

Sodium Reduction and Weight Loss in the Treatment of Hypertension in Older Persons

A Randomized Controlled Trial of Nonpharmacologic Interventions in the Elderly (TONE)

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Context.—Nonpharmacologic interventions are frequently recommended for treatment of hypertension in the elderly, but there is a paucity of evidence from randomized controlled trials in support of this recommendation.

Objective.—To determine whether weight loss or reduced sodium intake is effective in the treatment of older persons with hypertension.

Design.—Randomized controlled trial.

Participants.—A total of 975 men and women aged 60 to 80 years with systolic blood pressure lower than 145 mm Hg and diastolic blood pressure lower than 85 mm Hg while receiving treatment with a single antihypertensive medication.

Setting.—Four academic health centers.

Intervention.—The 585 obese participants were randomized to reduced sodium intake, weight loss, both, or usual care, and the 390 nonobese participants were randomized to reduced sodium intake or usual care. Withdrawal of antihypertensive medication was attempted after 3 months of intervention.

Main Outcome Measure.—Diagnosis of high blood pressure at 1 or more follow-up visits, or treatment with antihypertensive medication, or a cardiovascular event during follow-up (range, 15-36 months; median, 29 months).

Results.—The combined outcome measure was less frequent among those assigned vs not assigned to reduced sodium intake (relative hazard ratio, 0.69; 95% confidence interval [CI], 0.59-0.81; $P < .001$) and, in obese participants, among those assigned vs not assigned to weight loss (relative hazard ratio, 0.70; 95% CI, 0.57-0.87; $P < .001$). Relative to usual care, hazard ratios among the obese participants were 0.60 (95% CI, 0.45-0.80; $P < .001$) for reduced sodium intake alone, 0.64 (95% CI, 0.49-0.85; $P = .002$) for weight loss alone, and 0.47 (95% CI, 0.35-0.64; $P < .001$) for reduced sodium intake and weight loss combined. The frequency of cardiovascular events during follow-up was similar in each of the 6 treatment groups.

Conclusion.—Reduced sodium intake and weight loss constitute a feasible, effective, and safe nonpharmacologic therapy of hypertension in older persons.

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CLINICAL TRIALS have repeatedly demonstrated that antihypertensive drug therapy reduces the risk of stroke and coronary heart disease.^{1,2} During the past 2 decades, these findings have been confirmed in trials restricted to older patients with hypertension.^{3,4} Despite the proven benefits of antihypertensive medication, increasing interest in nonpharmacologic approaches to prevent and treat hypertension has been prompted by the knowledge that antihypertensive medication reduces rather than eliminates risk⁵; the potential for medication-related adverse effects,⁶ adverse events,⁷ and biochemical changes⁸; the high cost of many antihypertensive medications⁹; and the fact that observational and experimental studies have demonstrated a strong relationship between nutrition and blood pressure (BP).¹⁰

For editorial comment see p 878.

Clinical trials have demonstrated that weight loss and sodium reduction are effective in the treatment of middle-aged patients with hypertension.¹¹ These interventions are also recommended for the treatment of hypertension in older persons.⁴ Observational data support the latter approach,¹² but the experimental basis for the recommendation is limited.¹³ With this in mind, we conducted the Trial of Nonpharmacologic Interventions in the Elderly (TONE) to determine the feasibility, efficacy, and safety of sodium reduction and weight loss in older persons with hypertension.

METHODS

The TONE was conducted as an investigator-initiated study by scientists at 4 academic health centers in collaboration

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Lacy); Center for Biostatistics and Epidemiology, Pennsylvania State University College of Medicine, Hershey (Dr Kumanyika); and Clinical Applications and Prevention Program, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md (Dr Cutler). Dr Kumanyika is now with the Department of Nutrition and Dietetics, University of Illinois at Chicago. A complete list of the participating institutions and principal staff of the TONE Collaborative Research Group is given at the end of this article.

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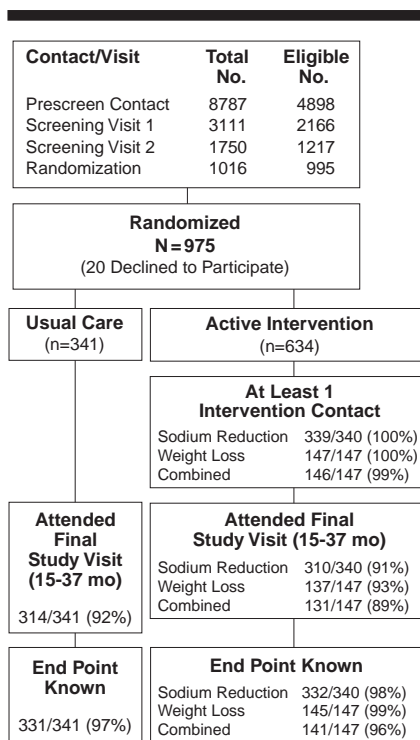


Figure 1.—Participation in screening and follow-up in the Trial of Nonpharmacologic Interventions in the Elderly.

with colleagues at the National Institute on Aging and the National Heart, Lung, and Blood Institute. The trial protocol was approved by institutional review boards at each of the participating centers, and written informed consent was obtained from all potential study participants. Oversight of the trial was also provided by an external Data and Safety Monitoring Board appointed by staff at the National Institute on Aging and the National Heart, Lung, and Blood Institute.

A description of the TONE design and methods has been published.¹⁴ Briefly, the trial was designed to test the following 2 hypotheses: (1) Prescribing a sodium reduction program for obese and nonobese older patients with hypertension reduces the rate of primary end points following the withdrawal of BP-lowering medications. (2) Prescribing a weight loss program for obese individuals reduces the rate of primary end points following the withdrawal of BP-lowering medications. The target sample size of 900 participants was designed to provide at least 80% statistical power, with a type I error of 0.05, to detect a 30% reduction in the rate of occurrence of the primary end point for those assigned to weight loss and a 25% reduction in the corresponding rate for those assigned to sodium reduction over an average follow-up of 30 months. The study was conducted as a multicenter, controlled clinical trial in which participants were ran-

domly assigned to 1 of 6 treatment cells across 2 strata of body weight. Using a 2 × 2 factorial design, obese participants (body mass index ≥ 27.8 kg/m² for men and ≥ 27.3 kg/m² for women) were randomized to one of the following groups: sodium reduction, weight loss, sodium reduction and weight loss combined, or usual care. Nonobese participants were randomized to either sodium reduction or usual care. Using a computer program, each participant's eligibility was confirmed prior to enrollment in the trial. Randomization was stratified by clinic and weight status to provide an even distribution of participants among the treatment groups at each site, and blocking of variable length (2, 4, and 8) was used to ensure temporal balance.

