

Hypertension

Editor's Comments Wading Through the Alphabet Soup

As the century draws to a close, a plethora of outcome studies are in progress to compare the effects of specific antihypertensive treatments on cardiovascular disease and a few have recently been completed. No longer is the question whether hypertension should be treated but rather in whom, how far and with what. In addition, the ongoing studies are designed to examine the benefit of blood pressure reduction on specific cardiovascular events and to determine whether some drugs convey more or less benefit than others. Each of these studies has been given an acronym, some descriptive, some catchy, leading to confusion regarding their design and intent. This issue of *Current Concepts in Hypertension* inaugurates a series of articles designed to provide a brief review of these studies as well as to summarize and provide commentary on recently completed studies of interest to those treating hypertensive patients.

In this issue is a brief summary of a recent nonpharmacologic study examining the impact of dietary modification on the development or progression of hypertension in a group of subjects at risk. The DASH Study has been cited as an important new element in preventing hypertension or controlling Stage I levels of blood pressure elevation by the most recent report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). While the findings of this study are most impressive, we

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The Losartan Intervention For Endpoint Reduction (LIFE) in Hypertension Study

The Losartan Intervention For Endpoint Reduction (LIFE) in Hypertension study is a double-blind, prospective, parallel group study designed to compare the effects of losartan with those of the β -blocker atenolol on the reduction of cardiovascular morbidity and mortality in hypertension. Approximately 9,000 hypertensive patients (initial sitting diastolic blood pressure 95 to 115 mm Hg and/or systolic blood pressure 160 to 200 mm Hg) with electrocardiographically documented left ventricular hypertrophy (LVH) will be studied in over 800 centers in Scandinavia, the United Kingdom and the United States.

LVH is defined by the core laboratory according to criteria based on the product of Cornell voltage ($RaVL + SV_3$) x QRS duration product criteria: $>2,440$ mm x msec in men and the product of QRS duration times Cornell voltage plus 6 mm exceeding the same value in women.¹ A Sokolow-Lyon voltage combination ($SV_1 + RV_5$ or V_6) >38 mm is accepted as an alternate criterion for LVH in both men and women.² Preliminary results from a pilot study in Scandinavia showed that the prevalence of electrocardiographic (ECG) LVH in hypertensive patients was approximately 22%.

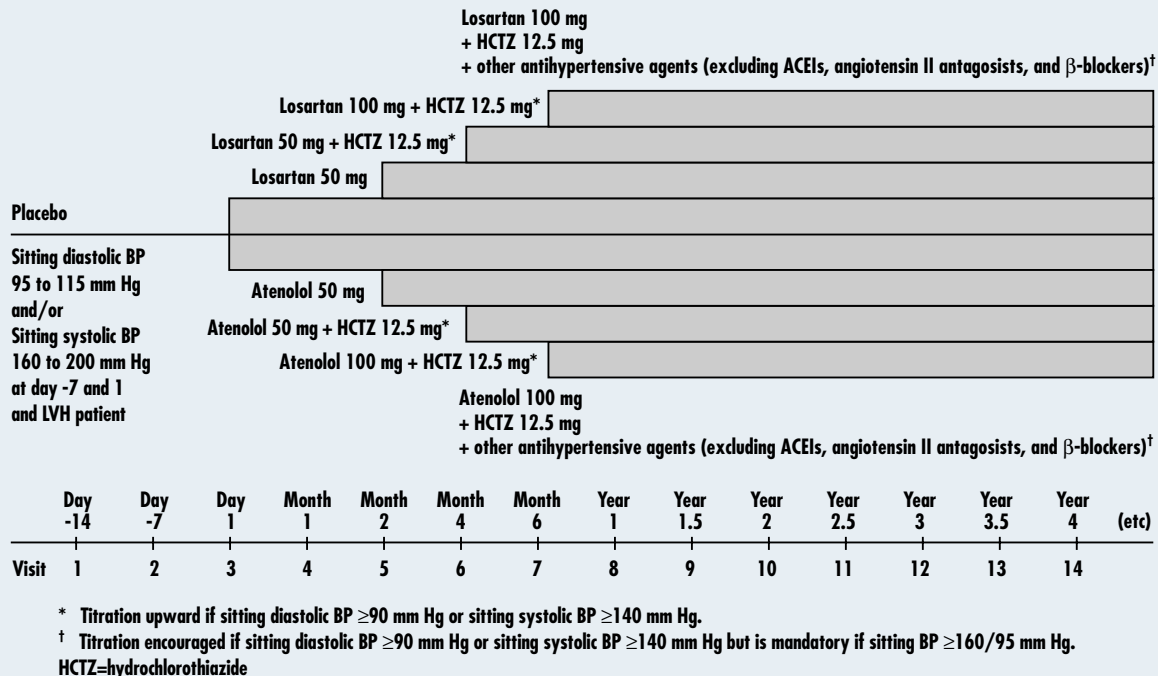
The rationale for use of ECG rather than echocardiographic criteria for LVH in the LIFE study is that an ECG can detect LVH with a high degree of specificity and identifies elevated risk as efficiently or better than echocardiography at a lower cost. The cardiovascular risk (depending on age and sex) of hyper-

