EXPERIMENTAL APPROACHES TO DETERMINING THE CHOICE OF FIRST-STEP THERAPY FOR PATIENTS WITH HYPERTENSION

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ABSTRACT

Detection, treatment and control of hypertension is one of the best proven approaches to prevention of cardiovascular disease. Antihypertensive treatment trials have convincingly demonstrated that diuretics and beta-blockers reduce the risk of stroke and coronary heart disease. Corresponding information is not yet

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available for newer classes of antihypertensive drug therapy such as calcium channel blockers, angiotensin converting enzyme inhibitors and alpha, receptor blockers. Several experimental studies are now addressing this question. The largest such trial (n=40,000) is the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). This manuscript describes two studies (TOMHS and the VA study on antihypertensive agents) that compared several classes of antihypertensive drugs with regard to blood pressure outcomes and ALLHAT, which is comparing the effect of four first-step approaches to antihypertensive therapy on combined incidence of fatal coronary heart disease and non-fatal myocardial infarction.

INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death on a worldwide basis (1). Illness from CVD is also an important contributor to morbidity and has important economic implications for the individual and society. Treatment of patients with clinical manifestations of CVD is important but sudden death and the fact that such treatment is often palliative rather than curative limit its effectiveness. Treatment and prevention of risk factors for CVD represent a more fundamental approach to reducing the burden of CVD in the general population (2).

High blood pressure (BP) is among the most important predictors of risk for coronary heart disease (CHD), stroke, congestive heart failure and renal failure (3,4). It is also one of the most prevalent risk factors for CVD, both in economically developed and economically developing countries (5,6). In combination, the strikingly increased risk of disease due to high BP and its high prevalence in the community makes this risk factor one of the most important causes of morbidity and mortality in most populations (3,4). Treatment trials have repeatedly demonstrated the value of antihypertensive drug therapy as a means to reduce the risk of stroke and CHD in patients with mild to moderate hypertension (7,8). Most of these trials have, however, been confined to first-step therapy with diuretics. In the remainder, participants have been randomized to a beta-blocker or to treatment with either a diuretic or a beta-blocker. The latter trials have suggested that diuretics and beta-blockers may provide a similar level of protection from CVD in most patients. For convenience, treatment with diuretics and beta-blockers will subsequently be referred to as "conventional therapy."

Several newer classes of antihypertensive drug therapy have been approved for management of hypertension during the past two decades. These include
calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and alpha, receptor blockers. In many countries, these newer agents have become increasingly common forms of drug therapy. For instance, in the United States the use of ACE inhibitors and calcium channel blockers increased dramatically during the five-year interval between 1986 and 1991 from less than 10% to more than 40% of all antihypertensive drug prescriptions (9). During the same time period, the corresponding percentages for diuretics and, to a lesser extent, beta-blockers declined progressively. Despite the popularity of the newer agents in clinical practice, however, the extent to which they reduce the long-term risk of CVD complications in patients with hypertension is uncertain (10). Given this, and the fact that the newer agents are substantially more expensive than either diuretics or beta-blockers, there is an urgent need to compare the benefits and risks of the newer and older agents in appropriately designed randomized controlled clinical trials. Recent reports suggesting the possibility of adverse CVD effects in patients taking calcium channel blockers (11-13) serve to underscore the need for experimental studies comparing the newer agents with conventional therapy.

