An Overview of Randomized Trials of Sodium Reduction and Blood Pressure

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To test for effects on systolic and diastolic blood pressure and to provide precise estimates of their magnitude, we conducted an overview of randomized clinical trials that aimed to reduce the intake of sodium in human subjects. We excluded from pooled analyses trials with confounded designs, those that compared intake levels beyond the usual range in the population, and those without published reports. Two reviewers abstracted information in duplicate and differences were reconciled. Twenty-three trials with outcome data from an aggregate of 1,536 subjects were included. Data were pooled both separately for hypertensive and normotensive subjects and for all trials combined. With the use of sample size weighting, blood pressure reductions (net of controls) were 4.9±1.3/2.6±0.8 mm Hg (systolic and diastolic, respectively, with 95% confidence limits) in hypertensive subjects and 1.7±1.0/1.0±0.7 mm Hg in normotensive subjects. The combined blood pressure reductions were 2.9±0.8/1.6±0.5 mm Hg. These changes were associated with mean reduction of urinary sodium excretion ranging from 16 to 171 mmol/24 hr for individual trials. A dose–response relation across trials was found, both in normotensive and in hypertensive subjects. These results indicate that sodium reduction lowers mean blood pressure in both hypertensive and normotensive individuals for periods of at least several months. The findings are highly consistent with results of observational epidemiological studies and have implications for preventive strategies of blood pressure control. (Hypertension 1991;17[suppl I]:I-27–I-33)

Randomized intervention trials, properly conducted, provide the best test of an effect of prophylactic or therapeutic treatments. Although the blood pressure effects of reducing dietary sodium have been studied since early in the century, randomized trials have been reported only within the past 17 years, largely the past 10 years. Trials have both increased in frequency and become more varied and complex in design. These changes reflect the importance of the question for public health and biology but also pose a challenge for summarizing and interpreting results. Several reviews have been published in recent years, but they did not present pooled analyses of all relevant trials to the time of the reviews, and several trials have since been completed. We favor pooling as part of a review because it formalizes the objective of including all relevant trials and an explicit method of combining their results. It also furnishes a quantitative estimate of the effect, which can then be evaluated with respect to observational epidemiology and public health implications.

Methods

Procedures for conducting this overview were formulated in advance, including criteria for selection of studies, data abstraction, and statistical analyses.

Selection Criteria

Candidate trials were limited to reports published through January 1990. Two authors (J.A.C., P.E.) were primarily responsible for generating the list, drawing on a previous review of one of us, reference lists in original articles and reviews, computer searches, and information from colleagues. The main criteria for inclusion were 1) random allocation of subjects to sodium reduction or a control condition (within either a parallel or crossover design), 2) trial design free of confounding by other blood pressure–lowering interventions (chiefly, antihypertensive drugs or potassium supplements), and 3) reporting of systolic or diastolic pressure (as contrasted with mean arterial pressure). Various considerations called for excluding trials in infants or young children. Two trials that assigned control subjects to a supplemented level well beyond usual intake were also excluded.

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nally, all of the trials included provided objective evidence that sodium intake was actually reduced.

Data Abstraction

Information was abstracted from each paper onto a standard form. Design features noted included the following: parallel-group or crossover study, blood pressure eligibility criteria, extent of blinding of intervention and blood pressure measurement, and duration of intervention phases. Sample size and outcome data were those from the last follow-up visits, unless only means over all visits were given. In a few trials for which the data on dropouts were provided, the proportions of missing final blood pressure values among those randomized were low. The main outcome measures were changes from baseline (parallel studies) or differences between treatment phases (crossover studies) in 24-hour urinary sodium excretion, as well as systolic and diastolic blood pressures; the latter were measured with the subjects seated, or if not available, supine. Means and standard deviations, standard errors, t ratios, or p values were recorded for each measure when reported. In some parallel studies only statistics for end follow-up measurements were reported. In a few instances, values had to be estimated from figures. Similar information, if reported, was also abstracted for potentially confounding variables, chiefly body weight, urinary potassium excretion, and alcohol intake. Demographic characteristics of study subjects were noted. All abstraction was conducted independently by two of us (chiefly, I.S. and P.E.), and differences were then reconciled.