Eligibility and Recruitment

Trial participants were men and women 60 to 80 years of age who had an average systolic BP less than 145 mm Hg and diastolic BP less than 85 mm Hg (mean of 9 measurements, 3 at each of 3 visits) while taking a single antihypertensive medication or a single combination regimen consisting of a diuretic agent and a nondiuretic agent. If individuals were taking 2 antihypertensive medications, they were enrolled if they could be successfully weaned to 1 antihypertensive medication during the screening phase. Trial eligibility was assessed during a prescreening contact, 2 subsequent screening visits (separated by 7-30 days), and a randomization visit within 7 to 60 days of the second screening visit. Inclusion criteria were the willingness of an enrollee and his or her physician to participate, stable health, independence in activities of daily living, and a presumed capacity to alter diet and physical activity in accordance with the requirements of any TONE intervention. Exclusion criteria included history of a heart attack or stroke within the preceding 6 months, current angina pectoris, congestive heart failure, insulin-dependent diabetes mellitus, serious mental or physical illness, unexplained or involuntary weight loss of 4.5 kg or greater during the previous year, a body mass index less than 21 kg/m² in men or women or greater than 33 kg/m² in men or greater than 37 kg/m² in women, presumed inability to comply with the protocol, hypercreatinemia (>152 μ mol/L [>2.0 mg/dL]), hyperkalemia (>5.5 mmol/L), hyperglycemia (nonfasting level >14.4 mmol/L [>260 mg/dL]), and anemia (hemoglobin level <110 g/L).

Participants were enrolled between August 30, 1992, and June 27, 1994. Details of the recruitment experience have been published.¹⁵ Briefly, 995 of 8787 adults who were initially contacted met the eligibility criteria for participation in the trial (Figure 1). Twenty of the 995

eligible candidates declined enrollment, based on the anticipated burden of the intervention and data collection requirements of the protocol. The remaining 975 (585 obese and 390 nonobese) were assigned to active intervention (sodium reduction, weight loss, or sodium reduction and weight loss combined) or usual care.

Intervention Goals and Methods

The goal for sodium reduction, both alone and combined with weight loss, was achieving and maintaining a 24-hour dietary sodium intake of 80 mmol (1800 mg) or less (as measured by 24-hour urine collection). The goal for weight loss, both alone and combined with sodium reduction, was achieving and maintaining a weight loss of 4.5 kg (10 lb) or greater. The usual care groups received no study-related counseling in lifestyle change techniques but were invited to meetings on topics unrelated to the goals of the trial. The active intervention program was based in part on experience in previous trials that improved BP control by focusing on dietary and lifestyle change.^{11,16} Social action theory and other approaches that enhance understanding and achievement of behavior change were incorporated into the interventions.¹⁷

Nutritionists and exercise counselors with experience in lifestyle change techniques were responsible for implementation of the active interventions. Using a combination of small group and individual meetings, they advised participants on ways to change eating patterns (for all active interventions) and increase physical activity (for weight loss with or without sodium reduction). In addition, they monitored individual and group progress at frequent intervals and helped participants adapt the TONE lifestyle recommendations to their individual circumstances. Each active intervention consisted of 3 phases (intensive, extended, and maintenance) with similar numbers of contacts. The primary goal during the initial 4-month intensive phase was to provide participants with the core knowledge and behavior skills necessary to achieve and maintain their desired reductions in sodium intake and body weight. During the next 4 months (extended phase), participants focused on problem solving and prevention of relapse. Thereafter (maintenance phase), continued attempts were made to maintain participant interest in the intervention program and to reengage those who were less active in practicing behavior change techniques. The frequency of scheduled intervention contacts varied from weekly during the intensive phase to biweekly during the extended phase and monthly during the maintenance phase. With time, however, increasing attempts were made to customize the

intervention program to meet the needs of individual participants.

Withdrawal of Antihypertensive Medication

Withdrawal of antihypertensive medication was a goal for all study participants. To increase the likelihood of success, the process of weaning participants was initiated 90 days (range, 76-104 days) after the first group intervention session. A corresponding time was used for an attempt to wean those randomized to usual care. Drug withdrawal was attempted in all participants who remained free of trial end points at the appointed time during follow-up, provided the participant and his or her primary care provider were in agreement. The medication withdrawal process was standardized across the 4 clinical centers and used drug-specific tapering regimens. Participants were evaluated at weekly intervals during tapering of their medication. After therapy with antihypertensive medication was stopped, participants had 3 additional bi-weekly visits to confirm that their systolic BP remained less than 150 mm Hg and their diastolic BP remained less than 90 mm Hg.

Data Collection Procedures

Study data were collected at the 4 eligibility and randomization contacts and at quarterly visits during follow-up from August 1992 until December 1995. Follow-up ranged from 15 to 36 months (median, 29 months). Outcome information was obtained by staff members who were blind to the participants' intervention assignment, at different times and different locations from those used for the intervention visits. Participants were instructed not to reveal their intervention assignment to the data collection staff. Intervention staff members were masked with respect to the participants' BP and drug withdrawal status. When questioned at the final follow-up visit, the data collectors guessed the correct treatment assignment in 31% of the obese participants (compared with an expected rate of 25% on the basis of chance) and in 45% of the nonobese participants (compared with an expected rate of 50% on the basis of chance).