TOMHS AND THE VETERANS ADMINISTRATION TRIALS OF FIRST-STEP THERAPY IN PATIENTS WITH HYPERTENSION

Two large investigator initiated randomized controlled trials have compared the value of antihypertensive therapy with newer and conventional antihypertensive drugs (14,15). The Treatment of Mild Hypertension Study (TOMHS) was a randomized, placebo-controlled, double-blind, multicenter (four centers) trial carried out in 902 middle-aged (45-69 years) men and women to compare six treatments for long-term care of patients with Stage I (mild) hypertension. Against a background of sustained treatment with non-pharmacologic nutritional-hygienic advice, participants were randomly assigned to take the diuretic chlorthalidone (15 mg/d; n=136), the beta-blocker acebutolol (400 mg/d; n=132), the alpha1 receptor blocker doxazosin mesylate (2 mg/d following one month of 1mg/d; n=134), the calcium channel blocker amlodipine maleate (5 mg/d; n=131), the ACE inhibitor enalapril maleate (5 mg/d; n=135), or placebo (n=234). All the drugs were administered once a day in the morning. If the patient’s diastolic BP remained ≥95 mm Hg, the starting dose was doubled and additional therapy was added as needed. The participants were
followed for an average of 4.4 years. Their mean starting level of systolic and diastolic BP was only 140.4 and 90.5 mm Hg, respectively. Despite this, sizable BP reductions were noted for all six treatment groups. Those who received active treatment experienced a greater reduction in systolic and diastolic BP than their counterparts in the placebo arm (-15.9 vs. -9.1 mm Hg for systolic BP and -12.3 vs. -8.6 mm Hg for diastolic BP). After four years of follow-up, 72% of those in the active treatment groups and 59% of those in the placebo group were still being managed on their originally assigned medication as monotherapy. Major nonfatal cardiovascular events were less common in the active treatment groups compared to the placebo group (5.1% vs. 7.3%; \( p = 0.21 \)) as was the frequency of all clinical events (11.1% vs. 16.2%; \( p = 0.03 \)). In addition, the incidence of most resting electrocardiographic abnormalities was lower and the quality of life was improved for those assigned to the active treatment group compared to their counterparts in the placebo group. Differences among the five drug treatment arms did not consistently favor one group in terms of regression of left ventricular mass, blood lipid levels, other biochemical measurements, ventricular ectopic beats and quality of life measurements.

The Veterans Administration study was a randomized, controlled, double-blind, multicenter (15 centers) trial carried out in 1292 male veterans (44% African Americans) who were randomly assigned to receive placebo or one of the following six antihypertensive drugs: the diuretic hydrochlorothiazide (12.5 to 50 mg/d), the beta-blocker atenolol (25-100 mg/d), the ACE inhibitor captopril (25-100 mg/d), the central agonist clonidine (0.2 to 0.6 mg/d), the calcium channel blocker diltiazem (120-360 mg/d in sustained release form), or the alpha, receptor blocker prazosin (4-20 mg/d). At baseline, their mean age was 59 years and their mean systolic and diastolic BP were 152 and 99 mm Hg, respectively. Drug doses were titrated to achieve a goal diastolic BP <90 mm Hg and the patients were treated for at least one year. The percent of participants in whom BP was successfully controlled (<90 mm Hg at the end of titration and <95 mm Hg at one year) was 59% for diltiazem, 51% for atenolol, 50% for clonidine, 46% for hydrochlorothiazide, and 42% for captopril and prazosin. Drug intolerance was more frequent with clonidine (14%) and prazosin (12%) than with the other agents, while biochemical abnormalities were most common in the diuretic group.
Although the TOMHS and the Veterans Administration trials provide useful comparative experience, neither provides definitive evidence regarding the optimal choice of first-step antihypertensive drug therapy. Several controlled clinical trials in which participants have been randomly assigned to treatment arms consisting of conventional and newer drugs are currently in the field or are about to get started. The results of these trials will be particularly helpful if the findings with different drug classes are consistent across different designs and study populations.

THE ANTIHYPERTENSIVE AND LIPID-LOWERING TREATMENT TO PREVENT HEART ATTACK TRIAL (ALLHAT)

The largest experimental study testing the efficacy of treatment with different classes of antihypertensive drug therapy is the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). A detailed description of the design of this trial has already been published (16). The remainder of this manuscript is devoted to a description of key elements in the design and organizational structure of ALLHAT. The study has two experimental components: an antihypertensive trial and a lipid-lowering trial.

