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Correspondence

Dietary Sodium and Blood Pressure

To the Editor: The DASH–Sodium Trial (Jan. 4 issue)[1] has demonstrated that a reduction in sodium intake over a period of 30 days lowers blood pressure. This finding is consistent with what more than 100 previous short-term, randomized trials have convincingly shown. What is remarkable — and disappointing, given this demanding and costly undertaking — is that the report was limited to the single selected favorable effect of salt on blood pressure, to the exclusion of other important physiological effects. For example, reducing the consumption of sodium also increases the plasma renin level by a factor of 3.6 and the aldosterone level by a factor of 3.2 — effects proportional to the degree of sodium reduction.[2]

The relation between sodium intake and all physiological phenomena is of great scientific interest. By contrast, patients, physicians, and public health advocates need to know how salt intake affects the quality and duration of life. The scanty published data available are not encouraging to those who preach salt restraint. An exception is the finding in a subgroup of obese subjects (28 percent) in the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study of a direct relation between salt intake and cardiovascular outcome. No such relation appeared in the nonobese majority (72 percent).[3] Moreover, in the entire survey population, there was an inverse relation between sodium intake and cardiovascular morbidity.[4]

Perhaps in some people the hemodynamic benefits of salt restriction will outweigh its hormonal and metabolic hazards. However, at this point, in the absence of strong evidence of a consistent health effect, a single universal recommendation for a reduction in dietary sodium reflects faith more than science.

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Editor's note: Dr. Alderman has attended consulting meetings with the Salt Institute.

1. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3-10.
2. Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. JAMA 1998;279:1388-91.
3. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA 1999;282:2027-34.
4. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). Lancet 1998;351:781-5.

To the Editor: Sacks et al. concluded that their results in the DASH–Sodium Trial "provide support for a more aggressive target for reduced sodium intake, in combination with the use of the DASH (Dietary Approaches to Stop Hypertension) diet, for the prevention and treatment of elevated blood-pressure levels." That conclusion is misleading at best.

Given the characteristics of the study cohort, which are greatly skewed toward the expression of salt sensitivity, the failure to provide the *Journal*'s readers with all the available data must be addressed. Even the very limited data provided in Figures 1 and 2 of the article indicate that from the standpoint of clinical application, any effect of salt restriction on blood pressure was limited to black women with hypertension. Thus, the authors' statement that these findings are broadly applicable to the entire population is not true. To prove otherwise, the authors are obligated to report, in a format similar to that of Figure 1, the analyses of subgroups defined according to race, presence or absence of hypertension, sex, age, and body-mass index.

Those data are necessary to document the principal finding of the study: for the vast majority of people, overall dietary improvements eliminate the effects of salt on blood pressure. Earlier reports[1,2] that adequate mineral intake from dairy products, fruits, and vegetables is far more important than salt in determining blood pressure have been confirmed by this study. If the authors had provided graphs that told the whole story, that conclusion would have been readily apparent.

Unfortunately, as currently presented, these data only provide further justification to the 70 percent of recently

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surveyed Americans who said they do not trust the government's dietary recommendations.[3] As others have put it, the salt-restriction advocates want to protect the public not only from salt but also from the data.[4]

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Editor's note: Dr. McCarron is a member of the Medical Advisory Board of the Salt Institute.

1. McCarron DA, Morris CD, Cole C. Dietary calcium in human hypertension. Science 1982;217:267-9.
2. McCarron DA, Morris CD, Henry HJ, Stanton JL. Blood pressure and nutrient intake in the United States. Science 1984;224:1392-8.
3. Patterson RE, Satia JA, Kristal AR, Neuhouser ML, Drewnowski A. Is there a consumer backlash against the diet and health message? J Am Diet Assoc 2001;101:37-41.
4. Freedman DA, Petitti DB. Salt and blood pressure: conventional wisdom reconsidered. Evaluation Review (in press).

To the Editor: The continuing controversy about general advice to reduce dietary sodium has arisen in part because the effect of sodium may be limited to subgroups of the population who are salt-sensitive. In their discussion of the effect of sodium reduction in persons without hypertension, Sacks et al. highlight the reductions in systolic blood pressure that occurred in subjects on the control diet. Figure 2 of the article shows that the reduction in sodium intake in subjects on the DASH diet had a significant effect on systolic blood pressure in persons without hypertension only if they were black and only when they switched from the high-sodium to the low-sodium diet.