Detailed information was collected at baseline, and an interval medical history (including medication information and symptoms) and measurements of body weight and BP were obtained quarterly. Additional BP safety monitoring visits were performed during drug withdrawal and whenever a participant's mean BP was elevated (systolic BP \geq 150 mm Hg or diastolic BP \geq 90 mm Hg) at a clinic visit. The BP was measured with subjects in the seated position by trained observers us-

ing Hawksley random-zero sphygmomanometers.¹⁸ Systolic BP was defined as that pressure at which the first Korotkoff sound was heard, and diastolic BP as that pressure at which the fifth Korotkoff sound could no longer be heard. Twenty-four-hour urine collections were obtained twice during the enrollment period and at the 9-month, 18-month, and final closeout visits for measurement of sodium content. For each participant, a 24-hour dietary recall history was obtained by a trained technician twice during enrollment, at the 9- and 12-month follow-up visits, and every 6 months thereafter. Nutrient calculations were performed using Minnesota Nutrition Data System software, developed by the Nutrition Coordinating Center at the University of Minnesota, Minneapolis (Food Database, version 6A; Nutrient Database, version 21).¹⁹ The modified Rose questionnaire was used to assist in screening for angina pectoris and myocardial infarction.²⁰ Urinary electrolyte levels were analyzed by flame photometry.²¹

Presumed adverse events were assessed using a standardized approach that included questioning of participants, family members, and physicians and a review of physician records. Each event was initially classified by a TONE study physician at the participant's clinical center and was subsequently reviewed for accuracy by members of a trialwide adverse events subcommittee who were blind to treatment assignment. Events were classified by type (myocardial infarction, stroke, etc) and time of occurrence (before, during, or after attempted antihypertensive drug withdrawal).

Primary End Point

The primary end point was defined as occurrence of high BP at 1 or more TONE study visits following attempted withdrawal of antihypertensive medication, treatment with an antihypertensive medication, or occurrence of a clinical cardiovascular disease complication during follow-up (myocardial infarction, angina, congestive heart failure, stroke, coronary artery bypass surgery, or coronary artery angioplasty). The decision to continue or restart treatment with antihypertensive medication was based on an inability to discontinue the participant's therapy with BP-lowering medication during drug withdrawal, measurement of high BP at 1 or more of the study follow-up visits following drug withdrawal, or a decision by the participant's physician or the participant. High BP during study follow-up visits was defined as a systolic BP of 190 mm Hg or greater or a diastolic BP of 110 mm Hg or greater at a single visit (average of 3 BP measurements), a mean systolic BP of 170 mm Hg or greater or a diastolic BP of 100 mm Hg or greater over

2 sequential visits (average of 6 BP measurements), or a mean systolic BP of 150 mm Hg or greater or a diastolic BP of 90 mm Hg or greater over 3 sequential visits (average of 9 BP measurements). A committee masked to intervention assignment confirmed the presence of all trial end points other than those based on study BP measurements.

Statistical Considerations

We used analysis of variance tests for continuous variables and χ^2 tests for discrete variables to highlight comparisons for which the randomization algorithm yielded a chance imbalance. Outcome analyses were conducted on an intention-to-treat basis using 2-sided significance levels of .05. Factors used to stratify randomization (clinical center and weight status) were included as covariates in the primary analyses. The primary hypotheses were tested by comparing the distribution of times until first occurrence of an end point (1) in participants assigned to sodium reduction (either alone or combined with weight loss) vs participants assigned to no sodium reduction (usual care for all participants or weight loss alone for obese participants) and (2) in obese participants assigned to weight loss (weight loss with or without sodium reduction) vs obese participants assigned to no weight loss (usual care or sodium reduction alone). Time to event was measured from the end of antihypertensive medication withdrawal to the occurrence of an end point. Treatment was considered a failure in participants who met an end-point criterion prior to or during antihypertensive medication withdrawal; these end points were included in all primary analyses. Kaplan-Meier curves were used to compare times to end points, and each hypothesis was tested using Cox proportional hazards regression models. Relative hazard ratios were used to summarize the impact of treatment assignment on the rate of end points over time. No statistically significant interaction was observed between the effects of sodium reduction and weight loss ($P=.34$).

Intervention-related BP changes from baseline to follow-up were assessed using Laird-Ware models to average BPs after intervention assignment and prior to drug withdrawal.²² Maximum likelihood techniques were used to generate these estimates. Likelihood ratio statistics and SEs were used to perform inference testing (SAS/STAT software, release 6.06, SAS Institute Inc, Cary, NC). In secondary analyses, among the subset of participants for whom antihypertensive medication was successfully withdrawn through closeout ($n=340$), BP changes from baseline were obtained by subtracting BP readings obtained at the

Table 1.—Baseline Characteristics of TONE Participants*

Characteristic	Overweight (n = 585)				Not Overweight (n = 390)	
	Sodium Reduction (n = 144)	Weight Loss (n = 147)	Combined Intervention (n = 147)	Usual Care (n = 147)	Sodium Reduction (n = 196)	Usual Care (n = 194)
Age, y†	66 (4)	66 (5)	66 (4)	66 (4)	67 (5)	67 (5)
60-69 y, %	83	75	80	80	74	76
Female, %	56	51	44	59	44	38
Race, %						
White	70	73	76	68	83	81
African American	30	26	24	32	16	18
High school graduate, %	87	87	91	85	92	90
Current smoker, %	5	3	7	5	6	7
≥1 Alcoholic drink/week, %	36	35	43	32	46	46
Body weight, kg†	88 (11)	87 (10)	86 (10)	86 (10)	72 (10)	73 (9)
Women	82 (9)	82 (9)	83 (9)	86 (8)	65 (7)	65 (7)
Men	93 (10)	92 (9)	91 (9)	91 (9)	78 (8)	78 (7)
Body mass index, kg/m ² †	31.2 (2.5)	31.0 (2.3)	31.2 (2.0)	31.3 (2.3)	25.4 (1.7)	25.5 (1.7)
Women	31.9 (2.6)	31.7 (2.8)	31.8 (2.6)	31.6 (2.7)	24.9 (1.7)	25.1 (1.7)
Men	30.0 (1.8)	30.3 (1.6)	30.7 (1.6)	30.2 (1.6)	25.6 (1.8)	25.7 (1.8)
Urinary sodium excretion, mmol/d†	158 (55)	157 (55)	155 (55)	155 (58)	136 (49)	138 (51)
Women	137 (51)	140 (45)	135 (51)	140 (49)	113 (35)	115 (46)
Men	178 (50)	175 (59)	176 (51)	176 (63)	154 (52)	151 (49)
Urinary potassium excretion, mmol/d†	58 (18)	60 (18)	58 (20)	59 (25)	63 (23)	60 (21)
Women	51 (15)	54 (15)	51 (17)	51 (17)	54 (19)	53 (19)
Men	67 (21)	66 (19)	63 (18)	70 (30)	70 (24)	64 (21)
Systolic blood pressure, mm Hg†	129 (9)	130 (9)	129 (9)	128 (10)	129 (9)	128 (9)
Diastolic blood pressure, mm Hg†	72 (8)	72 (8)	72 (7)	72 (7)	72 (7)	71 (7)
Duration of treatment with antihypertensive medications, y†	11.9 (9.3)	11.3 (9.2)	11.9 (9.5)	11.6 (8.0)	11.7 (9.0)	11.7 (8.8)