Statistical Analyses

For each trial, we attempted to estimate the variance of the treatment effect for the outcome measures: systolic blood pressure and diastolic blood pressure. Ideally, these values could be derived from standard deviations of paired differences between baseline and end follow-up for each group in a parallel design or between each of the two treatment periods in a crossover study, or if these statistics were not given, from exact t ratios or p values. If an exact variance of paired differences was not derivable, one was imputed, either by inverting a boundary p value (e.g., p<0.05 became p=0.05) or assuming a correlation of 0.5 between the initial and final blood pressure. (These are the basis for the standard errors shown in the tables.) We intended to calculate mean effect sizes weighting each trial by the inverse of the variance. Unfortunately, only nine of the trials provided an exact derivable variance for blood pressure effects. Fourteen required the aforementioned variance imputation. Therefore, we also pooled re- 

where n_t and n_c are sample sizes for the treatment and control groups.) The underlying variance for change necessary to calculate confidence limits for the pooled mean was estimated by the average of the exact derivable variance of paired differences.

In addition to estimating pooled effects and their 95% confidence limits, we explored two other areas analytically. First, we graphed the treatment effects against sample sizes to look for any indication of publication bias (against small negative studies) and confirmed the visual impression by linear regression. Second, we examined possible effects of certain design features and covariates, using graphic analysis, weighted linear regression, and rank-correlation. Attributes examined included baseline blood pressure group, amount of sodium reduction, study design (parallel, crossover), and study duration. Nominal p values less than 0.05 were deemed statistically significant.

Results

Twenty-three trials3,12-34 meeting our selection criteria were identified (Tables 1 and 2). Five of these were reported as two strata or two phases, so that there are 28 entries in the tables. Two trials were excluded because the high sodium intake consisted of an unusually high level achieved by use of sodium chloride supplements.9,10 One of these9 also presents additional complications (withdrawal of some of the data, republication of graphic data only). One otherwise eligible trial was excluded because only data on mean arterial pressure could be obtained, despite communication with the investigator.35

Trials in Hypertensive Subjects

Eighteen trials studied hypertensive subjects (Table 1). Eight of these were crossover trials, entirely or in part, with an aggregate of 221 subjects.3,12-18 Six used the placebo-controlled design introduced by MacGregor et al,12 and four of these noted additional procedures to blind blood pressure observers. The other two did not report any method of blinding. Treatment periods were 1–2 months in length; the median was 1 month. The net reduction in sodium excretion ranged from 56 to 105 mmol, with a median of 76. (We used only the high- and medium-intake arms of the trial of MacGregor et al16 to make the levels compared most similar to other trials and avoid double use of data from the medium-intake group in pooled analyses.) All of these trials reported lower systolic blood pressure during sodium reduction, and seven of the eight, lower diastolic blood pressure. Of these differences, four for systolic blood pressure and three for diastolic blood pressure were statistically significant. Seven of the trials provided data on weight and seven on potassium differences. There were small but significant differences in two trials: weight loss of 0.54 kg in MacGregor et al12 and increased potassium excretion of 10 mmol/24 hr in the trial of Richards et al.14 No trial reported data on alcohol intake.
TABLE 1. Randomized Trials of Sodium Reduction for Hypertensive Subjects