Secondary and Tertiary Objectives of LIFE

<p>Secondary Objectives Compare the long-term effects of losartan versus atenolol on:</p>	<ul style="list-style-type: none"> ● Cardiovascular mortality ● Total mortality ● Hospitalization due to angina pectoris and heart failure ● LVH regression ● Relationship between LVH regression and cardiovascular mortality and morbidity ● Incidence of coronary or peripheral revascularization procedures ● Incidence of silent MI ● Safety and tolerability ● Fatal and nonfatal MI ● Fatal and nonfatal stroke
<p>Tertiary Objectives</p>	<ul style="list-style-type: none"> ● Evaluate relationship between blood pressure control and cardiovascular morbidity and mortality ● Assess influence of various risk factors on cardiovascular event rates ● Compare long-term effects of losartan versus atenolol on: <ul style="list-style-type: none"> ● New-onset diabetes mellitus ● Healthcare resource utilization

Table 1

Titration Schedule for the LIFE in Hypertension Study



Dahlöf B, Devereaux R, DeFaire U, et al. The Losartan Intervention for Endpoint Reduction (LIFE) in hypertension study: rationale, design, and methods. The LIFE study group. *Am J Hypertens* 1997;10:705-713.

Figure 1

tensive patients with LVH compared with hypertensives without LVH is 1 to 6 times higher for angina pectoris, 2 to 5 times higher for myocardial infarction (MI), 6 to 17 times higher for heart failure, and 3 to 10 times higher for stroke. The importance of LVH is confirmed by the finding that, within 5 years of its appearance, one-third of men and one-fourth of women with LVH are dead, usually from coronary disease.

The major hypothesis of the LIFE study is that, in patients with essential hypertension and LVH, losartan will reduce the incidence of cardiovascular morbidity and mortality to a greater extent than the β -blocker atenolol, possibly through a greater effect on LVH regression. This hypothesis is based on the assumption that the renin-angiotensin system plays an important role in mediating hypertension-induced functional and structural cardiovascular abnormalities. Atenolol was selected as the comparative agent in the LIFE study because β -blockers reduce cardiovascular morbidity and mortality when used for treatment of hypertension and secondary prevention of heart attack, because it is the most widely used β -blocker, and because efficacy and tolerability have been compared with those of losartan.

The primary objective of the LIFE study is to evaluate the long-term effects (≥ 4 years) of losartan compared to atenolol in hypertensive patients with documented LVH on the combined incidence of cardiovascular mortality (death due to MI, stroke, sudden death, and progressive heart failure) and morbidity (nonfatal MI and nonfatal stroke). Secondary and tertiary objectives are shown in table 1. Study design is shown in figure 1. LIFE will continue for at least 4 years and until 1,040 patients experience one primary endpoint. It has been designed with a statistical power that will detect a difference of at least 15% in the incidence of combined cardiovascular morbidity and mor-

ality. It is the first prospective study with adequate power to link reversal of LVH to reduction in major cardiovascular events.