*TONE indicates Trial of Nonpharmacologic Interventions in the Elderly.
†Values are mean (SD).

final closeout visit from BP readings at entry into the trial. Changes from baseline in urinary sodium excretion levels and body weight were also calculated for this cohort. Rates of events per 100 randomized participants were calculated. Contrasts among the proportions of participants experiencing 1 or more events were evaluated using the Fisher exact test.

RESULTS

Baseline Characteristics

The mean (SD) age of the entire trial cohort was 66.5 (4.6) years, with 78% between 60 and 69 years; 24% of the participants were African American. Baseline characteristics were similar in each group (Table 1), except that there were slightly more men in the sodium reduction and weight loss combined group (56% [95% confidence interval (CI), 46%-64%]) than in the 3 other groups in the obese stratum (45% [95% CI, 40%-50%]). At entry, 32.2% of the participants were being treated with a diuretic inhibitor, 27.9% with a calcium channel blocker, 21.5% with an angiotensin-converting enzyme, 10.9% with a β -blocker, and 7.5% with another form of monotherapy.

Follow-up Participation Rates

Attendance rates at the 9-, 18-, and 30-month follow-up visits were 91% (n=884), 86% (n=829), and 86% (n=441), respec-

tively. Among those attending these visits, data collection was 100% complete for BP and body weight measurements and 98% (n=866), 96% (n=796), and 95% (n=419) complete, respectively, for 24-hour urine collections. At the final study visit, 91% (n=310), 93% (n=137), 89% (n=131), and 92% (n=314) of those assigned to sodium reduction, weight loss, sodium reduction and weight loss combined, and usual care, respectively, participated in collection of study data (Figure 1), and end-point status was ascertained at closeout for 98% (n=332), 99% (n=145), 96% (n=141), and 97% (n=331).

Intervention Results

The mean change in urinary sodium excretion was greater for those assigned vs not assigned to sodium reduction (net reduction, 46.6 [95% CI, 31.6-61.6], 49.3 [95% CI, 31.6-67.0], and 39.5 [95% CI, 25.0-54.0] mmol/d at the 9-, 18-, and 30-month follow-up visits, respectively; $P<.001$ for all) (Figure 2). Of those providing samples at the 9-month follow-up visit, 36% of the 443 participants assigned to sodium reduction vs 11% of the 424 participants not assigned to sodium reduction had a urinary sodium excretion level that met the intervention goal of 80 mmol/d or less. The corresponding percentages at the 18- and 30-month follow-up visits were 40% vs 12% and 38% vs 10%, respectively. Among the obese participants, mean 24-hour sodium excre-

tion was 28.7 mmol (95% CI, 19.5-37.9) less in those who were assigned to sodium reduction alone than in their counterparts assigned to sodium reduction and weight loss combined. This difference in urinary sodium excretion was consistent across the 9-month, 18-month, and final visits ($P=.86$).

The average reduction in weight for the participants assigned to weight loss was approximately 3.5 to 4.5 kg, resulting in net reductions of 3.8 (95% CI, 3.1-4.5), 3.6 (95% CI, 2.8-4.3), and 3.9 (95% CI, 2.7-5.1) kg at the 9-, 18-, and 30-month follow-up visits, respectively ($P<.001$ for all), vs an average 0.9-kg reduction (95% CI, 0.4-1.3) for those not assigned to weight loss (Figure 3). The mean weight loss was 1.0 kg (95% CI, -0.1 to 2.0 kg) greater in those assigned to weight loss alone than in those assigned to sodium reduction and weight loss combined across these time points. For those attending the 9-month follow-up visit, 47% of the 275 participants assigned to weight loss compared with 13% of the 260 participants not assigned to weight loss achieved the intervention goal of weight loss of 4.5 kg or greater. The corresponding percentages among those attending the 18- and 30-month follow-up visits were 42% vs 11% and 44% vs 13%, respectively.

Primary End-Point Results

The median interval from the start of intervention to withdrawal of antihyperten-

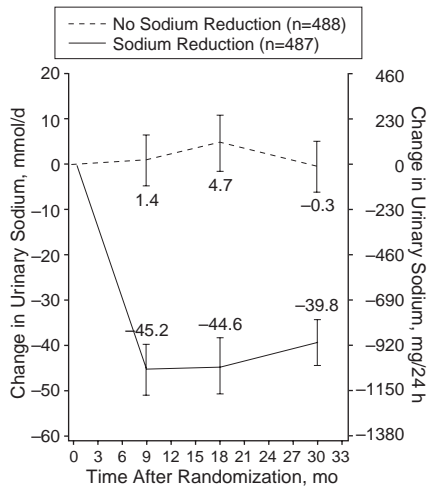


Figure 2.—Mean change in 24-hour urinary sodium excretion among the 487 participants who were and the 488 who were not assigned to the reduced sodium intake intervention of the Trial of Nonpharmacologic Interventions in the Elderly. Error bars indicate SEMs. The numbers used in the figure are given in millimoles per day.

