Baseline Characteristics of the Diabetic Participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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OBJECTIVE — Hypertension (HTN) is a major risk factor for cardiovascular disease (CVD) in the setting of diabetes. There is no consensus on how best to treat hypertension among those with diabetes. Here we describe the characteristics of a cohort of hypertensive adults with diabetes who are part of a large prospective blood pressure study. This study will help clarify the treatment of HTN in the setting of diabetes.

RESEARCH DESIGN AND METHODS — The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a double-blind randomized trial of 42,448 high-risk hypertensive participants, ages ≥55 years, designed to determine whether the incidence of fatal and nonfatal coronary heart disease (CHD) and combined cardiovascular events (fatal and nonfatal CHD, revascularization surgery, angina pectoris, congestive heart failure, and stroke) differs between diuretic (chlorthalidone) treatment and three alternative antihypertensive therapies: a calcium channel blocker (amlodipine), an ACE inhibitor (lisinopril), and an alpha-adrenergic blocker (doxazosin). The planned follow-up is an average of 6 years, to be completed March 2002.

RESULTS — There are 15,297 diabetic individuals in the ALLHAT study (36.0% of the entire cohort). Of these individuals, 50.2% are male, 39.4% are African-American, and 17.7% are Hispanic. Demographic and laboratory characteristics of the cohort are similar to those of other studies of the U.S. elderly population with HTN. The sample size has 42 and 93% confidence, respectively, for detecting a 16% difference between the diuretic and each of the nondiuretic treatments for the two study outcomes.

CONCLUSIONS — The diabetic cohort in ALLHAT will be able to provide valuable information about the treatment of hypertension in older diabetic patients at risk for incident CVD.

Diabetes Care 24:654–658, 2001

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Received for publication 20 July 2000 and accepted in revised form 27 October 2000.

Abbreviations: ADA, American Diabetes Association; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BP, blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; ECG, electrocardiogram; HTN, hypertension; IFG, impaired fasting glucose; LVH, left ventricular hypertrophy; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral arterial disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

It is estimated that 5.7–7.5 million Americans with diabetes have hypertension (HTN) (1,2). HTN occurs twice as often in diabetic individuals as it does in nondiabetic individuals (3). HTN is implicated in 30–75% of diabetes-related complications and 45% of diabetes-related deaths (4,5). Most affected are elderly individuals and members of minority groups (6). The high degree of coincidence of these two disorders is not surprising given that they share several common pathogenic factors, such as adiposity, diminished physical activity, and insulin resistance (7).

Despite the enormity of the problem, it is unknown whether any one class of blood pressure (BP) medication is more effective than another for the treatment of HTN in the setting of diabetes. Much of the information that is available is extrapolated from post hoc analyses of observational data (8) and small clinical trials (9–11), or from studies that have had unequal blood pressure control because of the use of placebo in the control groups (12–14). Studies using diuretics (13,15–19), calcium channel blockers (9–12,20–23), and beta-blockers (24–30) have yielded conflicting results. As a result, the most recent reports by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (31), the American Heart Association (32), and the American Diabetes Association (ADA) (33) have not made firm recommendations for the use of one class of medication over another. Only in the instance of proteinuria in type 1 diabetes is there a consensus by these organizations that ACE inhibitors are the medication of choice in diabetic individuals with HTN.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is the first clinical HTN trial in which a large number of people with diabetes (15,297) have been enrolled and prospectively designated

