⁴² a range that is unusually low compared with corresponding values in free-living populations.⁴⁶ In the same study, an inverse relationship was identified between urinary sodium and incident end-stage renal disease. No results were reported for CVD and stroke mortality or nonfatal CVD and stroke events. In addition to the possibility of an error in urine sodium measurement and the potential for confounding, the finding of a J-curve in this study is quite likely to have resulted from reverse causality. The study was conducted in a high-risk group of patients who had a 20-year median duration of diabetes mellitus and a high prevalence of disease risk factors (hypertension in 47%, micro- or macroalbuminuria in 30%, and an estimated glomerular filtration rate < 60 mL \cdot min⁻¹ \cdot 1.73 m⁻² in 12%). Although their mean age at baseline was only 39 years, almost 8% died during follow-up and 4.5% developed end-stage renal disease. In a sample of patients with so much illness and such a high prevalence of hypertension and other CVD and stroke and end-stage renal disease risk factors, one could anticipate a reduced level of sodium consumption because of loss of appetite or a desire to improve health, especially in those at greatest risk of a clinical event. Thus, the uptick in mortality at lower levels of urinary sodium seen

in this study may well have been a consequence rather than a cause of increased risk.

A J-shaped relationship between urinary sodium and risk of a composite outcome of CVD and stroke events (CVD mortality, myocardial infarction, stroke, and hospitalization for congestive heart failure) was also noted in a 5-year secondary analysis of 28 880 Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSEND) clinical trial participants.⁴³ For most of the cohort, a direct association was noted between urinary sodium and risk of CVD and stroke events, but a paradoxical inverse relationship was noted in the 12% with an estimated urinary sodium excretion < 3000 mg/d. An accompanying editorial⁴⁷ and subsequent publications^{48,49} have highlighted concerns and cautions in the interpretation of this report. Systematic error in the assessment of sodium intake is a strong possibility in this study. A single morning spot urine collection was used to extrapolate 24-hour urinary sodium excretion. As previously mentioned, spot urine specimens are a poor substitute for 24-hour collections. Although the authors cited a study to justify their use of spot urine sodium samples, their validation of the method was conducted in a sample of largely healthy control subjects rather than the type of sick patients in their risk analysis. The ONTARGET and TRANSEND trial participants differ from healthy control subjects in many ways, including their use of medications such as diuretics and inhibitors of the renin-angiotensin-aldosterone system that can greatly affect sodium levels in morning spot urine collections. The use of these drugs and the attendant potential for measurement error are likely to have been more common in those at greatest risk for CVD and stroke. Independent of the concern about the milieu for validation of their urinary sodium measurement, O'Donnell et al⁴³ used a simple Pearson correlation as their test of agreement between spot and 24-hour urinary excretion. Correlation coefficients can provide useful information on the association but have long been recognized as an inadequate and inappropriate test of agreement between different methods of measurement.⁵⁰ In addition to the likelihood of measurement error, residual confounding is a strong possibility in this study because it was not specifically designed to collect the type of confounder information appropriate for studies of the salt and CVD and stroke relationship. Over and above the concerns related to measurement error and confounding, reverse causality may have been responsible for the increased risk of CVD and stroke noted at lower levels of sodium in this study. Enrollment in ONTARGET and TRANSEND was confined to people at high risk of CVD and stroke events during follow-up. All participants were ≥ 55 years of age with CVD and stroke or high risk of CVD and stroke. At baseline, almost half the participants had a history of myocardial infarction, $> 20\%$ had a history of stroke, nearly 40% had diabetes mellitus, and 70% had hypertension. This is a classic framework for disease-induced changes in nutrition that lead to paradoxical findings in which illness is the cause rather than the consequence of level of sodium intake. It seems likely that

the severely diseased patients studied by O'Donnell et al would have changed their level of sodium intake as a consequence of medical advice, drug treatment, and illness-related loss of appetite.