Design and Objectives of Antihypertensive Component

In the antihypertensive trial, the incidence of fatal CHD and non-fatal myocardial infarction is being compared in high-risk hypertensives who are assigned, at random, to one of four classes of antihypertensive drug therapy. The four study drugs are the diuretic chlorthalidone (12.5-25 mg/d), the calcium channel blocker amlodipine (2.5-10 mg/d), the ACE inhibitor lisinopril (10-40 mg/d), and the alpha1 receptor blocker doxazosin (2-8 mg/d). All four study medications are being administered double-blind, once daily and the therapeutic goal is to reduce systolic and diastolic BP to <140 and <90 mm Hg, respectively. If satisfactory BP control cannot be achieved with the maximal dosage level of the study medication, additional open-label second-step treatment can be instituted using either reserpine (0.05-0.2 mg/d), atenolol (25-100 mg/d), or oral clonidine (0.1-0.3 mg/d). For those who are still uncontrolled, hydralazine (25-100 mg/d) can be added as a third-step treatment. The primary objective in the antihypertensive component of the study is to determine whether the combined incidence of fatal CHD and non-fatal myocardial infarction differs between the
diuretic treatment group and any of the three alternative first-step antihypertensive pharmacologic treatment groups. Additional objectives are to compare the effects of the treatments on CVD mortality and major morbidity, health care costs, and health-related quality of life.

**Design and Objectives of Lipid-Lowering Component**

Lipid lowering is being conducted in a subset of ALLHAT participants with cholesterol levels believed to confer an increased risk of CHD. In this context, the efficacy of cholesterol lowering is being evaluated in an open-label trial that compares groups assigned, at random, to the 3-hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor pravastatin (20-40 mg/d) or usual care (no investigator initiated lipid-lowering drug therapy). All participants receive instruction in the Step-One diet recommended for treatment of hypercholesterolemic patients (17). The primary objective of the lipid-lowering component is to compare the incidence of all-causes mortality in the two treatment groups. Secondary objectives are to assess long-term safety, the effect of lipid lowering on the combined incidence of fatal CHD and non-fatal myocardial infarction in persons ≥55 years of age and in other important subgroups of the population (women, African Americans, and type II diabetics), the effect of lipid lowering on myocardial infarction (based on centrally coded ECGs), the effect of lipid lowering on incidence and mortality from specified non-cardiovascular causes.

**Inclusion and Exclusion Criteria for the Antihypertensive Component**

The 40,000 participants being recruited into the antihypertensive component of the trial are all hypertensive (on therapy or meeting the JNC V BP criteria) and ≥55 years at baseline. In addition, they must have at least one additional major risk factor for CVD. The latter include:

- History of myocardial infarction or stroke (≥6 months prior)
- History of a revascularization procedure (ever)
- Documented atherosclerosis
- Type II diabetes mellitus
- HDL-cholesterol level <35 mg/dl (twice within the previous 5 years)
- Current cigarette smoking
- Left ventricular hypertrophy (ECG voltage criteria or echocardiographic measurement of a combined ventricular septum and posterior wall thickness ≥25 mm during the previous two years).
The principal exclusion criteria for the antihypertensive component include:

- Myocardial infarction (<6 months), stroke (<6 months), or symptomatic angina
- Congestive heart failure (treatment or an ejection fraction <35%)
- Renal insufficiency (serum creatinine ≥2 mg/dl)
- Contraindication or need for any of the blinded study medications
- Need for more than two antihypertensive medications to control BP (systolic and diastolic BP ≤160 and ≤100 mm Hg, respectively)
- Factors suggesting low adherence to the protocol
- Presence of a serious disease.

**Inclusion and Exclusion Criteria for the Lipid-Lowering Component**

Eligibility for the cholesterol component includes the following:

- Enrollment in the antihypertensive trial
- Fasting LDL-cholesterol 120-189 mg/dl (100-129 mg/dl for those with known CHD)
- Fasting serum triglycerides <350 mg/dl.

Exclusions for the cholesterol component include:

- Treatment with prescription medications for lipid lowering
- Treatment with high doses of non-prescription niacin (≥500 mg/d)
- Contraindication to HMG CoA reductase inhibitors
- Known untreated secondary cause of hyperlipidemia
- Alanine aminotransferase (ALT) > twice upper limit of normal.