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Footnotes

1. R-wave amplitude in aVL plus S-wave amplitude in V₃.
2. S-wave amplitude in V₁ plus R-wave amplitude in V₃ or V₆.

Editor's Comments (continued from page 1)

need to recognize that they are based on short term (eight weeks) observations that say nothing about cardiovascular disease outcome.

In addition to this completed study, this issue of *Current Concepts in Hypertension* features two articles that are devoted to an ongoing intervention trial, The LIFE study. The first, by Dr. Suzanne Oparil, outlines the rationale behind the study design and the second, prepared by Dr. Sveffe Kjeldsen, provides information about the population demographics of this multinational study for which enrollment has now been completed.

Finally, this issue of *Current Concepts in Hypertension* includes a reply card that can provide extremely important information. Your responses will help us understand how we can best provide future information and will tell us more about the readership of this series. It also is an excellent opportunity for you to dialog with us and share your opinions and interests.

Demographics of the LIFE Study

The Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension study is a multicenter, double-blind, randomized, prospective, active-controlled parallel group study designed to compare the effects of losartan with those of the β -blocker atenolol, both in dosages of 50 to 100 mg qd, on cardiovascular morbidity and mortality in patients with essential hypertension and electrocardiographically (ECG) documented left ventricular hypertrophy (LVH). Additional treatment may be given as open-label hydrochlorothiazide 12.5 to 25 mg and, if needed, any other antihypertensive medication except for other β -blockers, angiotensin I receptor antagonists or angiotensin-converting enzyme (ACE) inhibitors to reach a target blood pressure (BP) of <140/90 mm Hg. After the 2-week single-blind placebo run-in period, there will be at least 4 years of randomized active double-blind treatment until 1040 patients have experienced a primary cardiovascular event defined as cardiovascular death, nonfatal clinically-evident acute myocardial infarction, or nonfatal cerebral stroke. This study is endpoint-driven and has been calculated to have 80% power with 8300 patients enrolled to detect a 15% further reduction in the primary outcome rate from 15% in the atenolol group to 12.75% in the losartan group. The rationale, objectives, and design of the LIFE study, including outcome measures and statistical methods, have been published.¹

Altogether 9194 eligible patients in Scandinavia, the United Kingdom (UK), and United States (US) were enrolled at 945 study sites: Denmark (n=1391, 15%); Finland (n=1485, 16%); Iceland (n=133, 1%); Norway (n=1415, 15%); Sweden (n=2245, 25%); UK (n=817, 9%); and US (n=1708, 19%). Preliminary analysis showed the proportion of subjects who qualified, based on the Cornell voltage QRS duration product formula, was approximately 67% and 22% qualified, based on Sokolow-Lyon voltage; 11% fulfilled both criteria.

This population of hypertensives (mean BP 174.4/97.8 mm Hg) with LVH averaged 66.9 years of age at randomization. The women (54.1% of total) were older, had a higher body mass index (BMI), and were more likely to have isolated systolic hypertension. More men were working full-time and the men had higher Framingham Risk Scores for coronary heart disease (CHD) than the women. However, the predicted 5-year event rate attributable to factors other than gender was only moderately higher ($P<0.001$) in men (19.2%) than in women (16.9%).

More than 80% of patients were above the age of 60 years at randomization. The majority of patients had moderate hypertension at the randomization visit (55.8% with systolic BP 160 to 180 mm Hg and 53.7% with diastolic BP 95 to 105 mm Hg). Moreover, 27.4% had isolated systolic hypertension (systolic BP >160 mm Hg and diastolic BP <95 mm Hg) and 10.5% were randomized based on diastolic hypertension only. BP levels were similar in all countries.