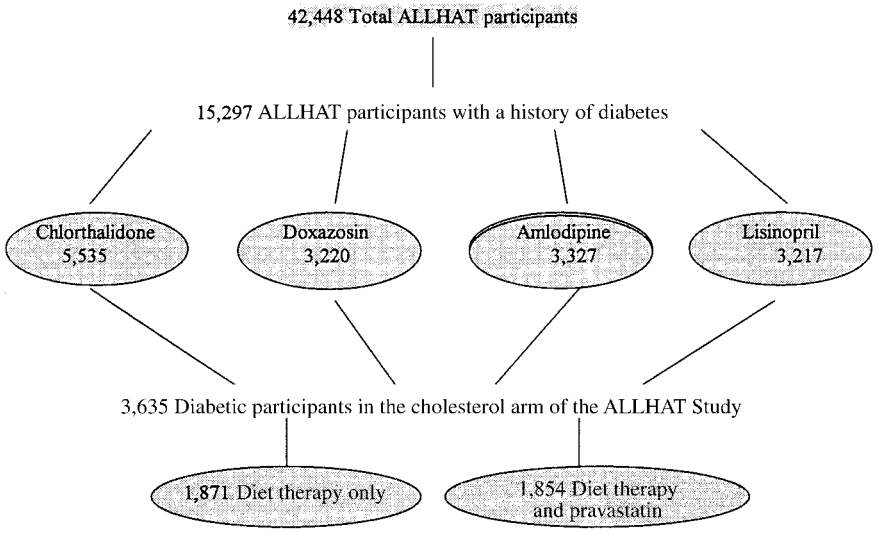

Figure 1—*Flow chart of the ALLHAT Study and the diabetic cohort. All participants had hypertension and were ≥ 55 years of age.*

for subgroup analyses. Four classes of antihypertensive medications are being randomly assigned and compared for outcome. ALLHAT therefore presents a potential opportunity to study the treatment of HTN in the setting of diabetes. In the present study, we describe the baseline characteristics of the diabetic cohort and test the feasibility of answering the ALLHAT questions in the diabetic cohort.

RESEARCH DESIGN AND METHODS

— ALLHAT, sponsored by the National Heart, Lung, and Blood Institute in conjunction with the Department of Veterans Affairs, is a practice-based, randomized, clinical trial of 42,448 high-risk hypertensive participants ages ≥55 years (Fig. 1). Details of the study design have been published (34). In brief, ALLHAT has two components. The antihypertensive component is a randomized double-blind trial designed to determine whether the combined incidence of fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI) differs between diuretic treatment (chlorthalidone, 12.5–25 mg per day) and the three alternative antihypertensive therapies: a calcium channel blocker (amlodipine, 2.5–10 mg), an ACE inhibitor (lisinopril, 5–40 mg), and an alpha-adrenergic blocker (doxazosin, 2–8 mg). The hypothesis underlying this protocol is that those treated with the latter medications will have an improved outcome as compared with those treated with the diuretic. The secondary aim of the HTN part of the study is to test whether the incidence of combined cardiovascular disease (CVD) (a composite of fatal CHD, nonfatal MI, stroke, revascularization procedures, angina, congestive heart failure [CHF], and peripheral arterial disease [PAD] differ between chlorthalidone and each of the nondiuretic treatments. To maximize statistical power, 1.7 times as many people are assigned to the diuretic arm as are assigned to each of the other three arms. All step 1 medications are formulated to look alike so the identity of each agent is masked at each dose.

The second part of the ALLHAT study, the lipid-lowering component, is a randomized, open-label trial designed to determine in 10,357 moderately hypercholesterolemic adults (a subset of the hypertension trial) whether lowering serum cholesterol with a hydroxymethylglutaryl-CoA reductase inhibitor (pravastatin) and a cholesterol-lowering diet (National Cholesterol Education Program Step I Diet) will reduce all-cause mortality as compared with a control group receiving dietary counseling and "usual" care.

Eligibility for participation in ALLHAT requires the participant to have at least one other risk factor for CVD in addition to HTN. These include the presence of underlying atherosclerosis, as evidenced by prior MI, stroke, vascular surgical repair or bypass, abnormal electrocardiogram (ECG), or vascular stenosis as detected by ultrasound; a history of diabetes; current smoking; left ventricular hypertrophy (LVH) confirmed by ECG or ultrasound; or two HDL cholesterol values <35 mg% on two separate readings over a 5-year period of time.

The BP goal in all four arms is a systolic BP of <140 mmHg and a diastolic BP of <90 mmHg. The dosage of step 1 blinded medication is increased as necessary to achieve the goal level of BP control. In the event that a participant's BP cannot be controlled using the maximum tolerated dosage of step 1 blinded medication, a choice of open-label step 2 antihypertensive medications—reserpine (0.05–0.2 mg/day), clonidine (0.1–0.3 mg twice/day), or atenolol (25–100 mg/day)—is available for use in addition to the blinded medication. If still not at goal, hydralazine (25–100 mg b.i.d.) can be added as a step 3 agent. The choice and dosage of the step 2 and 3 medications are at the discretion of the treating investigator.