**Sample Size and Study Power**

The antihypertensive component is intended to provide 82.5% power to test the hypothesis that the combined incidence of fatal CHD and non-fatal myocardial infarction will be 20% lower in the calcium channel blocker, or ACE inhibitor, or alpha, receptor blocker groups compared to the diuretic group, based on the following assumptions:

- Participant sample size of 40,000
- Six year incidence of fatal CHD and non-fatal myocardial infarction of 7.8% in the diuretic group
- 25% reduction in CHD event rates in patients randomized to the active versus control treatment arms of the lipid-lowering trial
- A non-compliance and loss to follow-up experience resulting in the need to recognize an effective reduction of 16.3% in the combined incidence of fatal CHD and non-fatal myocardial infarction for the calcium channel blocker, ACE inhibitor, and alpha, receptor blocker groups compared to the diuretic group
Rates of treatment crossover between each of the other study drugs and chlorthalidone of 2.75% in each of the first three years and 6% during the last three years of the study

Inability to determine the status of CHD in 16.8% of the study participants (8.6% of the person years of follow-up)

A type I (α) error = 0.05.

Variation in these assumptions yields power estimates from 86% to 77% depending on whether the assumptions are more optimistic or pessimistic. To maximize the statistical power for testing the primary hypothesis, 1.7 times as many participants are being assigned to the diuretic group compared to the other three treatment groups.

The lipid-lowering component is intended to provide approximately 85% power to test the hypothesis that all-causes mortality will be 14% lower in the HMG CoA reductase inhibitor (pravastatin) group compared to the usual care group, based on the following assumptions:

- Sample size of 20,000
- Six-year mortality of 12.2% (2.15% per year) in the usual care group
- A 14% reduction in mortality in the pravastatin group
- A “dropout” rate from pravastatin to no treatment of 5% in the first year and 2.5% in subsequent years; a “drop-in” rate of 2% per year from no treatment to pravastatin or a similar drug
- No loss to follow-up for mortality
- A 10% reduction in mortality in each of the three non-diuretic treatment arms of the antihypertensive component of the study
- A type I (α) error = 0.05.

Variation in these assumptions yields power estimates from 76-85% depending on whether the assumptions are more or less optimistic.

**Follow-Up**

During the first 12 months following randomization, participants are minimally expected to return for study visits after 1, 3, 6, 9, and 12 months. Subsequently, they are expected to return for study visits at four-month intervals. Additional visits are being conducted if there is a special indication. In addition to medical history and dosage titration history, a variety of laboratory data is being collected. The latter includes serum potassium, glucose, creatinine, alanine aminotransferase, and a fasting lipid profile at baseline. Serum potassium, creatinine, glucose and total cholesterol measurements are being obtained less frequently. More detailed and more frequent measures of lipid levels and serum
alanine aminotransferase are being obtained on participants in the lipid-lowering component. Resting 12-lead ECGs are being collected at baseline and following 24, 48 and 72 months after randomization. The ECGs are being reviewed at a central coding center using the Minnesota Code, which is a standardized classification system that documents prevalent and incident cardiac events.

**Organization and Timelines**

The study is being sponsored by the National Heart, Lung, and Blood Institute (NHLBI), in conjunction with the Veterans Administration and with support from the pharmaceutical industry. It is being conducted in a practice-based setting at clinical centers throughout the United States. The final number of centers needed to reach the recruitment goal is uncertain but as many as 400 centers may participate. The program office is based at the Division of Epidemiology and Clinical Applications (DECA) and the Division of Heart and Vascular Diseases (DHVD) of the NHLBI. Central coordination is being provided by the Clinical Trials Center at the University of Texas (Houston) School of Public Health. The Clinical Trials Center is being assisted by investigators and staff at central Drug Distribution, ECG Coding, and Laboratory centers. Regional coordination is being provided by physicians, nurses and other health professionals at eight academic centers across the country. Policy and management decisions are being made by a trial Steering Committee, with external review by a Data and Safety Monitoring Board.

A vanguard “feasibility” phase of the study was conducted at twenty clinical centers between February 1994 and August 1994. Based on this experience, it was decided that a full-scale trial should be initiated. Follow-up is scheduled for completion in 2002 unless interim monitoring by the Data and Safety Monitoring Board indicates the need for early termination of any of the treatment arms.

**REFERENCES**


