Sodium, Blood Pressure and Cardiovascular Disease:
A Compelling Scientific Case for Improving the Health of the Public

Running title: Whelton; Sodium, Blood Pressure and Cardiovascular Disease

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The relationship between sodium (Na) intake and human health indicators has been investigated in observational studies and randomized controlled trials (RCT). The most extensive body of information details the relationship between Na and blood pressure (BP). High BP was identified as the leading risk factor, among 67 studied, for worldwide mortality and disability adjusted life years \(^1\). It is also one of the best surrogate markers for cardiovascular disease (CVD), especially stroke \(^2\). Consistent with prior reports, three recent meta-analyses of RCT identified significant declines in BP following a reduction in Na intake \(^3\)\(^-\)\(^5\). The decrements in BP were greater in those with higher starting levels of BP, more successful intervention, older age, and African-American ethnicity. In the two meta-analyses with greatest relevance for clinical practice and public health, Na reduction was associated with a small but expected physiological increase in elements of the renin-angiotensin-aldosterone system \(^3\)\(^4\), little or no effect on total cholesterol \(^3\)\(^4\) or catecholamine levels \(^3\), and changes in urinary protein consistent with a beneficial effect on renal function \(^3\).

Most prospective investigations have identified a direct relationship between Na and CVD, especially for stroke and fatal CVD events. However, null, inverse and J-shaped relationships have also been observed. In a recent meta-analysis of 10 studies with 14 comparisons higher Na was associated with a mean, 95% confidence interval (CI) risk ratio of 1.24, 1.08-1.43 for stroke \(^3\). When the outcome was confined to fatal stroke, the risk ratio increased to 1.63, with a 95% CI of 1.27-2.10. The relationship between Na and coronary heart disease (CHD) was inconclusive but the pooled mean, 95% CI was 1.32, 1.13-1.53 in the five comparisons that reported on fatal CHD (“quality of evidence very low”). A common problem with the observational reports has been use of datasets from studies not designed to address the relationship between Na and CVD. These secondary analyses have had methodological weaknesses, including the potential for reverse causality, bias in assessment of Na intake, absent
or insufficient adjustment for confounding variables, and random error\textsuperscript{6,7}. The study by Joosten et al\textsuperscript{8} is not immune to these challenges. In addition to limitations mentioned by the authors, the presence of hypertension in almost one-third of the cohort makes reverse causality and underestimation of the relationship a possibility. Sensitivity analyses that exclude early years of follow-up do not eliminate this problem. Residual confounding and difficulty identifying causality for an exposure (Na) that is highly interrelated with caloric intake and other food components are also concerns. Despite these apprehensions, the authors’ attention to study design, conduct, analysis, and interpretation makes their investigation of much higher caliber than most previous reports. Only two of the preceding seven observational studies of Na and CHD were based on a larger number of CHD events\textsuperscript{9,10} and neither of these studies matched the capacity of the new report to minimize systematic and random error. Joosten et al did not identify an overall relationship between Na and CHD but they did observe a significant direct relationship between Na and CHD in susceptible persons with a higher level of plasma N-terminal pro-B-type naturetic peptide (NT-ProBNP) or hypertension. It seems plausible that higher levels of NT-ProBNP might serve as an indicator for individuals who are more salt sensitive\textsuperscript{11,12}, an entity that has been associated with an increased risk of hypertension, obesity and the metabolic syndrome\textsuperscript{13}. The study by Joosten et al is a welcome addition to the literature as provides valuable information of higher quality regarding the relationship between Na and CHD, an important area that has been understudied.