RESULTS

— Of the 42,448 participants in ALLHAT, 15,297 have a history of diabetes (36.0%). Diabetes status was ascertained from the participant's physician at the time of enrollment in the trial. Evidence confirming the participant's diabetic status was not sought. Approximately half the cohort is male, 41.1% is white, 39.4% is African-American, and 17.7% is Hispanic. The distribution by sex and race of descriptive characteristics, comorbidities, laboratory values, and medications of the cohort are shown in Table 1. Differences among the groups include the following: Hispanics are the leanest of the three ethnic groups and have the lowest levels of attained education, highest BP readings, and greatest number of comorbidities; African-Americans are the most likely to smoke and have evidence of hypertensive end organ disease (LVH on ECG and high creatinine levels); and whites are more likely to use daily aspirin and hormone replacement therapy. There are no differences among groups in the number of antihypertensive medications taken at baseline. Further analysis shows an equal distribution of ethnicity, sex, descriptive characteristics, comorbidities, and laboratory values by antihypertensive medication allocation (data not shown).

The sample size of 15,297 has 42% power to detect a difference in the primary outcome of the study (fatal CHD and nonfatal MI) between chlorthalidone

Table 1—*Baseline characteristics of the ALLHAT diabetic participants by race and sex*

	Male					Female				
Characteristic	White n = 3,851	Black n = 2,472	Hispanic n = 1,195	Other n = 155	Total n = 7,673	White n = 2,449	Black n = 3,551	Hispanic n = 1,520	Other n = 104	Total n = 7,624
Age (years)	67.0	66.0	66.1	65.3	66.0	67.3	66.1	66.7	64.8	66.6
Education (years)	12.6	10.3	9.5	12.7	12.9	11.7	10.0	7.2	9.8	10.0
BMI (kg/m^2)	30.6	30.1	29.1	28.1	27.6	32.7	32.7	30.1	27.0	32.1
Smoking (%)										
Current	12.0	19.0	11.0	10.0	14.0	11.0	11.0	7.0	8.0	10.0
Past	64.0	54.0	53.0	62.0	59.0	33.0	29.0	25.0	11.0	29.0
Never	24.0	28.0	37.0	28.0	27.0	56.0	60.0	68.0	82.0	61.0
Prior CAD (%)	18.0	12.0	12.0	15.0	15.0	15.0	12.0	10.0	20.0	13.0
Prior CABG (%)	20.0	7.0	9.0	15.0	14.0	10.0	4.0	4.0	4.0	6.0
LVH by ECG (%)	6.0	14.0	12.0	8.0	10.0	5.0	10.0	11.0	2.0	8.0
LVH by echocardiogram (%)	2.0	2.0	2.0	5.0	2.0	3.0	3.0	2.0	2.0	3.0
Prior MI/stroke (%)	25.0	20.0	18.0	23.0	22.0	15.0	12.0	10.0	10.0	12.0
Systolic BP (mmHg)	145.4	145.9	146.4	142.8	145.6	147.8	147.0	147.0	145.9	147.2
Diastolic BP (mmHg)	81.8	84.0	85.0	82.5	83.0	80.8	83.0	84.3	81.7	82.6
Pulse (beats/min)	73.6	75.2	73.6	74.1	74.1	76.1	76.7	74.5	76.5	76.0
Fasting glucose (mg %)	165.4	165.2	171.1	180.0	166.6	166.8	175.7	171.8	173.4	171.8
Potassium (mg %)	4.5	4.3	4.5	4.4	4.4	4.4	4.3	4.5	4.3	4.4
Creatinine (mg %)	1.1	1.2	1.1	1.1	1.1	0.9	1.0	0.8	0.9	0.9
HDL (mg %)	39.1	45.3	41.6	43.3	40.6	45.0	52.9	48.4	47.1	49.3
LDL (mg %)	140.8	132.8	141.9	139.9	127.9	147.5	149.2	145.1	146.8	140.0
Total cholesterol (mg %)	203.3	206.5	205.3	204.3	204.5	227.5	225.9	223.7	223.4	226.0
Triglycerides (mg %)	221.2	142.0	203.0	203.3	193.2	235.6	146.8	197.9	204.1	188.8
Aspirin use (%)	49.0	31.0	31.0	37.0	40.0	35.0	22.0	24.0	19.0	26.0
Estrogen use (%)	NA	NA	NA	NA	NA	23.0	11.0	9.0	13.5	15.0
Baseline BP meds (%)										
1–2>2 months	89.0	90.0	87.0	85.0	89.0	90.0	91.0	90.0	83.0	90.0
On drugs <2 months	3.0	3.0	4.0	6.0	3.0	2.0	3.0	3.0	3.0	3.0
Untreated	9.0	7.0	9.0	8.0	8.0	8.0	6.0	7.0	14.0	7.0
Number comorbidities (%)										
≤2	84.0	86.0	89.0	87.0	86.0	88.0	88.0	92.0	91.0	89.0
3	10.0	9.0	7.0	10.0	9.0	8.0	8.0	6.0	6.0	8.0
4	4.0	4.0	3.0	2.0	4.0	2.0	3.0	2.0	3.0	2.0
≥5	2.0	1.0	1.0	1.0	2.0	2.0	1.0	0.0	0.0	0.0
Comorbidity mean value*	1.2	1.2	1.0	1.1	1.2	1.1	1.1	0.9	0.9	1.1