sive drug therapy was 3.2 months and was similar for each active intervention. Antihypertensive drug therapy could be stopped in 86.8% of those assigned to usual care in 92.6% assigned to sodium reduction alone, in 93.2% assigned to weight loss alone, and in 93.2% assigned to weight loss and sodium reduction combined. The percentage of trial participants remaining free of trial end points (high BP at a TONE follow-up visit, continued use or resumption of antihypertensive medication, or a cardiovascular disease event) declined progressively during follow-up but remained consistently higher in those assigned vs not assigned to sodium reduction (Figure 4). Over the entire period of follow-up, the incidence rate for end points was only 0.69 (95% CI, 0.59-0.81) as large among those randomized to sodium reduction as among those not assigned to sodium reduction ($P<.001$). Kaplan-Meier estimation (mean) indicated that 38% (95% CI, 32%-44%) of those assigned to sodium reduction compared with 24% (19%-30%) of those not assigned to sodium reduction remained off antihypertensive medication with a BP less than 150/90 mm Hg and no evidence of a cardiovascular disease event 30 months after attempted withdrawal of antihypertensive drug therapy. The hazard ratio for trial end points during follow-up in the 2 subgroups of obese patients in whom the efficacy of sodium reduction was evaluated was 0.60 (95% CI, 0.45-0.81) for those assigned to sodium reduction alone (n=144) compared with usual care (n=147) and 0.74 (95% CI, 0.54-1.02) for those assigned to sodium reduction and weight loss combined (n=147) vs weight loss alone (n=147). The corresponding es-

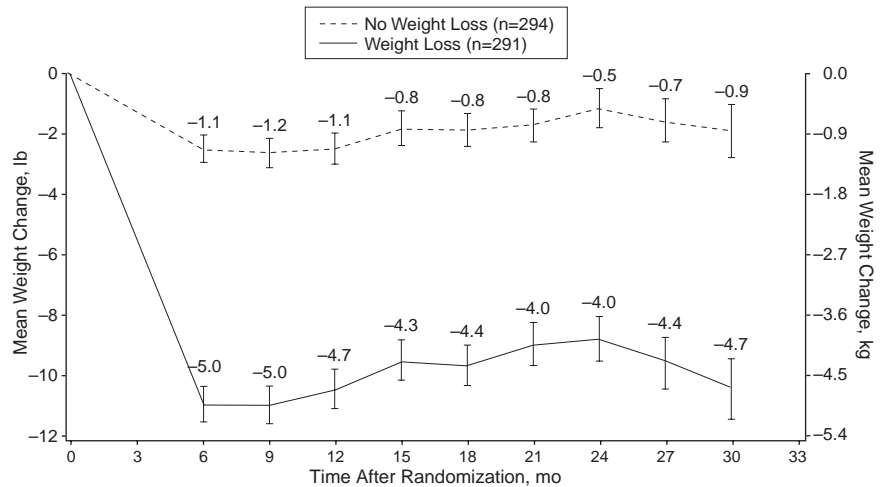


Figure 3.—Mean change in body weight among the 294 obese participants who were and the 291 who were not assigned to the weight loss intervention of the Trial of Nonpharmacologic Interventions in the Elderly. Error bars indicate SEMs. The numbers used in the figure are given in kilograms.

timate for comparison of those assigned to sodium reduction alone (n=196) vs usual care (n=194) among nonobese patients was 0.75 (95% CI, 0.59-0.95).

Among obese participants, the hazard ratio for end points was only 0.70 (95% CI, 0.57-0.87) among those randomized to weight loss compared with those not assigned to weight loss ($P=.001$); 39% (95% CI, 32%-46%) of those randomized to weight loss compared with 26% (95% CI, 19%-34%) of those not randomized to weight loss remained free of trial end points 30 months after attempted withdrawal of antihypertensive drug therapy (Figure 5). The hazard ratio for trial end points was 0.65 (95% CI, 0.50-0.85) for those assigned to weight loss alone (n=147) compared with usual care (n=147) and 0.79 (95% CI, 0.57-1.09) for those assigned to weight loss and sodium reduction combined (n=147) vs sodium reduction alone (n=144).

Throughout follow-up, the percentage of obese participants who remained free of end points was significantly greater in each of the 3 active intervention groups than in the usual care group (Figure 6). The hazard ratios for the 3 active interventions (relative to usual care) were 0.60 (95% CI, 0.45-0.80) ($P<.001$) for sodium reduction, 0.64 (95% CI, 0.49-0.85) ($P=.002$) for weight loss, and 0.47 (95% CI, 0.35-0.64) ($P<.001$) for sodium reduction and weight loss combined. The relative effect of the combined intervention did not differ significantly from the product of the separate effects of sodium reduction and weight loss ($P=.34$). Based on Kaplan-Meier estimates, the proportions of randomized participants projected to be free of end points at 30 months were 34% (95% CI, 25%-43%) for sodium reduction, 37% (95% CI, 28%-46%) for weight loss, 44% (95% CI, 32%-55%) for sodium reduction

and weight loss combined, and 16% (95% CI, 5%-27%) for usual care.

In an analysis limited to the 886 participants in whom medication was successfully tapered, the hazard ratio for experiencing a trial end point, relative to usual care, was 0.68 (95% CI, 0.54-0.82) for those assigned to sodium reduction, 0.75 (95% CI, 0.57-0.93) for those assigned to weight loss, and 0.55 (95% CI, 0.41-0.69) for those assigned to sodium reduction and weight loss combined.

BP Results

Systolic and diastolic BP did not differ across the treatment groups at baseline, but at the last visit before medication withdrawal was attempted, the mean systolic and diastolic BP values were significantly lower in all the intervention groups than in the usual care group (Table 2). Among the 328 participants who were still off antihypertensive medication at the final study visit, average systolic and diastolic BPs were 131 and 74 mm Hg, respectively, for the 127 participants assigned to sodium reduction, 133 and 75 mm Hg for the 52 assigned to weight loss, 130 and 73 mm Hg for the 66 assigned to sodium reduction and weight loss combined, and 134 and 75 mm Hg for the 83 assigned to usual care. The corresponding percentages for BP control at the goal of less than 140/90 mm Hg recommended by the fifth Joint National Committee for Detection, Evaluation, and Treatment of High Blood Pressure¹⁴ were 71%, 63%, 73%, and 65%, respectively.

