

Calcium Channel Blockers: New Trials and Trials In Progress

A number of clinical trials of newer calcium channel blockers, alone or in combination or in comparison with other drugs, have been designed primarily to assess the drugs' long-term efficacy and safety. These trials fall into several different

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chronologic categories—those recently concluded, with results to be presented soon; those launched within the past few years, with results expected within the next few years; and those to be launched within the first half of 1996, with results expected just before or soon after 2000.

STOP-Hypertension 2

Enrollment in the second Swedish Trial in Old Patients (STOP) ended on the last day of 1994 with 6,628 patients. Results should be available in 1996. The study (which uses the PROBE design—*p*rospective, *r*andomized, *o*pen study with *b*linded *e*ndpoint evaluation) was designed to compare the effects of newer antihypertensive agents—the ACE inhibitors enalapril and lisinopril and the calcium channel blockers isradipine and felodipine—with those of older agents, the diuretics (hydrochlorothiazide) and beta-blockers (metoprolol, atenolol, and pindolol), on cardiovascular mortality in patients aged 70 to 84.

HOT

The principal objective of the Hypertension Optimal Treatment (HOT)

study is to examine the relationship between different target diastolic blood pressures—90 mm Hg or less, 85 mm Hg or less, and 80 mm Hg or less—and cardiovascular mortality and morbidity. In effect, HOT is examining the issue of the J curve, the phenomenon wherein reduction of elevated blood pressure to some critical level decreases the risk for morbidity and mortality related to coronary heart disease, while further reduction may compromise myocardial perfusion and increase the risk of cardiovascular events. The study also is examining the effect on outcomes of low-dose aspirin therapy as a component of anti-hypertensive treatment and will allow analyses of the influence on outcomes of various risk factors, such as prior myocardial infarction or stroke, diabetes, smoking, age, and sex.

The first-line drug for all patients in HOT is the calcium channel blocker felodipine. Therapeutic tracks include increase of the initial dose of felodipine, addition of an ACE inhibitor or a beta-blocker, or both, and the further addition of a low-dose diuretic. This PROBE-design trial has enrolled approximately 20,000 patients aged 50 to 80 who have been followed up for about 2.5 years. The HOT trial has been running for 3 years and will conclude in 1996. Trial directors include Lennart Hansson, MD, University of Uppsala, Uppsala, Sweden, and Stevo Julius, MD, University of Michigan, Ann Arbor, Michigan.

ELSA

The European Lacidipine Study on Atherosclerosis (ELSA) is being con-

ducted in seven European countries. Lacidipine is a new-generation dihydropyridine that exhibits some exceptional properties, such as high lipophilicity and penetration deep into the cell membrane, which leads to protracted action independent of waning plasma concentration. Recruitment of approximately 2,300 hypertensive patients ended in November 1995. The trial consists of a 6-month period of treatment adjustment during which patients receive lacidipine or the beta-blocker atenolol and a follow-up maintenance therapy phase of about 3.5 years. The goal is to measure the effect of antihypertensive treatment with either of these two drugs on the development of carotid atherosclerosis.

The initial ELSA protocol called for stratification of patients by the presence or absence of carotid plaques or wall thickening. This protocol was amended when it was found that 82% of the first 989 hypertensive patients enrolled were positive for carotid plaques. Alberto Zanchetti, MD, Center of Clinical Physiology and Hypertension, Milan, Italy, is one of the trial's directors.

INTERCEPT

INTERCEPT (Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis) is the first prospective, double-blind trial to randomly assign myocardial infarction patients who first received aspirin plus thrombolysis with tissue plasminogen activator or streptokinase to a calcium channel blocker or placebo (or, optionally for some patients, a beta-blocker). Target enrollment is about 1,000 patients. The trial began in 1994 and will be completed at the end of 1996. Data should be forthcoming shortly thereafter.