The risk of coronary disease increases as the diastolic blood pressure increases within quintiles of systolic blood pressure.[1] A meta-analysis of observational studies of blood pressure, stroke, and coronary disease[2] presents data according to diastolic but not systolic blood pressure. A meta-analysis of randomized trials of antihypertensive-drug therapy shows a reduction in the risks of stroke and coronary heart disease in relation to reductions in diastolic but not systolic blood pressure.[3] To arrive at the best estimates of the expected reductions in disease events that would result from changes in the diets of various subgroups — especially persons without hypertension — information is required about the effect on diastolic blood pressure of lowering dietary sodium in the DASH and control diets for subgroups defined by ethnic background, presence or absence of hypertension, and sex.

The most recent meta-analysis of clinical trials of sodium reduction reported no significant effect of sodium reduction on diastolic blood pressure in persons without hypertension.[4]

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1. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. Arch Intern Med 1993;153:598-615.
2. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. I. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765-74.
3. Collins R, Peto R. Antihypertensive drug therapy: effects on stroke and coronary heart disease. In: Swales JE, ed. Textbook of hypertension. Oxford, England: Blackwell Scientific, 1994:1156-64.
4. Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. JAMA 1998;279:1388-91.

To the Editor: In their report of the 90-day DASH–Sodium Trial, Sacks et al. do not set their findings in the context of longer-term trials in which sodium intake has been manipulated to reduce blood pressure. We have iden-

TABLE 1. RESULTS OF LARGE RANDOMIZED, CONTROLLED TRIALS IN WHICH SODIUM INTAKE WAS LOWERED TO REDUCE BLOOD PRESSURE.*

TRIAL AND YEAR	NO. OF SUBJECTS	SYSTOLIC BLOOD PRESSURE			
		STUDY MO	NET MEAN CHANGE (95% CI)	STUDY MO	NET MEAN CHANGE (95% CI)
			mm Hg		mm Hg
HPT, 1990	392	6	−1.7 (−3.4 to 0.0)	36	+0.1 (−1.8 to +2.0)
TOHP-I, 1992	744	12	−1.9 (−3.0 to −0.8)	18	−1.7 (−2.9 to −0.6)
TOHP-II, 1997	1190	6	−2.9 (−3.9 to −1.9)	36	−1.0 (−2.0 to 0.0)
DASH–Sodium, 2000	204	1	−6.7 (−5.4 to −8.0)	—	—

*For the first three trials, the net mean change in systolic blood pressure was calculated by subtracting the mean change in the control group from the mean change in the experimental group. For the DASH–Sodium Trial, the data presented represent the mean change for the 204 participants in the control group from the high-sodium phase to the low-sodium phase of the control diet. CI denotes confidence interval, HPT Hypertension Prevention Trial, TOHP Trial of Hypertension Prevention, and DASH Dietary Approaches to Stop Hypertension. In the 1998 Trial of Nonpharmacologic Interventions in the Elderly, involving 681 subjects, the hazard ratios for the composite end point of hypertension, restarting medication, or a cardiovascular event by 30 months (in the sodium-reduction group vs. the control group) were 0.60 (95 percent confidence interval, 0.45 to 0.80) in obese subjects and 0.75 (95 percent confidence interval, 0.59 to 0.95) in nonobese subjects.

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tified 10 randomized, controlled trials that lasted six months or longer. Four trials, all conducted in the United States, were similar in size to the DASH–Sodium Trial, having at least 200 participants (Table 1, previous page).

In three of these trials, involving adults not receiving medication who had high-normal blood pressure,[1-3] the difference between the mean reduction in systolic blood pressure in the experimental group and that in the control group was modest after 6 months of intervention and became minimal after 12 months. In the fourth trial, the Trial of Nonpharmacologic Interventions in the Elderly,[4] however, there was observable but limited success in weaning seniors off antihypertensive medication by means of a low-sodium diet.