Adverse Events and Safety of Drug Withdrawal

A total of 145 cardiovascular disease events were identified during follow-up in the 4 randomized groups (Table 3). Of these, 4 were strokes, 17 were transient

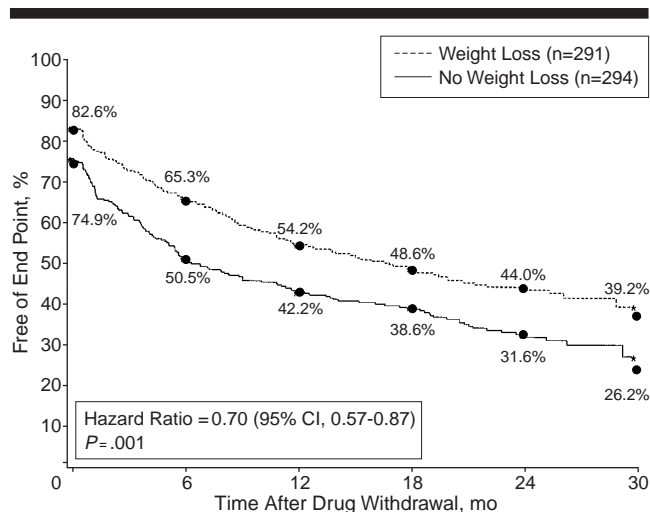
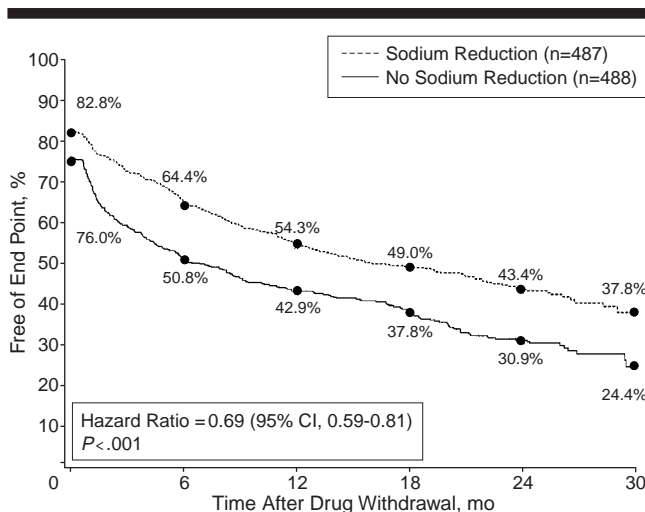


Figure 4.—Percentages of the 487 participants who were and the 488 who were not assigned to the reduced sodium intake intervention who remained free of cardiovascular events and high blood pressure and did not have an antihypertensive agent prescribed during follow-up. CI indicates confidence interval.

Figure 5.—Percentages of the 294 obese participants who were and the 291 who were not assigned to the weight loss intervention who remained free of cardiovascular events and high blood pressure and did not have an antihypertensive agent prescribed during follow-up. CI indicates confidence interval.

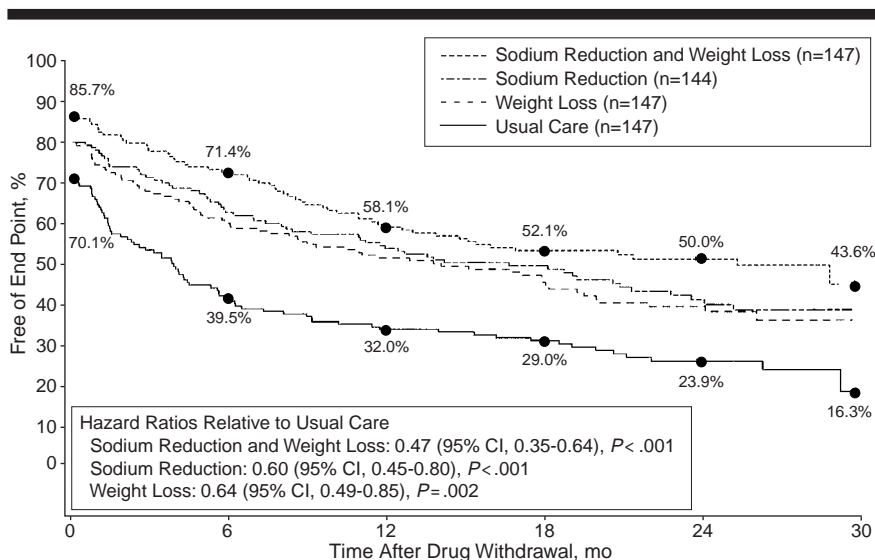


Figure 6.—Percentages of the 144 participants assigned to reduced sodium intake, the 147 assigned to weight loss, the 147 assigned to reduced sodium intake and weight loss combined, and the 147 assigned to usual care (no lifestyle intervention) who remained free of cardiovascular events and high blood pressure and did not have an antihypertensive agent prescribed during follow-up. CI indicates confidence interval.

ischemic attacks, 10 were myocardial infarctions, 49 were cases of angina pectoris, 6 were cases of congestive heart failure, 13 were arrhythmias, and 46 were other cardiac events. There were no significant differences in the rates of cardiovascular disease events during follow-up among those assigned vs not assigned to either sodium reduction or weight loss or among the single cells of the partial factorial design. Thirty-three events occurred during the interval between randomization and attempted drug withdrawal (mean time from randomization to event, 3.6 months), 58 during drug withdrawal or the period during which participants were off their antihyperten-

sive medication (mean time from randomization to event, 14.0 months), and 36 following resumption of antihypertensive medication (mean time from randomization to event, 15.9 months). Event rates per 100 person-years were similar for the 3 periods (7.8, 5.4, and 5.9, respectively, in the obese group and 5.8, 6.1, and 7.4 in the nonobese group). Multivariate prediction models identified age and BP during drug withdrawal as independent predictors of time to a first event. Headache was the most common noncardiovascular disease event (data not shown), noted in 137 participants. Sodium reduction was associated with a significant decrease in the rate of headaches among those assigned

to any vs no intervention involving sodium reduction (9.7 vs 16.8 per 100 randomized participants, $P < .001$).

For each randomized group, the reported average intake of micronutrients was at least two thirds of the recommended daily allowance at baseline and remained similar throughout follow-up. Eleven participants, 3 of whom had been assigned to a weight loss intervention group, had a weight loss pattern that triggered a weight-related safety alert (weight loss ≥ 9 kg or a decline in body mass index to < 25 kg/m²). In 2 of these 11 participants, the weight loss occurred during chemotherapy (for breast cancer in one and pancreatic cancer in the other), and in 2 others the weight loss was caused by an inappropriate self-imposed dietary restriction. Specific counseling was deemed necessary in 7 of the 11 participants. None experienced a clinical cardiovascular complication.