One of the 2 studies that reported an inverse relationship was conducted in a high-risk clinical setting, and the other was based on experience in the general population. Ekinci et al⁴⁴ reported an inverse relationship between urinary sodium, assessed by means of 1 or more 24-hour urine collections, and both CVD and all-cause mortality in 638 patients with type 2 diabetes mellitus who were followed up for a median of 9.9 years. The cohort was at high risk for CVD and mortality, with 27.4% of the study participants dying during follow-up. Illness was especially prevalent among those in the lowest tertile of baseline sodium excretion. For example, their prevalence of macrovascular disease at baseline was 67% and their estimated glomerular filtration rate was $67 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ (compared with 61% and $78 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ for counterparts in the highest tertile of baseline sodium excretion). This pattern of illness at baseline makes reverse causality a highly plausible explanation for the sodium-risk relationship observed in this study. Others have pointed to additional concerns, including the finding of a paradoxical inverse relationship between systolic BP and both CVD and all-cause mortality.⁵¹ In a secondary analysis of a general population sample of 3681 European adults who were followed up for a median of 7.9 years, Stolarz-Skrzypek et al⁴⁵ identified a significant inverse relationship between urinary sodium, based on a single baseline 24-hour urine collection, and CVD mortality. A large number of design and analytic concerns were raised in subsequent correspondence and commentaries.⁵²⁻⁵⁸ These included the potential for underestimation of sodium intake in the low-sodium group, the possibility of differential misclassification bias resulting from use of a continuous variable with known random measurement error to classify participants into multiple exposure categories, residual confounding, overadjustment for factors in the causal pathway, loss to follow-up, missing data, lack of adjustment for multiple testing, reverse causality, generalizability of the cohort, and the relatively small number of events (only 84 deaths attributable to CVD and stroke). Thus, both studies in diabetes mellitus^{42,44} suffer from serious methodological shortcomings and provide insufficient evidence to substantiate the presence of a paradoxical relationship between sodium and CVD or stroke in this setting.

Although convenient, secondary analyses of data sets that were not specifically designed to explore the sodium-risk relationship provide a risky basis for advising the public and for policy decision making. In contrast to the meticulous protocol-based investigations of sodium relationships in studies such as the International Study of Sodium, Potassium, and Blood Pressure (INTERSALT), INTERMAP, phases I and II of the Trials of Hypertension Prevention (TOHP), the Trial of Nonpharmacologic Interventions in the Elderly (TONE), and the Dietary Approaches to Stop Hypertension (DASH)-Salt trial, which included careful measurement of 24-hour urinary estimation of sodium intake, most of the new studies were secondary analyses that took advantage of data collected in studies that had a different purpose. None of the new risk studies that report a paradoxical relationship between sodium intake and CVD and

stroke risk was specifically designed to address sodium-risk relationships. Each of the new observational studies has limitations in study design, conduct, and interpretation. None is of sufficient quality to warrant a change in public policy. Recognizing these limitations, a preponderance of the evidence from these 6 studies⁴⁰⁻⁴⁵ is in keeping with established conclusions that sodium is positively related to CVD and stroke risk, with 2 studies observing this relationship throughout the entire range of sodium examined and 2 others identifying a positive relationship for the vast majority of participants studied.

Clinical Trials

Three meta-analyses of clinical trials were published in 2011.⁵⁹⁻⁶¹ One reported on the efficacy of sodium reduction in lowering BP.⁵⁹ The other 2 reports focused on the efficacy of sodium reduction in preventing CVD and stroke.^{60,61} Graudal et al⁵⁹ updated a previous report on the same topic by expanding the number of trials in their database from 114 to 167. The updated results were presented separately for patients with hypertension and people who were normotensive by race (white, black, and Asian). For the trials conducted in patients with hypertension, lower versus higher sodium intake resulted in a mean reduction in systolic BP of 5.18, 6.44, and 10.21 mm Hg in whites, blacks, and Asians, respectively. The corresponding reductions for the trials conducted in participants who were normotensive were 1.29, 4.02, and 1.27 mm Hg, respectively. In a forest plot detailing the effects of sodium reduction for the trials conducted in people who were normotensive, mean systolic BP was decreased in 50 (70.4%), was unchanged in 8 (11.3%), and was increased in 13 (18.3%). The authors also reported a significant increase in elements of the renin-angiotensin-aldosterone system, plasma epinephrine, norepinephrine, and triglyceride and a small but statistically significant increase in total cholesterol. Overall, the results of this meta-analysis are consistent with prior knowledge that BP is reduced after decreasing dietary sodium intake. It also confirms previous reports that larger reductions can be expected in those with a higher level of BP at baseline and in blacks. As in these authors' previous analysis, trials with a duration as short as 4 days were included, as were trials of short-term salt loading followed by abrupt reductions in sodium intake from very high to very low levels, ranging from almost 20 700 mg (900 mmol)/d to $\approx 920 \text{ mg}$ (40 mmol)/d. The latter studies would be expected to stimulate the renin-angiotensin-aldosterone system, to reduce plasma volume, and to increase lipid levels. Trials of very short duration and those with abrupt dramatic changes in sodium intake have no relevance for clinical practice or public policy recommendations.

