

POST-TRIAL FOLLOW-UP OF ALLHAT PARTICIPANTS PLANNED THROUGH 2006

Active follow-up of ALLHAT participants ended on March 31, 2002 (February 15, 2000 for doxazosin participants), for an average follow-up of 4.9 years (3.2 years for doxazosin). To answer additional scientific questions, a post-trial follow-up of participants through 2006 is planned to obtain data on post-trial morbidity and mortality. The extended follow-up will be carried out passively using national databases available through the National Death Index (NDI), Social Security Administration (SSA), Centers for Medicare and Medicaid Services (CMS), Department of Veterans Affairs (DVA), and United States Renal Data System (USRDS). When completed, endpoint data will be available for between 9 and 10 years of total follow-up.

The overall research objective of this extended follow-up is to compare long-term effects of antihypertensive treatment with a thiazide-type diuretic, a CCB, an ACE-inhibitor, or an α -receptor blocker when each drug is used as initial treatment with step-up drugs added as needed and, for the lipid component, to assess long-term effects of pravastatin compared with usual care. To meet these objectives, we will evaluate whether new differences emerge for outcomes that were not statistically different, especially CVD and total mortality, and whether the differences observed during the trial continue.

The ALLHAT extension protocol was developed by the CTC and the NHLBI Project Office and approved by the ALLHAT Steering Committee.

The original ALLHAT Protocol may be found at <http://allhat.sph.uth.tmc.edu/Forms/protocol.pdf>.

EXTENSION PROTOCOL

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) August 31, 2007

I. Introduction

The purpose of this document is to provide details on data to be collected during the post-trial phase of ALLHAT, to pose hypotheses the data can be expected to address, and to describe how the data will be analyzed. The previously published ALLHAT data presented here are from the September 30, 2002, locked ALLHAT database; the projections, however, are based on observed results from the Limited Access Data Set (LADS) of July 31, 2006, which is updated with deaths up to the end of the trial identified through June 27, 2006.

II. Background

a. ALLHAT Antihypertensive Trial (AHT)

The AHT was a multi-center randomized double-blind, active-controlled clinical trial, designed to determine whether the occurrence of fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI), the AHT primary endpoint, is lower for high-risk hypertensive patients ($n=42,418$) treated initially with a calcium channel blocker (CCB), an ACE inhibitor, or an alpha-blocker compared with those initially treated with a thiazide-type diuretic. Pre-specified secondary endpoints are listed in Tables 1 and 2.¹

Eligible participants were men and women ≥ 55 years of age with untreated SBP ≥ 140 mm Hg, and/or DBP ≥ 90 mm Hg, or who took antihypertensive medication (<3 drugs) with blood pressure $\leq 160/100$ mm Hg ($\leq 180/110$ mm for untreated and treated for less than 2 months), and who had at least one additional risk factor for CHD.¹ Of 42,418 randomized participants, 47% were women, 81% were aged 60 or older (mean 67), and 36% had type 2 diabetes. By race/ethnicity, 35% were black and 19% were Hispanic.²

a.1 Antihypertensive Trial: Chlorthalidone, Amlodipine, Lisinopril

Participants in the chlorthalidone ($n=15,255$), amlodipine ($n=9,048$), and lisinopril ($n=9,054$) treatment groups were followed for a mean of 4.9 years. The primary outcome occurred in 2,956 participants, with no difference between treatment arms. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% CI, 0.90-1.07) for amlodipine (6-year rate, 11.3%) and 0.99 (95% CI, 0.91-1.08) for lisinopril (6-year rate, 11.4%). Likewise, all-cause mortality did not differ between the randomized treatment groups. For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of heart failure (HF) with amlodipine (10.2% vs 7.7%; RR, 1.38; 95% CI, 1.25-1.52). For lisinopril vs chlorthalidone, lisinopril had higher 6-year rates of combined cardiovascular disease (CCVD; 33.3% vs 30.9%; RR, 1.10; 95% CI, 1.05-1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 1.02-1.30); and HF (8.7% vs 7.7%; RR, 1.19; 95% CI, 1.07-1.31).³ For stroke, there was a statistically significant race by treatment interaction; chlorthalidone was superior to lisinopril in preventing incident and recurrent stroke only in Blacks (RR; 95% CI=1.40; 1.17- 1.68 for Blacks and 1.00; 0.85- 1.17 for non-Blacks). When cardiovascular and renal outcomes were analyzed by e-GFR

(estimated glomerular filtration rate) strata the results were consistent with those for the entire cohort. *Post-hoc* analyses showed modestly higher incidence of diabetes in the diuretic group compared to both amlodipine and lisinopril groups. While there is no conclusive or consistent evidence that the diuretic-associated increase in incident diabetes leads to an increase in clinical events concerns have been raised about long term cardiovascular effects of the excess incident diabetes. In contrast, no excess morbidity or mortality was noted in the diuretic arm in ALLHAT participants with diabetes at baseline or diagnosed during the trial. A long-term follow-up of the SHEP trial cohort (14.3 years) confirmed these findings with respect to mortality in those with diabetes at baseline.⁴

a.2 Antihypertensive Trial: Chlorthalidone, Doxazosin

Participants in the doxazosin treatment group ($n=9061$), and the comparable chlorthalidone group ($n=15,255$), were followed for a mean of 3.2 years as the doxazosin arm was terminated early (February 15, 2000) due to a nearly two-fold higher risk of incident HF and futility of reaching a statistically significant difference in the primary endpoint.^{5,6} The primary outcome occurred in 1317 (818 + 499) participants, with no difference between treatment arms. Compared with chlorthalidone (4-year rate, 7.76%), the relative risk (RR) was 1.03 (95% CI, 0.92-1.15) for doxazosin (4-year rate, 7.91%). Likewise, all-cause mortality did not differ between the groups (RR, 1.03; 95% CI, 0.94-1.13). Significantly higher risks of stroke and combined CVD, however, occurred in doxazosin treated participants relative to those assigned to chlorthalidone: for stroke, RR = 1.26 (95% CI: 1.10-1.46); for combined CVD, RR = 1.20 (95% CI: 1.13-1.27). The RR (95% CI) for HF, a pre-specified component of CCVD, was 1.80 (1.61- 2.02).⁶ The clinical outcomes were similar for those with and without glucose disorders at baseline despite lower glucose levels in the doxazosin arm during follow-up.⁷