Clinical events experience from RCT, albeit limited, is consistent with a beneficial effect of Na reduction on CVD mortality and morbidity. In a high-risk group of Taiwanese veterans, substitution of a potassium enriched salt with approximately 50% less Na was reported to result in a significant 41% reduction in CVD mortality, an increase in life expectancy and a reduction
in inpatient care costs. However, the analysis did not account for use of a cluster design and the intervention included potassium supplementation as well as reduced Na. None of the other Na reduction RCT was powered to recognize an effect on CVD events but the three largest and longest behavioral intervention trials have provided results which are consistent with a beneficial effect of Na reduction. In the Trial of Nonpharmacologic Intervention in the Elderly (TONE), 975 seniors with well controlled hypertension were randomized to 29 months of Na reduction or control. The 487 assigned to Na reduction achieved about a 40 mmol/d lower level of Na excretion compared to the control group. This modest decrement in Na (approximately 25%) not only produced a significant decrease in systolic BP and a reduction in the need for antihypertensive medication (primary trial endpoint) but also yielded a non-significant 23% decrease in CVD events. In phases I and II of the Trials of Hypertension Prevention (TOHP) 3126 participants with high normal BP were assigned to Na reduction (n=1518) or control (n=1608). The Na reduction interventions were conducted over 18 months in phase I and 3-4 years in phase II, resulting in similar net decreases in 24-hour urinary Na for corresponding time points; 44 mmol/d and 38.2 mmol/d (decrements of approximately 30% and 21%, respectively) at the 18-month visit. These modest changes in Na intake resulted in a significant decrement in BP during phase I (primary trial endpoint) and a significant decrease in the incidence of hypertension during phase II (primary trial endpoint). Following completion of the trials, active and passive surveillance was employed to monitor health outcomes in both cohorts during 15 (phase 1) or 10 (phase 2) years of follow-up. In a pooled analysis of events over the entire period of observation, Na reduction was associated with a significant 30% reduction in CVD events and a non-significant 20% reduction in CVD mortality. Behavior change interventions are challenging and only yield a small reduction in Na. Dose-response relationships in TOHP
suggest interventions with a greater capacity to reduce Na intake should result in greater health benefits. 

Most adults in the US and other countries live in an environment where processed foods are pervasive. They consume levels of Na far in excess of physiologic need, with the vast majority of this excess coming from Na added during processing of foods. Using NHANES experience from 2003 to 2008, Cogswell et al. estimated a median Na intake of 3326 mg/d for men and 2357 mg/d for women. These high values probably underestimate Na intake by about 25% as they were derived from 24-hour dietary recalls and do not include Na added during food preparation or at the table. Despite this, their estimate of daily Na consumption exceeded the AHA recommendation of <1500 mg/d in 99.9% of men and 98.2% of women, and the US Government’s Dietary Guidelines for Americans recommendation of <2300 mg/d in 96.9% of men and 77.6% of women. Even in subgroups thought to be especially sensitive to dietary Na (≥50 years, non-Hispanic blacks, those with prehypertension, hypertension, diabetes or chronic kidney disease) almost everyone exceeded the AHA and US Government Na intake recommendation of <1500 mg/d (range: 98.5% to 99.7%). Global mean (95% CI) daily Na consumption has been estimated to be 3.95 (3.89-4.01) g/d, almost double the WHO recommendation of <2000 mg/d.

A modest 4% per year decrease in Na intake might prevent more than half a million deaths and add almost two million person-years of life in the US over a period of ten years. A gradual decrease in the addition of Na to food products represents the easiest “lifestyle” change for the general population and the intervention option with the greatest potential for success. This approach has already produced meaningful Na intake reductions in Finland and England, coupled with a significant decrement in population BP, stroke rates, and healthcare costs.
successful voluntary and mandated reformulation of food products to contain less added Na in these countries indicates that a gradual reduction in Na is feasible and acceptable. Feasibility is further underscored by the substantial variation in Na content for identical food products marketed by the same manufacturers in different countries. There is, however, no evidence that the US population has benefited from a reduction in the addition of Na during food processing.

Likewise, in Canada only 1% of meals served by 26 sit-down restaurant chains met the FDA criterion for a “healthy meal” (<600 mg) and the average Na content per meal was consistently in excess of the AHA and WHO daily intake guidelines for breakfast (2027 mg), lunch (2297 mg) and dinner (2297 mg). The American Heart Association, the Centers for Disease Control and Prevention, the New York City Health Department and many other federal, state and local agencies are actively engaged in initiatives to reduce Na and improve the health of the public. It remains to be seen whether these initiatives will prove to be more successful than previous attempts to reduce Na in the United States.

Conflict of Interest Disclosures: None.

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