Results from a previous meta-analysis that studied 28 trials of modest sodium reduction (17 in patients with hypertension and 11 in people who were normotensive) with a minimum duration of 4 weeks are of greater relevance.⁶² In this analysis, systolic BP was reduced by 4.96 and 2.03 mm Hg in the studies of patients with hypertension and people who were normotensive, respectively. There was a significant dose-response relationship between sodium reduction and a decrease in BP. A reduction of 2300 mg (100 mmol)/d in urinary sodium predicted a 7.11- and 3.57-mm Hg decrease in

systolic BP for the patients with hypertension and their counterparts who were normotensive, respectively. Sodium reduction was associated with a modest increase in renin and aldosterone levels in the 9 and 8 trials that reported this information. No change in cholesterol levels was detected in the 3 trials with this information. Subsequently, this finding was replicated across a range of sodium intake that is relevant to policy decision making in the large DASH-Sodium trial.⁶³ No significant difference in fasting blood lipid levels was noted across the 3 levels of sodium intake tested (1150 mg [50 mmol]/d, 2300 mg [100 mmol]/d, and 3450 [150 mmol]/d), in participants assigned to either the DASH or control diets.

The effect of sodium reduction on CVD and stroke and all-cause mortality was explored in 2 meta-analyses. Taylor et al⁶⁰ reported the experience in 7 trials (6250 participants; 665 deaths) with a follow-up of at least 6 months. Data were analyzed separately for the 3 trials conducted in participants who were normotensive, the 3 trials conducted in patients with hypertension, and the 1 trial conducted in patients with heart failure. For some of the analyses, data were not available from all of the trials. As a consequence of the small number of trials and the decision to explore the results in 3 separate strata (trials in patients with hypertension, people who were normotensive, and patients with heart failure), there was limited statistical power to recognize an effect of sodium reduction on CVD and stroke events or all-cause mortality. However, a trend toward fewer CVD and stroke events and lower all-cause mortality was apparent in the 6 trials conducted in patients with hypertension and individuals who were normotensive. In each of the 6 trials, all-cause mortality was either the same (1 trial) or lower (5 trials) in the participants who had been assigned to the lower-sodium regimen. The total number of deaths in the lower-sodium group versus control was 220 versus 345 for the trials conducted in patients with hypertension and 36 versus 43 for the trials conducted in normotensive individuals. The corresponding numbers for CVD and stroke events were 42 versus 51 (data from only 2 studies) for trials in patients with hypertension and 88 versus 112 for trials in people who were normotensive.

In the 1 trial conducted in patients with heart failure, the efficacy of sodium reduction was evaluated in 232 Italians with severe heart failure requiring hospitalization.⁶⁴ During the trial, they were concurrently being treated with an unusually aggressive drug therapy regimen, including loop diuretics (furosemide 250–500 mg twice daily), angiotensin-converting enzyme inhibitors (100%), spironolactone (87%), and other cardiovascular medications. In the context of this unusually aggressive drug therapy, patients assigned to sodium reduction had an increased risk of mortality. Even if the findings in this trial were to be replicated, experience in such a sick and highly medicated group has no relevance for the general population or even for most patients with heart failure. It does, however, underscore the importance of good clinical judgment in considering sodium reduction in very sick patients with complex medical conditions.

In a subsequent report that excluded the trial conducted in patients with heart failure, a nonsignificant trend for a reduction in all-cause mortality and CVD and stroke events

was noted in both the trials conducted in patients with hypertension and the trials conducted in individuals who were normotensive.⁶¹ The overall reductions in the patients with hypertension were 4% and 16% for all-cause mortality and CVD and stroke events, respectively. The corresponding reductions in people who were normotensive were 10% and 29%. When the experience for trials conducted in both settings was pooled, a statistically significant 20% reduction in CVD and stroke events was noted (95% CI, 0.64–0.99). The apparent beneficial effect of sodium reduction identified in this meta-analysis is consistent with long-term follow-up experience for participants enrolled in phases I and II of TOHP. A behavior change trial to evaluate the efficacy of sodium reduction in the prevention of hypertension was conducted over 18 months in phase I of TOHP and over 3 to 4 years in phase II, with subsequent follow-up for up to 15 and 10 years in phase I and II participants, respectively. During the trial phases, net sodium reduction in the intervention groups was 1014 mg (44 mmol)/24 h in phase I and 759 mg (33 mmol)/24 h in phase II. In a pooled analysis of 3126 phase I and II participants, those who had been assigned to the sodium reduction intervention experienced a significant 25% reduction in CVD and stroke events (95% CI, 0.55–0.99) after adjustment for clinic site, demographic information, and randomization to a weight loss intervention, with a similar pattern for the participants in both phases.⁶⁵ Further adjustment for baseline weight and sodium excretion identified a 30% reduction in CVD and stroke events (95% CI, 0.70–0.94). In the 1 trial specifically designed to test the efficacy of sodium reduction in reducing risk of CVD, the kitchens of retirement homes for 1981 high-risk veterans in Taiwan were randomly assigned to the use of regular salt or a potassium-enriched salt with ≈50% less sodium.⁶⁶ Those in the lower-sodium/higher-potassium group experienced a significant 41% reduction in CVD and stroke mortality, an increase in life expectancy, and a reduction in inpatient healthcare costs. Thus, the experience from randomized, controlled trials supports the value of modest sodium reduction as a means to lower BP and to prevent CVD and stroke events and death in both patients with hypertension and people who are normotensive.