The idea for the study arose from several sources. When data from the DAVIT-2 and MDPIT studies were pooled, the odds ratio was .61 for cardiac deaths and nonfatal reinfarctions among a total of 936 patients with non-Q-wave myocardial infarctions treated after the infarction with a heart-rate-lowering

calcium channel blocker (verapamil or diltiazem) and followed up for 12 to 18 months. The 95% confidence interval for this point value did not exceed unity; the two-tailed *P* value was 0.0068. Since timely thrombolytic therapy results in a reopened infarct-related artery and subsequent fairly rapid reperfusion, the post-thrombolytic myocardial infarction resembles a naturally occurring non-Q myocardial infarction. The prophylactic strength of agents currently used for secondary prevention (a beta-blocker or ACE inhibitor) is low in patients with non-Q infarction or normal left ventricular function. Therefore, the rationale for INTERCEPT is that a heart-rate-lowering calcium channel blocker may be a beneficial adjunctive anti-ischemic treatment in myocardial infarction patients who received thrombolytic therapy.

The directors of the study are Kim Fox, MD, Royal Brompton Hospital, London, England, and William Boden, MD, Tufts University School of Medicine, Boston, Massachusetts.

INSIGHT

The International Nifedipine Study; Intervention as a Goal in Hypertension Treatment (INSIGHT) began in September 1994. The planned completion date is 1999. Target enrollment is 6,600 hypertensive patients aged 55 to 80; to date, nearly 5,000 have been entered into the trial. This randomized, double-blind study is being conducted in nine European countries.

The primary objective of INSIGHT is to compare cardiovascular and cerebrovascular morbidity and mortality in high-risk hypertensive patients taking either extended-release nifedipine alone or in combination with atenolol, or amiloride plus hydrochlorothiazide with or without atenolol.

Patients in the trial complete a 2- to 4-week placebo run-in period. If the patient's blood pressure at the end of this period is 150/95 mm Hg or higher or more than 160 mm Hg systolic, the patient is randomly assigned to daily treatment with long-acting nifedipine or a

diuretic for 3 years. Both drugs are titrated and, when necessary to achieve long-term blood pressure control, other antihypertensive medications are added, including the beta-blocker atenolol and the ACE inhibitor enalapril.

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PROTECT

The Prospective Re-Infarction Outcomes in the Thrombolytic Era Cardizem CD Trial (PROTECT)* is being funded by Hoechst Marion Roussel Canada. This prospective, randomized, double-blind trial will be conducted at approximately 100 centers in Canada. It will compare the effects of diltiazem CD and propranolol in patients who have suffered a non-Q-wave myocardial infarction.

Enrollment begins in 1996. Approximately 3,000 men and women older than age 21 with non-Q myocardial infarction documented by clinical presentation, electrocardiogram, and elevations of creatine kinase or MB isoenzyme of creatine kinase will be recruited. Patients with left ventricular dysfunction or congestive heart failure will be excluded. Treatment will not begin until 2 to 4 days after the index myocardial infarction to allow the diagnosis of non-Q infarction to be confirmed.

The roughly 1,500 patients to receive diltiazem CD in this trial will exceed the total number of patients with myocardial infarction given this treatment in all previous trials. With its focus on non-Q myocardial infarction, PROTECT may add significantly to existing knowledge of the role of diltiazem and propranolol in managing this type of myocardial infarction.

Anatoly Langer, MD, director of the coronary care unit, Division of Cardiol-

*The Perindopril Regression of Vascular Thickening European Community Trial is known by this same acronym.

ogy, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada, is the trial's director.

CONVINCE

The Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) is a prospective, randomized study designed to determine whether a novel formulation of verapamil is as effective as a diuretic or beta-blocker in treating patients with essential hypertension. Entry criteria call for the enrollment of 15,000 patients who will be representative of the entire population of hypertensive patient in the United States. To be admitted into the trial, patients must have at least one of eight defined cardiovascular risk factors (eg, smoking, dyslipidemia, or prior myocardial infarction). Patients will be recruited through approximately 300 centers in the United States, Canada, and perhaps Europe as well. The trial will run 4 to 6 years.

The form of verapamil to be used in CONVINCE is Covera HS, which incorporates a new controlled-onset, extended-release (COER-24) delivery system. The system allows variable release of drug approximating the circadian pattern of blood pressure variation. For example, peak concentrations are attained in the hours just before and after awakening, when blood pressure undergoes its steepest rise. (*Editor's note:* At the time of printing, this version of verapamil has been granted "approvable" status by the Food and Drug Administration for the treatment of hypertension and angina.)