In all four trials, there was difficulty in maintaining sodium reduction at the targeted level over the long term, even though the interventions were intensive. This may explain the minimal efficacy, although an alternative hypothesis is that baroreceptor and renal homeostasis through renin–angiotensin mechanisms restored blood pressure to its preintervention level, despite the reduction in sodium.[5] Thus, it is improbable that the reductions in blood pressure ascribed by Sacks and colleagues to the manipulation of sodium intake (as distinct from the reductions that were due to the DASH diet) could be sustained over the long term in adults not receiving medication, either in a clinical situation or in the general population. Nevertheless, the issue of whether low sodium intake from childhood promotes lifelong normotension remains to be resolved.

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1. The Hypertension Prevention Trial Research Group. The Hypertension Prevention Trial: three-year effects of dietary changes on blood pressure. Arch Intern Med 1990;150:153-62.
2. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, Phase I. JAMA 1992;267:1213-20. [Erratum, JAMA 1992;267:2330.]
3. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, Phase II. Arch Intern Med 1997;157:657-67.
4. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). JAMA 1998;279:839-46.
5. Navar LG. The kidney in blood pressure regulation and development of hypertension. Med Clin North Am 1997;81:1165-98.

The authors reply:

To the Editor: The contribution of the DASH–Sodium Trial to the salt issue is data on the magnitude of the reduction in blood pressure related to a reduction in sodium. In our view, the magnitude is greater in the DASH–Sodium feeding study than has been reported in meta-analyses because people have serious difficulty finding enough low-sodium foods to enable them to adhere fully to reduced-sodium diets. We hope that the food industry will respond to the DASH–Sodium findings as a business opportunity.

We are surprised by Alderman's assertion that reduced sodium intake, especially to 65 mmol per day, is harmful. Reduced sodium does raise the plasma renin level, but so does diuretic therapy, which prevents cardiovascular disease. Moreover, in a large sample of the general population, the plasma renin level was not associated with cardiovascular disease.[1] Experience with antihypertensive drugs shows that any reduction in blood pressure reduces cardiovascular disease. Mortality trials are not required for drug approval. Should sodium reduction be different? Finally, the epidemiologic study by Alderman et al.[2] shows an increase in the rate of death from cardiovascular disease with higher salt intake when the analysis is appropriately adjusted for the total caloric intake of the subjects.

We assure McCarron and readers that the DASH–Sodium findings are qualitatively the same among all subgroups but differ quantitatively, as we showed in representative examples. We plan to publish the full subgroup results soon. The substantial reductions in blood pressure give additional strength to the long-standing dietary guidelines of public and private health organizations.

Petitti and Freedman focus on a subgroup effect that did not attain statistical significance, while ignoring the consistency of the direction of the results for all subgroups, which vary only in magnitude. Moreover, a substantial proportion of white and normotensive persons are indeed sensitive to salt.[3] Systolic blood pressure was prespecified as the trial's primary outcome because it is more closely linked than diastolic blood pressure to cardiovascular disease.[4]

We agree with the view of Bartlett et al. that difficulty in achieving long-term adherence to low-sodium diets limits the long-term reduction in blood pressure. In the outstanding trial of MacGregor et al.,[5] the reduction of sodium intake from 200 to 50 mmol per day in a highly motivated group of subjects with hypertension reduced systolic blood pressure by 18 mm Hg after one year — the same as the reduction after one month. There is no indication in the literature of an adaptation effect.

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1. Meade TW, Cooper JA, Peart WS. Plasma renin activity and ischemic heart disease. N Engl J Med 1993;329:616-9.
2. Alderman MH, Cohen H, Madhavan S. Dietary sodium intake and mortality: the National Health and Nutrition Examination Survey (NHANES I). Lancet 1998;351:781-5.
3. Stamler J, Neaton JD, Wentworth DN. Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. Hypertension 1989;13:Suppl I:I-2–I-12.

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4. Weinberger MH, Miller JZ, Luft FC, Grim CE, Fineberg NS. Definitions and characteristics of sodium sensitivity and blood pressure resistance. Hypertension 1986;8:Suppl II:II-127–II-134.
5. MacGregor GA, Markandu ND, Sagnella GA, Singer DR, Cappuccio FP. Double-blind study of three sodium intakes and long-term effects of sodium restriction in essential hypertension. Lancet 1989;2:1244-7.