COMMENT

The TONE study is the first trial of sufficient size and duration to provide convincing evidence regarding the feasibility, efficacy, and safety of dietary lifestyle interventions as a means to control high BP and decrease the need for antihypertensive medication in older patients with hypertension.

Our findings are consistent with a large body of observational data linking salt consumption and obesity with higher levels of BP¹⁰ and demonstrating BP lowering following salt reduction and weight loss at younger ages.^{11,16,23} The impressive results in TONE were obtained in the context of moderate reductions in sodium consumption and body weight. Specifically, the approximately 30% de-

crease in need for antihypertensive medication was achieved by reducing average sodium intake about 40 mmol/d or by reducing average body weight about 3.5 kg, indicating that it is feasible to achieve and maintain moderate decreases in sodium intake and body weight in older patients with hypertension and that such changes lead to clinically important reductions in the need for antihypertensive medication.

Evaluation of combined sodium reduction and weight loss was not a primary goal, but it was instructive that those assigned to the combined intervention group were the most successful in maintaining satisfactory BP control after withdrawal of their antihypertensive medication. This finding suggests that the mechanisms of action by which sodium reduction and weight loss lower BP in older persons are different and that combined sodium reduction and weight loss are in

order for older persons who are obese and have hypertension. In other studies, combined sodium reduction and weight loss interventions have been less effective than was the case in TONE.^{23,24} Our success may have been due in part to a greater ability to achieve and maintain behavioral interventions in older persons with a motivation to reduce their dependence on antihypertensive medication.

Safety is an important consideration with any intervention, and the TONE results are reassuring. Compared with usual care, the active interventions were well tolerated, and there was no suggestion that drug withdrawal was associated with excess morbidity or mortality. Likewise, there was limited evidence of adverse effects on other nutrients associated with any of the active interventions and limited evidence of excess weight loss in those assigned to weight loss. Our nutrition safety experience is consistent with the findings in other BP-related nutrition intervention trials.^{11,16} It is also in keeping with the knowledge that the sodium intake of our participants was far in excess of physiologic need and considerably higher than that of populations with a lower average BP and lower prevalence of hypertension.²⁵ A lower level of sodium intake was related to increased myocardial infarction in a work-site cohort study of men being treated for hypertension.²⁶ However, this report must be interpreted with caution because many potential confounders of the association were either unmeasured or imprecisely measured.²⁷ Moreover, an opposite trend was observed in women, and a subsequent analysis failed to confirm the association in the Multiple Risk Factor Intervention Trial cohort.²⁸ Given the experience in observational studies and in clinical trials, there is little reason to expect adverse cardiovascular disease effects as a result of weight loss in those with a high body weight.^{29,30} Indeed, weight loss in patients with hypertension has not only reduced BP but has also produced beneficial effects on blood lipid levels and left ventricular mass.^{31,32}

The potential for adverse effects includes the possibility of dietary inadequacy, interference with social aspects of eating, loss of lean body mass, loss of bone density, and musculoskeletal injury.³³ We included physical activity as a component of our weight loss program and attempted to avoid excessive dietary habits and excessive weight loss among participants to reduce the potential for such complications.

Weight loss was found to be a predictor of hip fracture among women aged 65 years or older by the Study of Osteoporotic Factors Research Group.³⁴ It is uncertain whether these findings apply to planned weight loss programs, such as TONE, that include increased physical activity and careful monitoring, but this is being addressed in a TONE substudy in which dual-energy x-ray absorption measurements were obtained at baseline and follow-up at 2 of the 4 clinical centers. Findings of observational studies suggest that reducing sodium intake may improve bone density.³⁵

The TONE program was not designed to assess the benefits of combined antihypertensive medication and lifestyle modification, but findings of the Hypertension Control Program and Treatment of Mild Hypertension Study suggest that combined pharmacologic and lifestyle intervention may be superior to lifestyle modification alone.^{11,36} Other promising nonpharmacologic interventions in older patients with hypertension should be assessed, especially increased physical activity,³⁷ potassium supplementation,³⁸ and modification of dietary patterns.³⁹

The TONE results have important implications both for public health professionals and for clinical practitioners. The finding that older patients with hypertension were able to make and sustain lifestyle changes suggests that deleterious lifestyle habits, such as excessive intake of salt or calories and physical inactivity, can be modified, even though they may have been practiced over many years. This observation, in combination with the impressive effects of these lifestyle changes on

Table 2.—Baseline Blood Pressure and Change From Baseline to Last Visit Prior to Attempted Medication Withdrawal

Intervention Assignment	Blood Pressure, mm Hg	
	Baseline (Mean ± SD)	Change* (Mean ± SE)
Sodium reduction (n = 340)		(n = 331)
Systolic	127.3 ± 11.8	-3.4 ± 0.8
Diastolic	71.3 ± 8.4	-1.9 ± 0.5
Weight loss (n = 147)		(n = 144)
Systolic	128.6 ± 10.8	-4.0 ± 1.3
Diastolic	70.7 ± 9.6	-1.1 ± 0.8
Combined intervention (n = 147)		(n = 145)
Systolic	127.6 ± 12.1	-5.3 ± 1.2
Diastolic	71.3 ± 8.9	-3.4 ± 0.8
Usual care (n = 341)		(n = 333)
Systolic	127.7 ± 12.1	-0.8 ± 0.8
Diastolic	71.5 ± 8.5	-0.8 ± 0.5
Total (N = 975)		(N = 953)
Systolic	127.5 ± 11.8	-3.5 ± 0.5
Diastolic	71.3 ± 8.7	-1.9 ± 0.3

*Change in blood pressure was calculated for the 953 participants who attended at least 1 study visit after randomization. $P < .001$ for all comparisons between the usual care and intervention groups for systolic or diastolic blood pressure.

