

Hypertension

Editor's Comments

This issue of ASH Current Concepts in Hypertension continues the theme developed in a previous issue of reviewing the major ongoing clinical hypertension trials being conducted in the United States and overseas.

Included are discussions about two major trials looking at morbidity and mortality outcomes with a new delayed and sustained-release formulation of verapamil compared to beta blockers, and the new angiotensin II-receptor blocker losartan compared to a beta blocker. The third trial which is discussed is examining whether or not patients with Stage I isolated systolic hypertension would benefit from drug treatment. This was a group not previously examined in the Systolic Hypertension in the Elderly Program.

William H. Frishman, MD
Co-editor

The LIFE Study:

A Comparison of Losartan and Atenolol for Prevention of Cardiovascular Events in Hypertensive Patients with Left Ventricular Hypertrophy

The LIFE (Losartan Intervention For Endpoint reduction in hypertension) is a major new morbid-event study in hypertension launched in the United States and Scandinavia in September 1995. The study is designed to test the hypothesis that losartan will reduce major cardiovascular events by 15% compared to atenolol in hypertensive patients with left ventricular hypertrophy (LVH). The design of LIFE will compare losartan, the first angiotensin-receptor antagonist to come on the market for treating hypertension, to atenolol, a long-acting β_1 adrenoceptor antagonist proven to reduce cardiovascular complications. The endpoints of the study will be the "hard" ones of cardiovascular death and nonfatal myocardial infarction (MI) or stroke. Participants will be required to have electrocardiographic (ECG) evidence of LVH because of documentation that LVH strongly predicts MI and death in hypertensive patients, independent of the level of arterial pressure and other risk factors.

Why Do Another Morbid Events Study in Hypertension?

Antihypertensive treatment has greatly prolonged survival in hypertensive patients, with dramatic reductions in treatment trials of stroke mortality but less complete benefit—from half to at most two thirds of what might be expected from the observed lowering of blood pressure—with regard to the more common complication of MI. Because of the high prevalence of hypertension and MI in the adult population, successful prevention of MI by antihypertensive treatment has alluded present treatments that would be of great public health benefit. Advances in available treatments and in understanding of the evolution of hypertensive cardiovascular disease make it possible to address this question in a new way that heightens the likelihood of success.

“ . . . development of losartan as the first of the class of angiotensin I (AT₁) receptor blockers . . . achieves complete, long-acting blockade of the effects of angiotensin ”

Why Might Losartan be Especially Beneficial?

Over the past several years evidence from epidemiologic studies and trials of heart failure treatment has shown activation of the renin-angiotensin system predisposes to MI and interruption of this system may reduce this risk by 20% or more. Parallel meta-analyses of human LVH regression studies have suggested angiotensin-converting enzyme inhibition (ACEI) is more

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effective in this regard than other types of antihypertensive treatment. At the same time, development of losartan as the first of the class of angiotensin I (AT_1) receptor blockers to reach the market has provided an agent that achieves complete, long-acting blockade of the effects of angiotensin without the common adverse effect of cough seen with ACEIs.

Why Choose Atenolol as the Comparative Agent?

In keeping with the rationale of Report of the Fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-V), the proper comparative agent in a morbid events study needs to be one that has been proven to prolong life in hypertensive patients in comparison to placebo, ie, a diuretic or a β -blocker. Because the LIFE study includes both patients with uncomplicated hypertension for whom it is a primary prevention trial and hypertensive patients with prior MI for whom the goal is secondary prevention of recurrent events, the proven benefit of β -blockers in both settings made this the logical class of comparative agent. The available evidence of prognostic benefit, β_1 selectivity, and multinational availability of a long-acting form made atenolol the most logical choice within this class.

Why Use ECG LVH to Identify High-risk Hypertensives?

LVH was chosen as the primary feature to identify hypertensive patients at high risk because of its close association with the hypertensive disease process and known ominous prognostic implications. The ECG was chosen to detect LVH because its universal availability and low cost make it a feasible tool to identify a large number of high risk hypertensive patients. Framingham and many other studies over the last 30 years have shown that while ECG LVH is relatively uncommon, its detection identifies individuals at ≥ 2 -fold risk of MI and other complications. Advances in ECG methodology from Cornell and other centers have enhanced the previously low sensitivity of this technique without compromising its ability to identify increased LV mass determined by either necropsy or echocardiography.