A Pneumococcal Conjugate Vaccine and Acute Otitis Media

To the Editor: In the report by Eskola et al. (Feb. 8 issue)[1] of the efficacy of a pneumococcal conjugate vaccine against otitis media, the data argue strongly against their conclusion that "the effect of the pneumococcal conjugate vaccine can be substantial." In the case of 94 percent of those immunized with the pneumococcal conjugate vaccine, otitis media would not have been prevented. The study also substantiates one of the greatest feared limits of the heptavalent pneumococcal conjugate vaccine — that the frequency of disease would remain the same as a result of increases in the rates of infection with all the pneumococcal serotypes that were not included in the vaccine (a phenomenon sometimes referred to as serotype replacement). The data of Eskola et al. demonstrate a 33 percent increase in the incidence of otitis media from pneumococcal serotypes that were not included in the vaccine.

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1. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344:403-9.

To the Editor: Eskola et al. state that "up to 1.2 million of the 20 million yearly episodes of acute otitis media in the United States could theoretically be prevented if the [pneumococcal conjugate] vaccine were widely used." This theoretical benefit must not be used as an official justification for vaccination.

The vaccine was officially recommended for use in all children on the basis of its efficacy against invasive diseases.[1] The reported relative reduction in the risk of episodes of 6 percent achieved by vaccination still leaves the total risk high enough for many immunized children to have acute otitis media. This factor could lessen the credibility of the recommendation for vaccination.

A more powerful trial[2] reported a reduction in acute otitis media of up to 22.8 percent in one subgroup of children with frequent episodes. Since 14 percent of children account for approximately 50 percent of the episodes of acute otitis media, the number of episodes could be significantly reduced by the selection of appropriate candidates for immunization. In countries that will not adopt the U.S. recommendation, selective vaccination of high-risk subgroups is a better way to keep the public trust.

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1. Committee on Infectious Diseases. Recommended childhood immunization schedule: United States, January-December 2001. Pediatrics 2001; 107:202-4.
2. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000;19:187-95.

To the Editor: Given the poor overall efficacy of the pneumococcal conjugate vaccine in the study by Eskola et al., the authors' conclusions are a bit too optimistic. According to the protocol, all infants received four vaccinations, which were certainly not painless and which led to the prevention of only 6 percent of all cases of acute otitis media.

For the moment, more could be gained by changing our attitude toward acute otitis media. In the Netherlands, acute otitis media is seen as a self-limiting disease. Often, parents do not take their children to the doctor for this common childhood disease. The efficacy of antibiotics for this disease is moderate,[1] even in the youngest children.[2] Educating doctors and parents about acute otitis media will lead to a decrease in antibiotic prescriptions for this illness, as has been shown in a recent trial.[3]

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1. Del Mar C, Glasziou P, Hayem M. Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis. BMJ 1997; 314:1526-9.
2. Damoiseaux RAMJ, van Balen FAM, Hoes AW, Verheij TJ, de Melker RA. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. BMJ 2000;320:350-4.
3. Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavy J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. BMJ 2001;322:336-42.

To the Editor: The vaccine manufacturer's vice president and contractors conclude that the new pneumococcal vaccine is "efficacious in the prevention of acute otitis media." Given the 95 percent confidence interval of −4 to 16 percent, the data presented by Eskola et al. do not support this conclusion. As the authors admit, "the negative number indicates" that the treated group could have had more episodes than the controls. These same data — 1251 episodes in the vaccine group as compared with 1345 episodes in the control group, a clinically and statistically insignificant difference in the rate of 3.6 percent (absolute benefit) — were presented to an advisory committee of the Food and Drug Administration (FDA) in November 1999. Therefore, the FDA rejected the use of this vaccine for otitis media. Moreover, the authors' use of the number of episodes instead of the number of patients as the experimental unit is incorrect because it inflates the outcome.

The most interesting results concern the pneumococcal ecology. In a short time span, the predicted serotype replacement[1] (also observed with other bacterial vaccines[2-4]) was realized. Eskola et al. report that the "number of episodes due to all other [pneumococcal] serotypes increased by 33 percent." With this clear warning sign, it is a perilous experiment in microbial ecology to push the use of the heptavalent pneumococcal vaccine.

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1. Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? Lancet 2000;356:1210-1.
2. Perdue DG, Bulkow LR, Gellin BG, et al. Invasive Haemophilus influenzae disease in Alaskan residents aged 10 years and older before and after infant vaccination programs. JAMA 2000;283:3089-94.
3. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001;357:195-6.
4. Lipsitch M. Bacterial vaccines and serotype replacement: lessons from Haemophilus influenzae and prospects for Streptococcus pneumoniae. Emerg Infect Dis 1999;5:336-45.