<table>
<thead>
<tr>
<th>Author and year published</th>
<th>Sample* size</th>
<th>Blinding</th>
<th>Study length (months)</th>
<th>Urinary Na change (meq/day)</th>
<th>BP change (mm Hg) (SEM)</th>
<th>Reported confounding factors†</th>
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<tr>
<td>Crossover studies</td>
<td></td>
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<tr>
<td>Parigi3 1973</td>
<td>15</td>
<td>NR</td>
<td>1</td>
<td>−98</td>
<td>−6.7 (3.76)</td>
<td>(Wt)</td>
</tr>
<tr>
<td>MacGregor12 1982</td>
<td>19</td>
<td>Placebo, BP obs</td>
<td>1</td>
<td>−76</td>
<td>−10 (3.06)</td>
<td>(K)</td>
</tr>
<tr>
<td>Watt13 1983</td>
<td>18</td>
<td>Placebo</td>
<td>1</td>
<td>−56</td>
<td>−0.5 (1.50)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>Richards14 1984</td>
<td>12</td>
<td>NR</td>
<td>1</td>
<td>−105</td>
<td>−5.2 (4.10)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>Grobbee15 1987</td>
<td>40</td>
<td>Placebo, BP obs(RZ)</td>
<td>1.5</td>
<td>−72</td>
<td>−0.8 (1.80)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>MacGregor16 1989</td>
<td>20</td>
<td>Placebo, BP obs</td>
<td>1</td>
<td>−82</td>
<td>−8.0 (2.60)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>Dodson17 1989</td>
<td>9</td>
<td>Placebo, BP obs(RZ)</td>
<td>1</td>
<td>−76</td>
<td>−9.7 (4.33)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>ANHMRG18 1989</td>
<td>88</td>
<td>Placebo</td>
<td>2</td>
<td>−67</td>
<td>−3.6 (0.70)</td>
<td>(K)</td>
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<tr>
<td>Parallel studies</td>
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<tr>
<td>Morgan19 1978</td>
<td>31/31</td>
<td>BP obs</td>
<td>24</td>
<td>−27</td>
<td>−1.5 (4.60)</td>
<td>NR</td>
</tr>
<tr>
<td>Morgan20 1981 (male)</td>
<td>6/6</td>
<td>BP obs</td>
<td>2</td>
<td>−98</td>
<td>−6.0 (4.08)</td>
<td>K</td>
</tr>
<tr>
<td>Morgan20 1981 (female)</td>
<td>6/6</td>
<td>BP obs</td>
<td>2</td>
<td>−78</td>
<td>−4.0 (3.30)</td>
<td>K</td>
</tr>
<tr>
<td>Silman21 1983</td>
<td>10/15</td>
<td>BP obs(RZ)</td>
<td>12</td>
<td>−53</td>
<td>−8.7 (10.23)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>Puska22 1983</td>
<td>15/19</td>
<td>BP obs</td>
<td>1.5</td>
<td>−117</td>
<td>+1.8 (4.14)</td>
<td>(Wt,K)</td>
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<tr>
<td>Fagerberg23 1984</td>
<td>15/15</td>
<td>NR</td>
<td>2.3</td>
<td>−89</td>
<td>−13.3 (5.46)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>Maxwell24 1984</td>
<td>18/12</td>
<td>NR</td>
<td>3</td>
<td>−171</td>
<td>−2.0 (4.96)</td>
<td>K</td>
</tr>
<tr>
<td>Ertweerman25 1984</td>
<td>44/50</td>
<td>BP obs(RZ)</td>
<td>6</td>
<td>−58</td>
<td>−2.7 (2.20)</td>
<td>NR</td>
</tr>
<tr>
<td>Chalmers26 1986</td>
<td>48/52</td>
<td>NR</td>
<td>3</td>
<td>−54</td>
<td>−5.1 (1.42)</td>
<td>(K)</td>
</tr>
<tr>
<td>Logan27 1986</td>
<td>37/38</td>
<td>BP obs</td>
<td>6</td>
<td>−32</td>
<td>−1.1 (2.15)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>Dodson17 1989</td>
<td>17/17</td>
<td>BP obs</td>
<td>3</td>
<td>−59</td>
<td>−13.0 (5.99)</td>
<td>(Wt,K)</td>
</tr>
<tr>
<td>ANHMRG18 1989</td>
<td>50/53</td>
<td>Placebo</td>
<td>2</td>
<td>−71</td>
<td>−5.5 (1.48)</td>
<td>(K)</td>
</tr>
<tr>
<td>Costa29 1981</td>
<td>20/21</td>
<td>NR</td>
<td>12</td>
<td>−18.3</td>
<td>−5.9 (4.35)</td>
<td>NR</td>
</tr>
</tbody>
</table>

BP, blood pressure; SEM, standard error of mean; SBP, systolic blood pressure; DBP, diastolic blood pressure; Wt, weight; obs, observer; NR, not reported; RZ, random-zero sphygmomanometer; ANHMRG, Australian National Health and Medical Research Council; Alc, Alcohol; P/S, polyunsaturated fatty acids/saturated fatty acids ratio.

*In parallel study "/" denotes treatment group/control group.
†Parentheses denote controlled factors, and no parentheses denote possible confounders.

Twenty trials reported results for hypertensive subjects from parallel designs. For two of these, the parallel trial consisted of the initial portion of a crossover study included above, and when all trials in hypertensive individuals are pooled, only the treatment effect values from the parallel portions are included. Including these two trials, a total of 652 subjects were studied. Although only one trial was placebo-controlled, all except four reported using procedures to blind blood pressure observers. The duration of follow-up ranged from 1.5 to 24 months; the median was 3 months.