LIFE Study Design

The LIFE study will enroll 8,300 patients aged 55 to 80 years with hypertension and ECG LVH, including 3,000 in the US, 2,000 in Sweden and 1,100 each in Denmark, Finland, and Norway. Patients will have seated systolic blood pressure of 160 to 200 mm Hg or seated diastolic blood pressure of 95 to 115 mm Hg after 2 weeks on placebo. The qualifying ECG must show LVH by criteria based on the Cornell QRS voltage (S wave in V1 and R wave in aVL) and the QRS duration, as verified by an ECG core laboratory established at the University of Goteborg in Sweden. Enrollment is to be completed by the end of 1996.

Treatment will be triple-blinded (to patient, investigator, and the drug company), beginning with random assignment of 50 mg of losartan or atenolol. If needed, upward titration of medication will first add 12.5 mg of hydrochlorothiazide to each arm followed by doubling of the dose of the blinded study medication prior to addition of higher diuretic doses or other medications if a fourth treatment step is needed. The trial will continue for at least 4 years

after enrollment of the last patient and until a total of 1,040 patients have suffered a primary endpoint (cardiovascular death, nonfatal MI or nonfatal stroke).

In addition to the primary comparison of the effects of losartan and atenolol on morbid events, additional studies planned within LIFE will test the relevance of LVH and its change to the prognosis of treated hypertension, and will determine whether losartan is more effective than atenolol for LVH regression. This will be accomplished by parallel studies evaluating the change in LV mass and other variables by echocardiograms at baseline and at the end of the first to fourth year of treatment in 1,000 participants, by analyses using serial computerized ECGs in several thousand LIFE participants, and by use of the Cornell voltage-duration product and other standard ECG measures from the conventional ECG in all participants.

Outcome of LIFE: What Will We Learn and When Will We Learn It?

At the end of the LIFE study, there will be sufficient outcome events to determine efficacy of AT_1 angiotensin receptor blockade in a study designed to have a power of 80% to detect a 15% difference in the number of patients in the two treatment arms suffering morbid events. A positive result, which is not assured because of the choice of a comparative agent with a strong track record of cardiovascular protection, would verify the importance of effective interruption of angiotensin effects to obtain optimal outcome. The time-line of study enrollment and projected morbid event rates

“At the end of the LIFE study, there will be sufficient outcome events to determine efficacy of AT_1 angiotensin receptor blockade . . .”

makes it possible that the study outcome could be known by early 2001. In addition, the echocardiographic and ECG studies have powers $>90\%$ to determine whether change in LVH predicts prognosis important after the effects of blood pressure change and treatment type have been taken into account and whether losartan is more effective than atenolol for this purpose.

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The CONVINCe (Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints) Study

The CONVINCe (Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints) Study is a major new clinical trial on hypertension announced at the most recent national meeting of the American Heart Association. This study will compare two treatment regimens for hypertension. Each of the treatment strategies in CONVINCe is novel. One regimen will begin with the calcium antagonist, verapamil, which was formulated to bring the concepts of chronobiology and chronotherapeutics to the treatment of hypertension. The comparator will also be different from regimens used in most previous clinical trials because, even before randomization occurs, it individualizes treatment by allowing a physician to choose either a diuretic or a β -blocker as the standard of care (SOC) for a given patient.

Study Design

CONVINCe is a randomized, multicenter, double-blind, parallel-group, two-arm, actively controlled trial comparing controlled-onset extended-release (COER) verapamil to the currently recommended Joint National Committee-V (JNC-V) standard of care (SOC) using either a diuretic or a β -blocker as the first line of treatment. Hypertensive patients will be randomized to receive COER verapamil, hydrochlorothiazide (HCTZ) or a β -blocker (atenolol), preselected by the treating physician for each patient prior to randomization (Fig 1). Medications will be titrated until goal blood pressure (BP) (<140/<90 mm Hg) is reached. A total of 15,000 patients will be enrolled at more than 300 clinical sites in the United States, Canada, and Europe and treated for 4 to 6 years.