To the Editor: As a general pediatrician, I think we must proceed with caution when relaying the data of Eskola et al. to our patients' parents. Although the vaccine reduced the incidence of acute otitis media caused by pneumococcus, especially by the strains included in the vaccine, the overall reduction in cases of acute otitis media was only 6 percent. The clinical significance of this finding is questionable.

I have already had several parents ask me why their child had an ear infection after having received the "ear-infection vaccine." At a time when many parents are already suspicious of the reported safety and efficacy of vaccines, unrealistic expectations may hinder the use of this vaccine and therefore limit the documented protection it affords against invasive pneumococcal disease.[1]

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1. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000;19:187-95.

The authors reply:

To the Editor: It is important to make a distinction between the effect of the pneumococcal conjugate vaccine on a larger population and the expected benefits in an individual child. Even though the proportion of vaccine-preventable episodes of otitis media is small, the absolute number of potentially preventable attacks at the population level is considerable, because otitis media is such a common disease. The impact on otitis media has been estimated to account for 60 percent of the cost savings expected from the prevention of pneumococcal disease through a vaccination program.[1] Thus, our conclusion that the effect of the pneumococcal conjugate vaccine on otitis media could be substantial is correct and is an important message to policymakers who are deciding whether the vaccine should be included in national immunization programs. However, we fully agree that the information given to parents should focus on protection provided by the vaccine against invasive pneumococcal disease. Furthermore, the suggestion of targeting the vaccine to selected otitis-prone groups would be difficult to implement and would obscure the primary objective of preventing invasive disease.

We cannot agree with Dr. Cantekin that using the number of episodes instead of the number of children as experimental units is incorrect. The tendency to recurrence is characteristic of acute otitis media. A vaccine that does not afford protection against recurrent attacks would be of little value. We therefore purposely calculated the efficacy of the vaccine against all episodes of otitis media, not just the first ones (i.e., counting only one episode per child). This approach did not inflate the outcome, as shown by the efficacy rates against first as compared with all episodes of otitis media (52 percent vs. 57 percent for infections caused by serotypes included in the vaccine and 12 percent vs. 6 percent for episodes from any cause). The reduction of 12 percent is statistically significant (95 percent confidence interval, 1 to 22 percent).

We share the concern about the increase in otitis media caused by the serotypes that were not included in the vaccine among those who received the conjugate vaccine. However, we find it reassuring that after several years of follow-up, no indication of serotype replacement has been observed in invasive disease among the participants of the California trial.[2,3] The long-term effects of serotype replacement remain unknown. This warrants careful serotype-specific surveillance of the effect of vaccination on both pneumococcal carriage and invasive disease, rather than the discontinuation of vaccination. Fortunately, data on the effect of broad-scale vaccination on the pneumococcal serotypes causing invasive disease are rapidly accumulating in the United States, where the pneumococcal conjugate vaccine is now in wide use.

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Editor's note: Dr. Eskola has been an employee of Aventis Pasteur since the beginning of 2000. Drs. Eskola and Kilpi have served as consultants to Wyeth Lederle Vaccines.

1. Lieu TA, Ray GT, Black SB, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. JAMA 2000;283:1460-8.
2. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000;19:187-95.
3. Shinefield HR, Black S. The efficacy and safety of heptavalent pneumococcal conjugate vaccine in children. Presented at the Millennium Second World Congress on Vaccines and Immunization, Liège, Belgium, August 29–September 3, 2000. abstract.

The Effect of Risedronate on the Risk of Hip Fracture in Elderly Women

To the Editor: The report by McClung et al. (Feb. 1 issue)[1] is unconvincing, because information is not presented to show that the women in the treatment and placebo groups had similar clinical risk factors for hip fracture. This information should have been included in the table showing the base-line characteristics of the groups.

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1. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med 2001;344:333-40.

To the Editor: McClung et al. state that "complete follow-up data were available for 64 percent of the women."

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In other words, follow-up data were incomplete for 36 percent, or 3324, of the 9331 women. One wonders how to interpret an estimated overall absolute difference in the incidence of hip fracture of 1.1 percentage points, or 42 women with fractures, in the light of such incomplete data. A slight preponderance of fractures among those lost to follow-up in the risedronate group could render the results inconclusive.