Except for the study in Taiwan, none of the previously mentioned trials that reported on all-cause mortality and CVD and stroke events was designed to have sufficient statistical power to provide a conclusive test of the efficacy of sodium reduction in preventing morbidity and mortality. Some authors have proposed more definitive randomized trials to test the effects of sodium reduction on clinical outcomes as a requirement for public policy related to sodium intake.^{14,15,17,60} They argue that randomized trials with clinical outcomes are the gold standard for determining the health effects of interventions and are needed to resolve the debate on the health effects of a reduced sodium intake. This point of view makes sense as an aspirational goal, but the practical reality of such an approach is daunting. Clinical event trials are well suited to testing interventions in high-risk populations in which disease complications and the beneficial effects of interventions can be recognized over a relatively short period of follow-up, usually no more than 5 or 6 years. However, clinical outcome trials for behavioral inter-

ventions aimed at such preventive therapies as sodium reduction, weight loss, cholesterol reduction, and physical activity are not feasible in general populations because there is a long interval between the exposure and clinical manifestations of deleterious effects on health. It has been estimated that a sodium reduction clinical events trial would require randomization of $\approx 28\,000$ participants with a follow-up of at least 5 years.⁶¹ A behavioral intervention trial of sodium reduction would be especially difficult to conduct in the United States because sodium intake is determined largely by the nature of the food supply, with 70% to 80% of the sodium ingested in the United States coming from processed foods. The challenges of achieving and sustaining an experimental contrast would result in a high probability of a false-negative result. An alternative possibility is to conduct event-based CVD and stroke outcome trials in countries like China where the main source of sodium intake is discretionary and there is potential for sustained reduction in sodium intake. This would still be a challenging proposition and may be complicated by the rapid changes in culture and transformation in food habits that are occurring in many such countries.⁶⁷

Nutritional Adequacy

Maillot and Drewnowski⁶⁸ used a mathematical model to explore the nutritional adequacy of diets that meet the recommendations for sodium intake presented in the 2010 *Dietary Guidelines for Americans*. They used dietary recall experience in 4295 adults who had participated in the 2001–2002 NHANES to identify the type of feeding pattern that would be necessary to ensure the adequacy of intake for 27 nutrients at different levels of estimated sodium consumption. Nutritional adequacy was relatively easy to achieve with usual eating patterns for diets with a sodium intake >2800 mg/d. Progressively larger deviations from usual eating patterns were required to achieve nutritional adequacy as diets with lower levels of sodium intake were tested, with the greatest deviations being required for men in the lowest age group tested (20–30 years). These findings are not surprising in the context of eating the usual US diet that is based largely on the consumption of commercially processed foods with a high level of “hidden” sodium. They underscore the need for a reduction in the amount of sodium added during food processing to allow achievement of sodium guidelines with usual eating patterns. The 2010 Dietary Guidelines Advisory Committee also conducted a modeling study of dietary patterns that achieve nutrient adequacy while meeting sodium goals.⁶⁹ They determined that nutrient adequacy could be achieved at a sodium intake of ≤ 1500 mg/d when foods with lower sodium content were chosen in place of higher-sodium options.

Summary and Conclusions

A comprehensive approach to cardiovascular health promotion and disease prevention includes the consumption of a healthy diet, physical activity, maintenance of ideal body weight, and avoidance of tobacco products.¹ Although important, sodium reduction is only 1 component of a healthy diet. Sodium reduction is consistent with the achievement of other dietary goals and is facilitated by many of them, including a reduction in calorie intake and increased consumption of potassium.