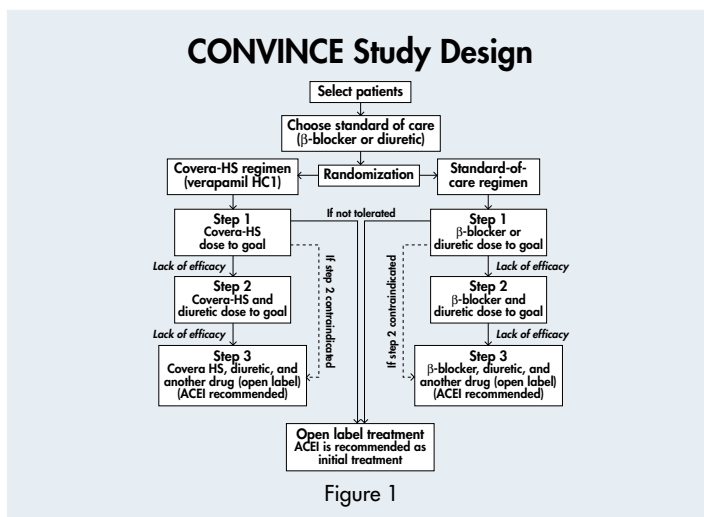


Figure 1

Objectives

The primary efficacy objective of CONVINCe is to compare COER verapamil with HCTZ or atenolol in preventing the first occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or any cardiovascular disease-related death. Secondary efficacy objectives are to determine whether treatment affects the occurrence of fatal or nonfatal MI, fatal or nonfatal stroke, or any cardiovascular disease-related death; to compare treatments with respect to the proportion of patients reaching goal BP; and to compare rates of the primary outcome measures occurring between 6 AM and noon. The safety objectives are to determine whether these treatments affect occurrence of all-cause mortality or new cancers (excluding nonmelanoma skin cancer),

hospitalization for bleeding, or withdrawal from blinded medication due to adverse events.

Therapy

The SOC arm of CONVINCe will begin with the physician's choice (preselected prior to randomization) of either 12.5 mg of HCTZ or 50 mg of atenolol administered in the morning. The other arm of CONVINCe will begin with 180 mg of COER verapamil, taken at bedtime using the gastrointestinal therapy (GIT) system for delivery.

The COER verapamil delivery system is a close relative of the GIT system but has a "delay coat" over the push-pull osmotic delivery system. This delay coat prevents any gastrointestinal juices from entering the tablet until 4 to 6 hours after administration to minimize drug delivery during the night, when BP is typically the lowest. Figure 1 illustrates the step-wise therapy progression to bring BP under control in both arms of the study. After the delay coat disintegrates the GIT system is activated and delivers verapamil initially at a fast rate, so the "peak" plasma concentration of verapamil occurs from 6 AM to 8 AM. This corresponds both to the time when BP is highest and when there is the highest risk for acute MI, stroke, angina, and sudden death. After the early morning increase in delivery rate, GIT delivers an even, time-independent dose of verapamil into the gut and circulation. Recent studies have shown this chronobiological method of verapamil delivery into the circulation results in reduced early morning BP, heart rate, and double product in hypertensive patients, as demonstrated using 24-hour ambulatory BP monitoring.

Summary

The primary objective of CONVINCe is to compare the two regimens' incidence of MI, stroke, and cardiovascular death. CONVINCe has an 80% power to detect a 15% difference between treatment regimens, assuming a 5-year event rate of 15% for the SOC arm, a two-sided significance level of 0.05 using the log-rank test, and appropriate adjustments to sample size for compliance and dropouts. A secondary objective is to compare the two regimens' incidence rate during the early morning hours (6 AM to noon).

Recruitment for CONVINCe was to begin in September 1996 and continue for 2 years. Clinical centers in the US, Canada, and eight European countries are expected to enroll patients with 4 to 6 years of planned followup (average 5 years). We hope to complete the study during the summer of 2002 and have final results available in the fall of that year. To participate in this study call 312-563-2313 for further information.

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Focus on Isolated Systolic Hypertension

About half of all Americans over age 60 have hypertension. As our population continues to age the diagnosis and management of blood pressure problems in these individuals will require a growing commitment from primary care physicians.