For purposes of presenting outcome data, men and women were treated as separate strata in one trial. Reduction in sodium excretion, net of controls, was 27–171 mmol/24 hr, with a median of 65 mmol. In one
Table 2. Randomized Trials of Sodium Reduction for Normotensive Subjects

<table>
<thead>
<tr>
<th>Author and year published</th>
<th>Sample size</th>
<th>Blinding</th>
<th>Study length (months)</th>
<th>Urinary Na change (meq/day)</th>
<th>BP change (mm Hg) (SEM)</th>
<th>Reported confounding factors</th>
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<td>SBP</td>
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<td></td>
<td>DBP</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skrabal30, 1981</td>
<td>20</td>
<td>NR</td>
<td>0.5</td>
<td>-170</td>
<td>-2.7 (2.36)</td>
<td>Wt(K)</td>
</tr>
<tr>
<td>Cooper31, 1984</td>
<td>113</td>
<td>BP obs</td>
<td>2</td>
<td>-69</td>
<td>-0.6 (0.84)</td>
<td>Wt(K)</td>
</tr>
<tr>
<td>Watt32, 1985(HH)</td>
<td>35</td>
<td>Placebo, BP obs(RZ)</td>
<td>0.9</td>
<td>-74</td>
<td>-1.4 (0.74)</td>
<td>(Wt),K</td>
</tr>
<tr>
<td>Watt32, 1985(LL)</td>
<td>31</td>
<td>Placebo, BP obs(RZ)</td>
<td>1</td>
<td>-60</td>
<td>-0.5 (0.82)</td>
<td>(Wt),K</td>
</tr>
<tr>
<td>Myers33, 1989</td>
<td>172</td>
<td>BP obs</td>
<td>1</td>
<td>-130</td>
<td>-3.5 (1.25)</td>
<td>(Wt),K</td>
</tr>
<tr>
<td>Parallel studies</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Puska22, 1983</td>
<td>19/19</td>
<td>BP obs</td>
<td>0.5</td>
<td>-117</td>
<td>-1.5 (3.32)</td>
<td>Wt,K</td>
</tr>
<tr>
<td>HPTRG34, 1990</td>
<td>174/177</td>
<td>BP obs</td>
<td>36</td>
<td>-16</td>
<td>+0.1 (1.00)</td>
<td>Alc(P/S)</td>
</tr>
</tbody>
</table>

BP, blood pressure; SEM, standard error of mean; SBP, systolic blood pressure; DBP, diastolic blood pressure; NR, not reported; Wt, weight; obs, observer; HH, subjects with parents in the top third of their age-specific BP distribution; RZ, random-zero sphygmomanometer; LL, subjects with parents in the bottom third of their age-specific BP distribution; Alc, alcohol; P/S, polyunsaturated fatty acids/saturated fatty acids ratio; HPTRG, Hypertension Prevention Trial Research Group.

*In parallel study "/" denotes treatment group/control group.
†Parentheses denote controlled factors, and no parentheses denote possible confounders.

Trial29 no urinary data were reported, but intracellular sodium concentration was lower in the intervention group by 22.8% after 12 months of follow-up. Net changes in blood pressure were all in a negative direction, except in the trial of Puska et al22 and for diastolic blood pressure in Maxwell et al.24 The reductions were significant in six trials for systolic and nine trials for diastolic blood pressure. Two trials reported no data on confounders25-29; six provided data on changes in weight, eight on potassium, three on alcohol, and one on fat intake. There were small, significant differences with regard to weight in three trials,22,24,27 potassium in three trials,20-22 and alcohol in one.22

The pooled estimates of blood pressure effects (using sample size weights) and their 95% confidence limits are as follows for systolic and diastolic blood pressure, respectively: crossover trials, -4.33(±1.43)/-1.98(±0.94) mm Hg; parallel trials, -5.28(±1.74)/-3.37(±1.10) mm Hg; and all trials in hypertensive individuals, -4.92(±1.27)/-2.64(±0.82) mm Hg. Using inverse variance weights, the estimates were found to be slightly smaller: -4.04(±1.20)/-2.51(±0.73) mm Hg. Thus, all of the estimates are highly statistically significant.