The overwhelming majority of subjects were Caucasian. Self-reported alcohol and tobacco use were moderate or low; 32.0% of men and 57.6% of women reported they never used alcohol whereas 80.3% and 86.5%, respectively, did not smoke. 46.7% of men were previous tobacco smokers. The average total cholesterol level (slightly above 6.0 mmol) was somewhat compensated for by high-density lipoprotein (HDL) cholesterol of about 1.50 mmol and a total-to-HDL

cholesterol ratio of 4.3. Both total cholesterol and HDL cholesterol were higher in women than men.

Almost 15% of LIFE participants had one or more manifestations of CHD. Previous strokes and/or transient ischemic attacks were reported by 7.6%, lipid disorders by 16.7%, and diabetes mellitus by 12.1% of patients. A variety of other disorders were less frequently reported. Although only 2.5% were reported to have overt obesity, 21.3% had a BMI of 30 to 35, 5.4% of 35 to 40 and 1.9% >40 kg/m².

Almost one third of the patients (29.5%) had been untreated for at least 6 months for their high BP prior to the placebo period (fewer in the US [Fig. 2]), while 39.3% were on treatment with 1 antihyperten-

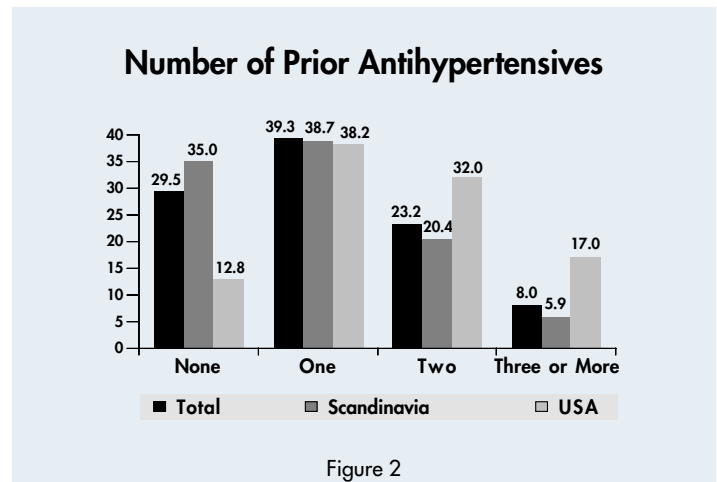


Figure 2

sive agent, 23.2% with 2, and 8.0% on treatment with 3 or more antihypertensive agents. Diuretics were taken by 27.2%, more women (31.4%) than men (22.3%), β -blockers by 26.5%, calcium-channel blockers by 24.1% (men 26.3%, women 22.3%), and ACE inhibitors by 21.3% (men 24.9%, women 18.0%). One of 5 (20.8%) was on aspirin. Other drug therapies were less frequent.

Thus, by applying simple 12-lead ECG criteria for LVH (Cornell voltage QRS duration product formula plus Sokolow-Lyon voltage read by a core laboratory), hypertensive patients with LVH, with an average 5-year CHD risk of 22.3% according to the Framingham Score were identified. This population is now treated (goal <140/90 mm Hg) in adherence with the protocol for at least 4 years after final enrollment (i.e. through April 2001) and until at least 1040 patients suffer myocardial infarction, stroke, or cardiovascular death.

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The Effect of Dietary Patterns On Blood Pressure: Results From the Dietary Approaches to Stop Hypertension (DASH) Clinical Trial

In addition to weight, salt, and alcohol, other diet-related factors may influence blood pressure (BP). In observational studies, significant inverse associations of BP with magnesium, potassium, calcium, fiber, and protein intake have been reported. However, in trials that tested these nutrients, often as dietary supplements, BP reduction has typically been small and inconsistent.

provided 8 to 10 servings of fruits and vegetables and 2 to 3 servings of low-fat dairy products each day. Stable body weight was maintained and sodium was held constant in each diet at approximately 3 g/d. Trained and certified observers, who were blinded to diet assignment, measured blood pressure with a random zero sphygmomanometer on 7 occasions at baseline and again at the end of intervention feeding.