Data are means. *Comorbidity score includes presence of cardiovascular disease (prior MI, CABG, cerebrovascular accident), low HDL, LVH, ST-T changes on ECG, and current smoking. CAD, coronary artery disease; CABG, coronary artery bypass grafting.

and each of the nondiuretic treatments. This calculation assumes a 16% risk reduction in outcome (two-sided alpha of 0.0178) and is based on a 4-year cumulative incidence rate for fatal CHD and nonfatal MI of 6%, as previously reported in ALLHAT (35). On the other hand, there is 93% power to detect a difference in the secondary outcome of combined CVD (a composite of fatal CHD, nonfatal MI, stroke, revascularization procedures, angina, CHF, and PAD) between chlorthalidone and each of the nondiuretic treatments. These calculations are based on a 4-year cumulative incidence rate for combined CVD of ~20% (35).

Of the 27,151 ALLHAT participants with no history of diabetes, 20,079 (74%) have a fasting glucose level available for analysis. Of these, 1,735 (8.6%) have a fasting glucose of 6.1–6.9 mmol/l, equivalent to impaired fasting glucose (IFG) as determined by ADA fasting criteria. Another 1,293 (6.4%) have a fasting glucose ≥7.0 mmol/l, equivalent to diabetes as defined by ADA criteria. Of these 1,293, 753 (3.8% of the total nondiabetic cohort) have a fasting glucose ≥7.8 mmol/l, equivalent to diabetes as defined by the World Health Organization criteria.

CONCLUSIONS — The distribution of the baseline descriptors and comorbidities in the diabetic cohort of the ALLHAT study are consistent with previous reports of older individuals in the U.S. For example, women in ALLHAT have slightly higher systolic BP values and higher BMI values than men. The Third National Health and Nutrition Examination Survey (NHANES III) reported similar findings for women >60 years (6,36,37). With regard to race, NHANES III reported that older African-American men and women are less likely to have evidence of prior coronary artery disease or coronary artery bypass grafting (38,39), and are more likely to have elevated creatinine levels than other racial groups (40). African-American men were also more likely to be current smokers in that study (6). We

have found similar results. Other studies have shown Hispanic men and women to have poorly controlled BP and to have high systolic and diastolic BPs (41). White women are also more likely than African-American women to use hormone replacement therapy (42). These latter two findings are also present in ALLHAT diabetic participants. Based on these results, ALLHAT appears to have recruited a representative sample of the older U.S. population with hypertension.

ALLHAT was not prospectively designed to evaluate treatment effects in the diabetic subgroup. Diabetic participants were, however, prospectively designated for subgroup analyses. Post hoc power calculations show that there is a low degree of confidence that ALLHAT will be able to detect a 16% difference between chlorthalidone and each of the nondiuretic treatments for fatal and nonfatal CHD, the primary outcome of the study. On the other hand, ALLHAT should be able to detect, with a very high degree of confidence, a 16% difference in outcomes for combined CVD between chlorthalidone and each of the nondiuretic treatments. This latter finding should allow for hypothesis testing in the diabetic cohort that parallels ALLHAT questions for the entire cohort.

The limitations of ALLHAT, from a diabetes point of view, should be noted. Owing to its large size and the difficulty inherent in following a geographically dispersed cohort, a large simple trial model was adopted. Such a model has been used in other large CVD trials (43,44). It is characterized by an uncomplicated trial design and measures only a limited number of variables and end points. As such, data on points of interest to the diabetes research community, such as insulin levels, HbA_{1c} levels, microalbuminuria, use of insulin and oral hypoglycemic agents, and so forth, are unavailable in ALLHAT. Also, at least 15.0% of the nondiabetic participants in the study have undiagnosed IFG or diabetes, which are associated with increased CVD risk. These individuals will need to be accounted for in future analyses.

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