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To the Editor: McClung et al. found that risedronate in addition to calcium and vitamin D reduced the risk of hip fracture in women 70 to 79 years old who were recruited on the basis of a low bone mineral density at the femoral neck. This suggests that screening for low bone mineral density followed by an appropriate treatment may be worthwhile even in elderly women, as long as they have a very low bone mineral density. To assess whether the incidence of hip fracture continues to rise when the bone mineral density decreases to very low values, even in very elderly women, we reanalyzed the data from a prospective cohort study of 7598 women 75 years old or older (the Epidémiologie de l'Ostéoporose [EPIDOS] study).[1,2] The age-adjusted incidence of hip fracture increased from 5.7 per 1000 person-years among women with a T score of −2.5 or lower to 36.5 per 1000 person-years among women with a T score lower than −4. In the trial of risedronate conducted by McClung et al., no effect was observed among the women 80 years old or older. However, most women in this subgroup were enrolled on the basis of clinical risk factors only, and many did not have very low bone mineral density. In the EPIDOS study, among 4478 women 80 years old or older, 77 percent had one or more clinical risk factors.[3] Of these, only 27 percent had a T score below −3. These results emphasize the need to measure bone mineral density at the femoral neck to identify elderly women in whom therapy to prevent fracture is appropriate.

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1. Schott AM, Cormier C, Hans D, et al. How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. Osteoporos Int 1998;8:247-54.
2. Mazess RB, Barden H. Bone density of the spine and femur in adult white females. Calcif Tissue Int 1999;65:91-9.
3. Dargent-Molina P, Favier F, Grandjean H, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. Lancet 1996;348:145-9. [Erratum, Lancet 1996;348:416.]

Dr. McClung replies:

To the Editor: Dr. Royce raises an important point. The proportions of both the older and younger women with various risk factors were balanced among the treatment groups, so the observed treatment effect was not the result of differences in risk at base line. Dr. Goodman expresses appropriate concern about the potential effect of the incomplete follow-up of the elderly women in our study. The demographic characteristics with respect to the risk of fracture were very similar between the women for whom we had complete follow-up data and those for whom we did not. Using the observed incidence of hip fractures that occurred during follow-up, Dr. Goodman estimates that an additional 42 hip fractures would have been observed if all the women had been followed for three years. If we make the conservative assumption that there is no treatment effect in these women, these fractures would be proportionally distributed between the treatment groups, with 14 in the placebo group and 28 in the risedronate group. In this case, the reduction in the risk of hip fracture in the combined risedronate groups would have remained significant (risk reduction, 24 percent; 95 percent confidence interval, 3 percent to 41 percent; $P=0.03$).

The information provided by Dr. Schott and colleagues from their large observational study supports our findings that elderly women with fall-related risk factors do not necessarily have low bone density and may not be candidates for drug therapy to reduce the risk of hip fracture. Although bone mass decreases with advancing age, we cannot assume that all older women have osteoporosis.

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Treatment of Calcium-Channel–Blocker Intoxication with Insulin Infusion

To the Editor: Overdose of calcium-channel blockers remains an important cause of fatal poisoning.[1] Conventional therapy, consisting of intravenous fluids, calcium, dopamine, dobutamine, norepinephrine, and glucagon, often fails to improve hemodynamic function in intoxicated patients.[2] Recent recommendations for treatment of intoxication with calcium-channel blockers include induction of hyperinsulinemia and euglycemia as adjunctive therapy.[3] We report two cases of overdose of calcium-channel blockers in which a striking benefit was achieved with hyperinsulinemia–euglycemia therapy.

A 34-year-old nondiabetic woman with hypertension and renal failure ingested 12 extended-release tablets containing 2.5 mg of amlodipine each. Hypotension and bradycardia developed. Because of her history of renal failure, the treating physicians did not administer calcium and instead provided intravenous fluids, vasopressors, and glucagon.

A 48-year-old nondiabetic man with hypertension, chronic obstructive pulmonary disease, congestive heart failure, and depression was witnessed ingesting an unknown amount of extended-release diltiazem. He became hemodynamically unstable in the emergency department and did not respond to calcium, intravenous fluids, and vasopressors.