Trials in Normotensive Subjects

Six trials have reported results for normotensive subjects (Table 2). One of these22 also provided data on hypertensive subjects, which is included above. Another trial32 randomized subjects and analyzed their data by two strata according to parental blood pressure levels, so these are treated as separate trials in the following description. Thus, five of the seven trials used crossover designs,30-32 with a total of 371 subjects. The two parallel trials reported results on 38 and 351 subjects, respectively.30,34 The two trials (strata) of Watt et al32 were placebo-controlled; all of the remaining, except one,30 reported blending of blood pressure observers. The durations of these trials ranged from 2 weeks to 36 months, the latter being the only study longer than 2 months. Except for this trial (the Hypertension Prevention Trial or HPT), net sodium reductions were moderate to large: 60-170 mmol/24 hr. For the HPT, the estimated difference in 24-hour excretion, derived from overnight urine collections, was 16 mmol. All of these trials except the HPT reported lower systolic blood pressure with sodium reduction. (At 6 months of follow-up, a difference of -1.7 mm Hg systolic was also seen in the HPT, when the difference in urinary excretion was 21 mmol/24 hr.) For diastolic blood pressure, four trials observed a decline, and three reported an increase. Among the seven trials, one reported statistically significant decreases in systolic and diastolic blood pressure.33 The pooled results were as follows, for systolic and diastolic blood pressure, respectively, with 95% confidence limits: with sample size weights, -1.70(±0.98)/-0.97(±0.65) mm Hg; and with inverse variance weights, -1.04(±0.76)/-0.17(±0.76) mm Hg. Thus, all of the effects are statistically significant, except for diastolic blood pressure with inverse variance weights.

All Trials

The pooled results for all trials combined, using sample size weights, were as follows, for systolic and diastolic blood pressure and their 95% confidence
limits: $-2.91(\pm 0.76)/-1.60(\pm 0.49)$ mm Hg. However, as suggested above, blood pressure effects were substantially and significantly larger in hypertensive than in normotensive subjects. Among the trials in hypertensive subjects, effects were larger in parallel than crossover trials, although not significantly so. (This analysis could not be meaningfully conducted for the trials in normotensive subjects because there were only two parallel trials in such subjects.) Sample-size weighted regressions of blood pressure effects according to changes in sodium excretion were carried out separately for trials in hypertensive and normotensive subjects. In these models we assumed a regression through the origin (i.e., that absence of a change in sodium intake would be associated with no blood pressure effect, all other factors being equal). All of the slopes were statistically significant. For systolic blood pressure the coefficients were 0.022 ($p=0.003$) mm Hg/mmol/24 hr and 0.057 ($p=0.001$) for normotensive and hypertensive subjects, respectively. For diastolic pressure, they were 0.013 ($p=0.01$) and 0.027 ($p=0.02$), respectively.

By using rank-correlation, the study duration was inversely related to the amount of sodium reduction but had a direct though nonsignificant association with the blood pressure effects across all trials combined. Finally, a graphic examination of effect size against sample size showed some suggestion of publication bias based on systolic blood pressure but little based on diastolic blood pressure. If bias were absent, such a scatterplot should show effect sizes randomly scattered about the horizontal mean effect size line, with more variation for smaller sample sizes. A regression line fit to this scatterplot was not significantly negative for systolic blood pressure or for diastolic blood pressure, even when adjusting for type of study (parallel, crossover) and sodium reduction.

Discussion

Pooled results from 23 randomized trials of sodium reduction, involving 1,536 subjects with blood pressure outcome data, indicate significant blood pressure-lowering effects: approximately 5/3 mm Hg in hypertensive subjects and 2/1 mm Hg in normotensive subjects. These reductions were associated with moderate changes in urinary sodium excretion, 50–100 mmol/day in most trials. This relation is likely to be causal because: 1) internal evidence from the trials suggests that it is not due either to chance or to bias, 2) there is evidence for a dose–response relation, 3) external evidence from other intervention studies is supportive, and 4) the results are consistent with a large body of epidemiological, physiological, and animal experimental evidence.

The pooled estimates of blood pressure effects are all different from the null by 3–8 standard errors, except for diastolic pressure using inverse variance weights. Thus, chance is effectively excluded as an explanation. Only randomized trials were included so that allocation bias is unlikely. Observer bias related to blood pressure measurement was adequately ad-

dressed in most of the trials; seven were placebo-controlled, and there was no indication that smaller effects were seen in this subset. However, these placebo trials were mostly of crossover design, and crossover studies tended to show smaller effects, perhaps because of bias due to undetected carryover effects. For this reason, we have greater confidence in results of parallel trials. The majority of trials were not confounded by concomitant changes in weight or potassium intake. Although data on alcohol, other nutrients, or exercise were seldom provided, of these factors only alcohol at moderately high levels is an established predictor of blood pressure levels. Finally, as for publication bias, there was some visual evidence that small negative trials were underrepresented in the data on systolic blood pressure, but the absence of significant regressions of blood pressure on sample size weakens the evidence.