Table 3.—Cardiovascular Events During Follow-up of TONE Participants According to Intervention Assignment*

Type of Adverse Event	No. (Rate/100 Participants)				P†	
	Sodium Reduction (n = 370)	Weight Loss (n = 147)	Combined Sodium Reduction and Weight Loss (n = 147)	Usual Care (n = 371)	Sodium Reduction vs No Sodium Reduction	Weight Loss vs No Weight Loss‡
Stroke	1 (0.3)	0 (0.0)	1 (0.7)	2 (0.6)	>.99	>.99
Transient ischemic attack	8 (2.3)	0 (0.0)	1 (0.7)	8 (2.3)	.80	.37
Myocardial infarction	2 (0.6)	2 (1.4)	2 (1.4)	4 (1.2)	>.99	>.99
Angina	10 (2.9)	10 (6.8)	10 (6.8)	19 (5.6)	.16	.07
Congestive heart failure	4 (1.2)	1 (0.7)	0 (0.0)	1 (0.3)	>.99	>.99
Arrhythmia	6 (1.8)	2 (1.4)	1 (0.7)	4 (1.2)	.58	.72
Other	13 (3.8)	6 (4.1)	8 (5.4)	19 (5.6)	.44	>.99
Total cardiovascular	44 (12.9)	21 (14.3)	23 (15.6)	57 (16.7)	.24	.35

*TONE indicates Trial of Nonpharmacologic Interventions in the Elderly.

†By the Fisher exact test comparing rates of participants who experienced at least 1 event.

‡Overweight participants only.

BP control, warrants implementation of programs designed to help older patients with hypertension reduce their intake of salt and to facilitate weight loss in those who are obese. The widespread availability of senior center and retirement community eating programs as well as meal-delivery programs makes it feasible to achieve a moderate reduction in sodium intake through passive means, by changing food production and procurement procedures without major changes in the food supply. Achievement of a more meaningful reduction in sodium intake, however, will require enhanced availability of foods that have less sodium added during processing and more widespread access to dietary and behavioral intervention counseling programs. Health maintenance organizations, integrated health systems, senior centers, and retirement communities could make weight loss intervention programs similar to those implemented in TONE more readily available to seniors. Health care providers should support the active involvement of eligible patients in such pro-

grams as a means to improve BP control and reduce the need for antihypertensive medication.^{4,6}

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Maternal Smoking and Inhibition of Fetal Growth Factor

To the Editor.—Maternal smoking during pregnancy often results in smaller than normal neonates.¹ The mechanisms by which maternal smoking impairs fetal growth are as yet undefined. Insulinlike growth factor I (IGF-I) is an essential regulator of fetal growth² and may be a target for the growth-retarding effects of smoking.

We measured concentrations of IGF-I and its major binding protein (IGF-BP3) in cord serum of 10 smoking and 9 non-smoking mothers (median age, 27 years and 28 years, respectively) who, after an otherwise entirely uneventful pregnancy, gave birth to normal-term neonates. The smoking group by history had had at least 15 cigarettes daily for longer than the last 2 months of gestation. The nonsmoking control group was neither actively nor passively exposed to cigarette smoke. For assessment of nicotine exposure, we also determined concentrations of the nicotine metabolite cotinine in maternal hair obtained at delivery. Hair samples of 50 mg were digested overnight at 50°C with 0.6N sodium hydroxide. The cotinine content of the extract was measured by enzyme-linked immunosorbent assay.³ The detection limit of the cotinine assay was 0.1 ng/mg of hair and the interassay coefficients of variation were less than 9%. Concentrations of IGF-I and IGF-BP3 in umbilical cord serum (after separation from each other by acid extraction) were determined by specific radioimmunoassays,^{4,5} and the coefficients of interassay variation of both assays were less than 7%.

Maternal hair cotinine content, fetal birth weights, and cord serum concentrations of IGF-I and IGF-BP3 for the smoking and nonsmoking groups are shown in the Table. These findings show that IGF-I concentrations in cord serum of neonates born to nicotine-exposed mothers were significantly lower than neonates of non-nicotine-exposed mothers. Since IGF-BP3 concentrations were similar in both groups, we suspect that the decrease of IGF-I concentrations in the nicotine-exposed group was not caused by increased binding to IGF-BP3 but rather by decreased production or enhanced degradation of IGF-I.

Growth retardation in neonates of smoking mothers may be related to an influence of nicotine on the generation or processing of IGF-I. In light of the well-recognized lifelong health consequences of fetal growth retardation after maternal smoking in pregnancy, further detailed investigations of the effects of nicotine exposure on the IGF system in the perinatal period are warranted.

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Maternal Hair Cotinine, Birth Weight of Normal-Term Neonates, and Cord Serum IGF-I and IGF-BP3 After Smoking in Pregnancy*

Criteria	Smoking Group	Nonsmoking Group	P Value†
Cotinine, ng/mg of hair			
Mean (SD)	4.51 (1.72)	0.45 (0.31)	.001
Median	4.44	0.58	
Range	2.41-7.98	0.10-0.99	
Birth weight, g			
Mean (SD)	2952 (336)	3456 (401)	.04
Median	2978	3497	
Range	2628-3215	3212-3725	
IGF-I, nmol/L			
Mean (SD)	2.3 (1.6)	7.0 (3.5)	.03
Median	3.0	7.6	
Range	0.7-5.6	3.0-11.1	
IGF-BP3, nmol/L			
Mean (SD)	63.9 (17.7)	66.9 (23.3)	.79
Median	72.0	64.9	
Range	41.8-94.1	37.8-97.1	

*IGF-I indicates insulinlike growth factor I; IGF-BP3, insulinlike growth factor binding protein 3.

†Student *t* test for unpaired data.

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CORRECTION

Incorrect Number and Phrasing.—In the Original Contribution entitled “Sodium Reduction and Weight Loss in the Treatment of Hypertension in Older Persons,” published in the March 18, 1998, issue of THE JOURNAL (1998;279:839-846), there was an incorrect number in the abstract, a misspelled word in the footnotes, and incorrect phrasing in the “Methods” section. On page 839, in the abstract, under the heading “Participants,” the sentence should start “A total of 975 men and women . . .” On page 839, in column 2, the last sentence in the first footnote should read “A complete list of the participating institutions and principal staff of the TONE Collaborative Research Group is given at the end of this article.” On page 841, in column 1, the third sentence under the heading “Data Collection Procedures” should read “Outcome information was obtained by staff members who were blind to the participants’ intervention assignment, at different times and different locations from those used for the intervention visits.” On page 846, in column 2, in the first paragraph of the acknowledgments, starting with the fifth line, the rest of the paragraph should read “the National Heart, Lung, and Blood Institute, and by General Clinical Research Center grant 5MO1RR00722 from the National Center for Research Resources, National Institutes of Health, Bethesda, Md.”