When conventional therapy failed to improve the hemodynamic status of these patients, hyperinsulinemia–euglycemia therapy with a continuous infusion of insulin at a rate of 0.5 IU per kilogram of body weight per hour rapidly

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TABLE 1. CLINICAL COURSES OF TWO PATIENTS TREATED WITH HYPERINSULINEMIA–EUGLYCEMIA THERAPY.

PATIENT NO.	VITAL SIGNS BEFORE THERAPY	SERUM GLUCOSE CONCENTRATION BEFORE THERAPY	CONVENTIONAL THERAPY ATTEMPTED	VITAL SIGNS AFTER THERAPY	RATE OF INSULIN INFUSION	TIME FROM INSULIN INFUSION TO DISCONTINUATION OF OTHER VASOACTIVE DRIPS	VITAL SIGNS AFTER INSULIN INFUSION ALONE	DURATION OF INSULIN DRIP	SUPPLEMENTAL GLUCOSE ADMINISTERED
		mg/dl			IU/kg/hr	min		hr	
1	Pulse, 60; blood pressure, 40 mm Hg by palpation; afebrile	325	4 liters of intravenous fluids; 20 μg/kg/min of dopamine; 10 μg/kg/min of dobutamine; 14 μg/kg/min of norepinephrine; 5 mg of intravenous glucagon	Unchanged	0.5	45	Pulse, 100; blood pressure, 150/60 mm Hg	6	None
2	Pulse, 68; blood pressure, 60/40 mm Hg; afebrile	170	2 liters of intravenous fluids; 4 g of calcium gluconate; 20 μg/kg/min of dopamine; 10 μg/kg/min of dobutamine	Unchanged	0.5	30	Pulse, 65; blood pressure, 115/60 mm Hg	6	100 ml/hr of 10% dextrose

reversed cardiovascular collapse in both. Despite the high doses of insulin administered, the first patient required no supplemental glucose, whereas the second received 10 percent dextrose at 100 ml per hour to maintain an average serum glucose concentration of 140 mg per deciliter. The clinical courses of the two patients are outlined in Table 1.

The clinical features of toxicity from calcium-channel blockers arise from blockade of L-type calcium channels in myocardial cells, smooth-muscle cells, and beta cells.[4] Antagonism of these channels produces bradycardia, conduction delay, peripheral vasodilation, hypoinsulinemia, hyperglycemia, metabolic acidosis, and shock. Hypoinsulinemia may be a critical factor in overdose of calcium-channel blockers.[5] In an unstressed state, myocytes oxidize free fatty acids for metabolic energy.[3,4] In a state of shock, such as that associated with overdose of calcium-channel blockers, myocytes use glucose for fuel.[3,4] Hypoinsulinemia may prevent the uptake of glucose by myocytes, causing a loss of inotropy, decreased peripheral vascular resistance, and shock.[3]

The exact mechanism of action of hyperinsulinemia–euglycemia therapy is poorly defined. Hyperinsulinemia–euglycemia therapy improves inotropy and peripheral vascular resistance and reverses acidosis, possibly by improving the uptake of carbohydrates by myocytes and smooth-muscle cells.[3,4] Although hypoglycemia may occur with this therapy, the ease with which serum glucose can be measured by bedside capillary testing minimizes the likelihood of this complication. As other case reports have suggested, hyperinsulinemia–euglycemia therapy is safe and effective for life-threatening overdose of calcium-channel blockers.[3]

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1. Litovitz TL, Klein-Schwartz W, Caravati EM, Youniss J, Crouch B, Lee S. 1998 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1999;17:435-87.
2. Enyeart JJ, Price WA, Hoffman DA, Woods L. Profound hyperglycemia and metabolic acidosis after verapamil overdose. J Am Coll Cardiol 1983;2:1228-31.
3. Yuan TH, Kerns WP II, Tomaszewski CA, Ford MO, Kline JA. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. J Toxicol Clin Toxicol 1999;37:463-74.
4. Kline JA, Leonova E, Raymond RM. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. Crit Care Med 1995;23:1251-63.
5. Ohta M, Nelson J, Nelson D, Meglasson MD, Erecinska M. Effect of Ca++ channel blockers on energy level and stimulated insulin secretion in isolated rat islets of Langerhans. J Pharmacol Exp Ther 1993;264:35-40.

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