Table. Principal Findings From Studies Published Since the 2011 American Heart Association Presidential Advisory⁴ on Sodium Reduction

Experimental and laboratory studies

Excess sodium leads to high BP, attenuation of the effects of antihypertensive medications, ventricular hypertrophy, diastolic dysfunction, perivascular fibrosis of the coronary arteries, and progressive renal injury, which also promotes sodium sensitivity.

US population surveys

Sodium intake is well in excess of national recommendations, and there is no evidence of a trend for a decline in consumption.

Observational studies

Most recent reports on the relationship between dietary sodium and CVD and stroke events were based on secondary analysis of data sets from studies not designed to address the relationship between sodium intake and CVD and stroke risk. Measurement error, residual confounding, and reverse causality complicate the interpretation of these reports. A preponderance of the evidence is in keeping with conventional conclusions that higher sodium intake is adversely related to CVD and stroke risk.

Clinical trials

Trials provided confirmation of previous meta-analyses indicating that a reduction in sodium lowers BP in both patients with hypertension and individuals who are normotensive. The statistical power to identify the effect of sodium reduction on CVD and stroke events was limited, but a consistent trend suggested the benefit of a lower sodium intake in trials in patients with hypertension and people who are normotensive. Meta-analysis of these trials identified a statistically significant 20% reduction in CVD and stroke events.

Nutritional adequacy

Nutritional adequacy is easy to achieve with current eating patterns at sodium intakes much less than typical for the US general population and can be achieved at a sodium intake of ≤ 1500 mg/d when foods with lower sodium content are chosen in place of higher-sodium options.

BP indicates blood pressure; CVD, cardiovascular disease.

Available data, including those from studies published since the 2011 AHA presidential advisory on sodium reduction, provide strong scientific support for the AHA guidelines to reduce sodium intake to <1500 mg/d (Table). New animal and human studies continue to provide important evidence that excess sodium promotes structural and functional impairment of the heart, great vessels, and kidneys. These pathophysiological changes progress over time to severe disease manifested by acute clinical events, costly hospitalizations for cardiac failure and end-stage renal disease, and death. Calls for abandoning the AHA dietary guidelines for sodium consumption are based on flawed analyses of data from observational studies that were not planned to study sodium relationships, with great potential to yield misleading results, and on misinterpretation of clinical trial results. Editors and policy decision makers should be especially vigilant in their review and interpretation of secondary analyses of observational data sets that were not designed to address the relationship between sodium and CVD and stroke. This includes studies of the association between sodium intake and CVD and stroke risk in cohorts with sick patients. Given the increase in case series, population genetics investigations, and use of administrative data sets linked to clinical outcomes information, such studies are likely to become more common. Likewise, reviewers, editors, and policy decision makers need to scrutinize the conduct and interpretation of clinical trial meta-analyses that

explore the efficacy of sodium reduction in lowering BP and CVD and stroke events. Calls for additional research should not be used as an excuse to postpone initiatives aimed at meeting the current AHA guidelines for sodium reduction in the community.

Scientific evidence for the benefits of sodium reduction is strong, and sodium is often an unnecessary food additive in the era of refrigeration. The challenge for the healthcare community and our society is to effect a meaningful reduction in sodium intake.^{4,7} Most US adults consume sodium far in excess of physiological need and guideline recommendations.^{1–3,70} Most of this excess comes from the addition of sodium during food processing.^{33,71} A progressive reduction in the amount of sodium added to food products represents one of the most appealing and cost-effective strategies available to meet the AHA goal for sodium intake in the community. Coupled with portion control, greater dependence on minimally processed foods and foods prepared at home with lower-sodium ingredients could reverse the long-standing trend for static or increasing levels of sodium

consumption in the US general population.^{29,30} This shift to a more natural, lower-sodium diet would also lead to an increased intake of potassium and a lower sodium-potassium ratio, which may be even more desirable than a change in either electrolyte on its own.^{72,73} Although challenging, experience indicates that meaningful reductions in population sodium intake are possible.⁶ A comprehensive community-based approach in Finland resulted in a reduction in urinary sodium excretion of $\approx 25\%$ between 1979 and 2002.⁷⁴ In England, a program of voluntary salt reduction targets for all foods has yielded a 15% decrement in general population urinary salt excretion over the 10-year period between 2000 to 2001 and 2011.⁷⁵ Broadening of current US initiatives such as the voluntary sodium reduction program in New York City should be equally effective in reducing sodium intake in the United States. The AHA remains committed to improving the health of all Americans through the implementation of its national goals for health promotion and disease prevention, including the goal to reduce dietary sodium to <1500 mg/d.

Disclosures

Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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†Significant.

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