Until recently there was a relatively casual approach to hypertension in the elderly, often because physicians believed increases in systolic blood pressure were a normal part of the aging process. However, epidemiologic studies have shown that, for the elderly as well as the young, elevated systolic blood pressure greatly increases the risk of cardiovascular disease.

“... for the elderly as well as the young, elevated systolic blood pressure greatly increases the risk of cardiovascular disease.”

Enthusiasm for treating older patients with hypertension has been stimulated by pivotal clinical trials that have demonstrated meaningful reductions in stroke, congestive heart failure, and other cardiovascular disease. The Systolic Hypertension in the Elderly Program (SHEP), and the Swedish Trial in Old People with hypertension (STOP) confirmed the value of antihypertensive therapy for patients in their 60s, 70s, and 80s.^{1,2} It has become difficult to justify withholding treatment for older patients with hypertension.

Vascular Changes

Stiffening of major large arteries is part of the aging process. Because diastolic blood pressure is influenced by elastic recoil of the aorta and other major blood vessels, progressive reduction in diastolic measurements is one of the signs of age-related changes in arterial properties. The reduced windkessel buffering action results in increased systolic blood pressure and reduced diastolic blood pressure. Moreover, stiffening of the distal arterial circulation results in premature and exaggerated reflected waves that further increase systolic blood pressure.

For these reasons we anticipate the appearance of two characteristics in the patient with isolated systolic hypertension (high systolic blood pressure and normal or low diastolic blood pressure). First, the high systolic pressure, particularly the augmented and prolonged systolic pressure wave, increases stress on the left ventricular wall and predisposes to hypertrophy and ischemia. Second, the low diastolic pressure indicates arterial stiffening and signifies atherosclerotic changes in such critical parts of the circulation as the coronary and carotid arteries. Not surprisingly, these patients are highly susceptible to clinical cardiovascular problems.

Treatment of Isolated Systolic Hypertension

The SHEP experience confirmed the clinical benefits of treating isolated systolic hypertension. Because this study started several years ago it used a diuretic and a β -blocker as its active therapies. Experience with such newer drug classes as the calcium channel blockers or the angiotensin converting enzyme inhibitors is only now being obtained in patients with this condition. Diuretics in

clinical trials have produced sufficient adverse effects to require stopping or modifying treatment in many patients and have caused concern because of possible unwanted effects on electrolytes and other metabolic measurements. Moreover, such symptomatic complaints as dizziness or light-headedness may be more common in older patients than in the relatively robust volunteers selected for clinical trials.

Key Questions

There is growing interest in using newer antihypertensive drug classes to treat systolic hypertension. Calcium channel blockers effectively decrease blood pressure in older hypertensive patients, and it is necessary to confirm that the newest members of this class, particularly the intrinsically long-acting dihydropyridines, effectively control systolic hypertension.

A further question relates to the recommendation of JNC V³ to treat Stage 1 systolic hypertension, specifically in patients with systolic blood pressures between 140 mm Hg and 159 mm Hg. Will it be possible to achieve efficacy in these mildly hypertensive patients without adversely affecting quality of life?

The Stage 1 Systolic Hypertension (SISH) Trial

“This double-blind, randomized study will compare the long-acting dihydropyridine felodipine with the established diuretic chlorthalidone.”

This double-blind, randomized study will compare the long-acting dihydropyridine felodipine with the established diuretic chlorthalidone. Patients will have Stage 1 systolic hypertension with normal diastolic blood pressure (<90 mm Hg). During the 20 weeks of study, investigators will compare the efficacy of the two active drugs and also ensure that they are each significantly more effective than placebo. Blood pressure measurements, symptomatic complaints, and treatment-induced changes in electrolyte and other routine chemistry values will be carefully monitored.

The results of this ongoing study will guide clinicians in the practical management of older patients with milder forms of isolated systolic hypertension. This multicenter program has a commercial sponsor and the study Chairman is Dr. William Frishman.

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1. JAMA. 1991; 265:3255-3264.
2. Lancet. 1991; 338:1281-1285.
3. *The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, MD: National Institutes of Health, 1993.

Dr. Weber is a program sponsor for Pfizer, Inc.

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Thanks for your help!

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 Current Concepts in Hypertension

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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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