Henry Black, MD, chairman of the department of preventive medicine at Rush-Presbyterian-St. Luke's Medical Center in Chicago, is the principal investigator.

PREDICT

The Prospective Randomized Evaluation of Diltiazem CD Trial (PREDICT) is designed to examine the long-term effects of diltiazem CD in the treatment of hypertension. Between

6,000 and 7,000 patients aged 55 and older with mild to moderate essential hypertension will be enrolled in PREDICT through a large number of study centers in the United States. The population to be recruited will include high-risk patients with a history of myocardial infarction, stroke, coronary heart disease, or adult-onset diabetes. Approximately equivalent numbers of men and women and members of several racial groups are expected to be included. Enrollment begins in mid-1996 and will be completed by mid-1997; the follow-up period is 3 years. Three committees, two of them independent, will monitor PREDICT. In addition to a data and safety monitoring board, there will be an independent endpoint committee.

Patients will be randomly assigned to receive either diltiazem CD or the diuretic chlorthalidone. The primary objective of the trial is to compare the rates of fatal and nonfatal cardiovascular events in the two treatment groups. Chlorthalidone has been proved in appropriately designed trials to reduce the incidence of both stroke and myocardial infarction in patients with hypertension.

The pharmaceutical company Hoechst Marion Roussel and the chairman of the trial steering committee, William Applegate, MD, professor and chairman, Department of Preventive Medicine, University of Tennessee, Memphis, anticipate that PREDICT will add significantly to the body of information being generated by the Anti-hypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT).

NORDIL

The Nordic Diltiazem Trial (NORDIL), being conducted in Sweden and Norway, is recruiting 11,000 patients for a 5-year study to compare the effects of diltiazem, beta-blockers, and diuretics in preventing cardiovascular morbidity and mortality in hypertensive patients. In this prospective trial, patients are randomly assigned to open-label treatment, but the endpoint

evaluation is blinded (the PROBE design).

SYST-EUR

Systolic Hypertension-Europe (SYST-EUR) is a 6-year trial principally evaluating the effect of antihypertensive treatment on stroke morbidity and mortality in approximately 3,000 patients older than age 60 who have isolated systolic hypertension. Drugs used are nifedipine and, if necessary, enalapril and hydrochlorothiazide. Secondary objectives are to assess the effects of treat-

The main hypothesis of ALLHAT is that at least one of the newer antihypertensive agents may prove superior to diuretics.

ment on quality of life and to determine whether 24-hour ambulatory blood pressure monitoring improves the prediction of cardiovascular complications. Final results should be available before 2000.

ALLHAT

Preeminent among studies in progress is the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT), sponsored by the National Heart, Lung, and Blood Institute and receiving funding aid from the pharmaceutical industry.

At the AHA meeting, Suzanne Oparil, MD, immediate past-president of the American Heart Association, made a special plea for more centers to participate in ALLHAT. She called the study a massive undertaking. Set to enroll 40,000 high-risk patients (about 55% non-white), ALLHAT has just passed the 12,000 patient mark. Results are expected in 2002.

The main hypothesis propelling this study is that at least one of the newer antihypertensive agents may prove superior to diuretics in protecting against events such as myocardial infarction, stroke, mortality related to cardiovascular events, and possibly even mortality from all causes. Patients will be ran-

domly assigned to treatment with the calcium channel blocker amlodipine, the ACE inhibitor lisinopril, the alpha₁-blocker doxazosin, or the diuretic chlorthalidone.

ALLHAT also has another randomization involving pravastatin, an HMG-CoA reductase inhibitor that reduces low density lipoprotein-cholesterol (LDL-C). This makes the trial scientifically compelling, since this combined approach—lipid lowering and blood pres-

sure lowering—addresses the premise that elevated blood pressure is a marker of a more complex disorder and that prevention of serious events depends on interventions more complex than simply lowering blood pressure.

Physicians interested in taking part in ALLHAT should contact the clinical coordinating center (800-690-7870) or the National Heart, Lung, and Blood Institute (301-496-4236) for further information.