Evaluation of a dose–response relation across the trials showed significant associations for normotensive and hypertensive subjects, with coefficients tending to be larger for the latter, as expected. However, there was considerable scatter in the data for hypertensive subjects, and when models were run that did not specify a line through the origin, these slopes did not differ significantly from zero. Perhaps a better approach to the dose–response issue is represented by the recent three-arm trial reported by MacGregor et al.16 In this double-blind crossover study using three levels of sodium intake, the relation of blood pressure levels to sodium dose was impressively linear. Because of the importance of the issue, more trials addressing the dose–response relation would be valuable.

Several trials not meeting our pooling criteria are of interest. Although unpublished during the period of this review, the Study of Sodium and Blood Pressure (SNaP) trial13 is a double-blind crossover trial in normotensive adults, reports results quite consistent with this overview (blood pressure changes of 3.6/2.3 mm Hg).36 The trial of Tuck et al13 reported a 3 mm Hg lower mean arterial pressure for sodium reduction compared with controls (not statistically significant), with large concurrent weight reductions in both arms. In a unique trial in infants from birth to 6 months of age, Hofman et al.37 observed a significant 2.1 mm Hg reduction in systolic blood pressure, associated with a 52% lower urine sodium concentration, a finding lending particular support to the notion of primary prevention. In contrast, the Di
tary Intervention Study in Hypertension38 can be seen as a trial of secondary prevention, as the end point was return of hypertension after antihypertensive drugs were withdrawn. In both obese and nonobese strata, the odds of remaining off mediation during a 1-year follow-up was doubled by sodium reduction. Stamler and colleagues39 conducted a similar trial, the Hypertension Control Program, with similar results over a 4-year period; however, the multifactor intervention precluded identification of a specific effect of sodium. Some of the same investi-
gators carried out a primary prevention trial with a similar combined intervention and recently reported a 54% reduction in incidence of hypertension over 5 years of follow-up. A number of trials19,20,41,42 have compared sodium reduction to drug treatment and have generally found similar blood pressure control, but some of these trials are difficult to interpret due to drug treatment in both arms. Finally, there have been three community intervention trials43–45 testing the effects of nutritional education or environmental alteration of available dietary sources of salt. In the one randomized study,43 there was little net change in either sodium intake or blood pressure; in the other two,44,45 moderate-to-large reductions in sodium intake were associated with lower mean blood pressure.

Supporting evidence for the causal nature of the results seen in the randomized trials can be found in other papers of this supplement, which deal with animal models, mechanisms in human subjects, and epidemiological associations within and across populations. With regard to the last, the magnitude of the associations, as estimated in the Intersalt study46 and from other observational studies,47 are similar to those observed in the pooled results of trials in normotensive subjects. Although these effects have been described as clinically "small,"48 the importance of such effects for populations is elucidated elsewhere in this supplement.49 As some lines of evidence suggest, the sodium effect may have been diluted by heterogeneity of response to sodium in the population, with "sensitive" and "resistant" subgroups. However, such characteristics have yet to be shown to be valid and reliable predictors of long-term blood pressure responses to dietary salt.

The trials encompassed by this overview were generally short-term, a few weeks to a few months in duration. There were only four trials of 1 year or longer; among normotensive subjects, the HPT was the only one, and that trial achieved a disappointingly small reduction in sodium intake. The large size of this lengthy trial may have strongly influenced our finding of a lesser sodium reduction over time. In the regression analysis, however, there was also a paradoxical trend toward an increasing blood pressure effect over time.

Although there was a suggestion that the incidence of hypertension was lower in the sodium reduction group of the HPT,44 further trials will be needed to demonstrate that long-term moderation of salt intake is both feasible and effective in preventing hypertension. However, the results presented here add weight to the concept that lower average sodium intake should form part of the strategy to lower blood pressure in the population.

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References


42. Beard TC, Cooke HM, Gray WR, Barge R: Randomized controlled trial of a no-added-sodium diet for mild hypertension. Lancet 1982;2:455-458


47. Elliott P: Observational studies of salt and blood pressure. Hypertension 1991;17(suppl I):I-3-I-8


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