More than 95% of participants completed the 8-week intervention phase. Figure 3 displays within-diet change in BP from baseline to the end of the intervention period for each diet group. For systolic and diastolic BPs, a gradient across diets was evident. Compared to the control diet, the fruits and vegetables' diet reduced systolic and diastolic BPs by 2.8 mm Hg ($P<0.001$) and 1.1 mm Hg ($P=0.07$), respectively. Corresponding reductions from the combination diet were 5.5 mm Hg and 3.0 mm Hg (each $P<0.001$). Compared to the fruits and vegetables diet, the combination diet reduced systolic BP by 2.7 mm Hg ($P=0.001$) and diastolic BP by 1.9 mm Hg ($P=0.002$). The BP reductions from the fruits and vegetables diet and combination diet were sustained for the duration of the 8-week intervention as seen in 83% of study participants with complete sets of weekly BP measurements (Fig 4). In the subgroup of 133 participants with hypertension, the combination diet reduced systolic BP by 11.4 mm Hg and diastolic BP by 5.5 mm Hg, in comparison to the control diet (each $P<0.001$).

In DASH, the diet rich in fruits, vegetables, and low-fat dairy products; reduced in saturated fat, total fat, and dietary cholesterol; and moderately increased in protein significantly reduced BP. A diet rich in just fruits and vegetables also reduced BP but to a lesser extent. The

Mean (95 Percent CI) Changes in Systolic Blood Pressure From Baseline to End of Intervention, by Diet

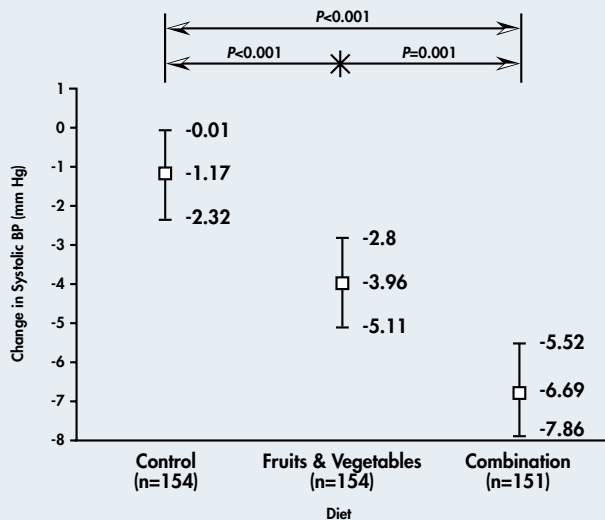


Figure 3

Because of these observations, DASH, a multicenter, randomized feeding study tested the effects on BP of whole dietary patterns rather than individual nutrients.¹ Trial participants (n=459, 49% women, 60% African American) had diastolic BPs between 80 and 95 mm Hg at entry and were provided all of their food for 11 weeks.² Participants were fed the control diet for 3 weeks and then randomly assigned to eat, for an additional 8 weeks, (a) the control diet; (b) a diet rich in fruits and vegetables but otherwise similar to the control diet or; (c) a combination diet rich in fruits, vegetables, and low-fat dairy products; reduced in saturated, total fat, and dietary cholesterol; and moderately increased in protein. The control diet was typical of what many Americans eat (35.7% of calories from fat, 13.8% of calories from protein, 233 mg/d of cholesterol, 1752 mg/d of potassium, 176 mg/d of magnesium, and 443 mg/d of calcium).

The diet with fruits and vegetables (b above) was designed to increase potassium, magnesium, and fiber by approximately 2.5 times the corresponding values in the control diet. In the combination diet, the percentages of calories from fat and protein were 25.6% and 17.9%, respectively. In addition, its potassium, magnesium, calcium, and fiber were approximately 2.5 times the corresponding values in the control diet. To achieve this nutrient profile, the combination diet

Mean (95 Percent CI) Changes in Diastolic Blood Pressure From Baseline to End of Intervention, by Diet

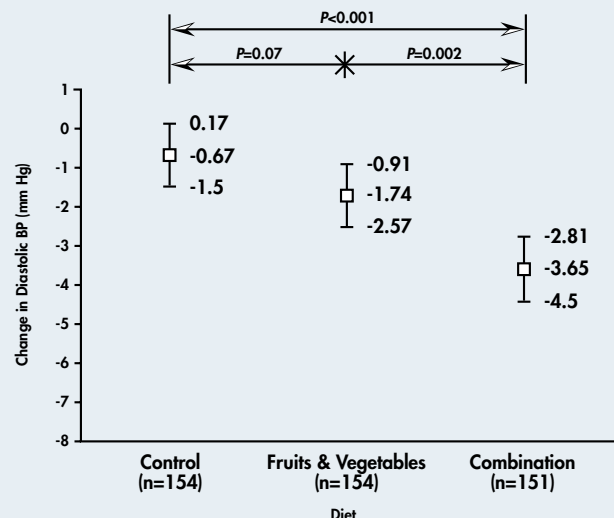


Figure 4

trial was not designed, however, to identify effective and ineffective components of the diets.

The results of the DASH trial should be broadly applicable to the United States (US) population. By using commonly available foods, including meats, the trial tested dietary patterns that the general US population could potentially adopt. Furthermore, the study sample was broadly representative, covering a wide age range which included equal numbers of men and women, consisted of 60% African Americans, and included persons with high normal BP and individuals with stage 1 hypertension. Application of the BP reductions observed in DASH to the US population could theoretically reduce incidence of coronary heart disease by 15% and stroke by 27%.

In conclusion, a diet rich in fruit, vegetables, and low-fat dairy products; and reduced in saturated fat, total fat and dietary cholesterol; and moderately increased in protein can substantially lower BP. This diet offers an additional nutritional approach to preventing and treating hypertension.

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ASH American Society of Hypertension

The American Society of Hypertension (ASH) is the largest US organization dedicated exclusively to hypertension and related cardiovascular disease. ASH was founded in 1985 by Dr. John Laragh and 16 other world-famous clinicians and scientists in an effort to evaluate the vast accumulation of data on hypertension and to provide a separate forum for those involved in the study or management of high blood pressure. The mission of the Society became "to organize and conduct educational activities designed to promote and encourage the development, advancement, and exchange of scientific information in all aspects of research, diagnosis, and treatment of hypertension, and related cardiovascular diseases."

Today, the Society boasts a membership of over 3,000 strong with 95% of its members holding an MD, PhD, or other advanced degree. The Society continues to fulfill its mission by annual meetings that provide registrants with the rare opportunity to exchange information and ideas with more than 2,500 fellow scientists from around the world. Highlights of the meeting include state-of-the-art lectures by renowned faculty, plenary sessions, original communications, poster presentations, technical and scientific exhibits, and provocative special symposia.

In addition, the Society publishes the prestigious *American Journal of Hypertension*, a monthly publication containing the latest information in both basic science and clinical research.

Membership in ASH is open to all those who have undertaken and accomplished meritorious original scientific investigation in the field of

hypertension and/or related cardiovascular disease, those involved in the diagnosis and treatment of hypertension and related cardiovascular disease, and those with a demonstrated serious interest in the field. Among the benefits of ASH membership are association and interaction with clinicians and scientists who are world leaders in the field, a subscription to the *American Journal of Hypertension* and all its supplements, a listing in the ASH Member Directory used for patient referral, and a savings of 50% or more on registration fees for the annual scientific meeting.

The American Society of Hypertension sponsors three award programs annually. The first award program focuses on the area of ongoing research training in the field of hypertension for young clinicians planning a career in academic medicine. Another recognizes and rewards three scientists who have carried out a significant body of work in the field of hypertension or related cardiovascular diseases. The last award program recognizes and rewards five young physicians, currently residents or fellows, who have a demonstrated interest in the study of hypertension or who plan a career change into the field.

For further information on ASH membership, awards programs, future meeting dates or to add your name to the ASH mailing list, contact:

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