The ALLHAT antihypertensive trial results led to a conclusion that inexpensive thiazide-type diuretics are superior to an ACE-inhibitor, a calcium channel blocker and an alpha-receptor blocker in preventing one or more major forms of CVD. They should be preferred first-step antihypertensive therapy.

b. ALLHAT Lipid-Lowering Trial (LLT)

The LLT was a randomized open-label clinical trial in a subset of ALLHAT participants ($n=10,335$) assigned to either pravastatin (PV) or usual care (UC). Eligibility criteria included 1) prior enrollment in ALLHAT; 2) fasting LDL-C of 120 to 189 mg/dL for those with no known CHD, or 100 to 129 mg/dL for those with known CHD, and 3) fasting triglyceride (TG) levels < 350 mg/dL. Mean follow-up was 4.8 years. All-cause mortality (primary endpoint) did not differ between the two randomized treatment groups (relative risk [RR], 0.99; 95% confidence interval [CI], 0.89-1.11; $P=.88$), with 6-year mortality rates of 14.9% for the PV group vs 15.3% for UC. CHD event rates (fatal CHD or non-fatal MI) were not significantly different between the groups (HR, 0.91; 95% CI, 0.79-1.04; $P=.16$), with 6-year CHD event rates of 9.3% for the PV group and 10.4% for UC. CVD or any other cause-specific mortality did not differ significantly between the two randomized treatment groups. Similarly, no difference was observed in the incidence of cancer. However, statistically significant race by outcome interaction (black versus non-black) was noted for stroke and CHD events with a greater benefit for CHD in Blacks and for stroke in non-Blacks.⁸ These unexpected outcomes by race are currently being explored in a manuscript in progress.

These results led to a conclusion that pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL-C. The results may be due to the modest differential in total cholesterol (9.6%) and LDL-C (16.7%) between PV and UC compared with prior statin trials supporting their use for cardiovascular disease prevention.

III. Research Questions

An important expectation at the outset of ALLHAT was that better metabolic profiles of the newer antihypertensive drugs might provide an advantage over the diuretic. The ALLHAT results confirmed the superior metabolic profiles of the newer drugs, but did not find them superior to the diuretics in preventing clinical outcomes. Moreover, the diuretic was superior to each of the comparator drugs in preventing one or more cardiovascular outcomes. For the LLT, the expectation was that total mortality and CHD events, as well as cause-specific mortality will be lower in PV compared to UC. After an average 4.8 years of follow-up, no difference was observed in either total mortality or CHD event rates possibly due to a lesser difference in the total and LDL-cholesterol levels than in other trials, and there was no difference in the incidence of cancer.

For the AHT, the overall objective of this passive post-trial mortality and morbidity surveillance using administrative data bases is to assess long-term effects of antihypertensive treatment with a thiazide-type diuretic, a CCB, an ACE-inhibitor, or an α -receptor blocker when each drug is used as initial treatment with step-up drugs added as needed. To meet this objective, we will evaluate 1) whether statistically significant differences in clinical outcomes observed during the trial persisted or disappeared; 2) whether differences emerge for outcomes that were not statistically different at the trial's end; and 3) whether observed differences in non-fatal outcomes result in long-term differences in CVD and/or total mortality. For the LLT, as no statistically significant differences were observed during the trial, the post-trial surveillance can only consider the questions related to persistence of the lack of differences between treatment groups or a potential emergence of differences.

In engaging the research questions, it has to be recognized that given the passive nature of this follow-up we will not have any information about medications used by ALLHAT participants after the trial close-out. In addition, information about post-trial hospitalizations will be available only for the Medicare and VA populations. These issues will be addressed through appropriate analytical approaches.

In the AHT, we expect that following the trial's closeout, the majority of patients continued to be treated with antihypertensive drugs. While a number of them, especially those whose BP was controlled during the trial, likely continued on medications they had been on during the trial, others might have their treatment regimens changed for various reasons and these would generally reflect treatment patterns in the community. As a result, there would be a lesser difference in treatment regimens across ALLHAT original randomized treatment groups. While we would expect a large proportion of participants, especially in the chlorthalidone group, to be treated with a thiazide or a thiazide-type diuretic alone or in combination with other drugs, it will likely not be chlorthalidone due to prevailing practice patterns and a general perception of these diuretics having a class effect. We also expect BP control to be slightly lesser than during the trial, but not differ across treatment groups.

Two large clinical trials, the Hypertension Detection and Follow-up Program (HDFP) and the Multiple Risk Factors' Intervention Trial (MRFIT), published results of a long-term mortality follow-up of patients randomized to treatment of hypertension and related them to BP treatment and control.^{9, 10} HDFP Post Trial Follow-up (PTS) actively followed all participants ($n=10,940$) for 8.2 years. The trial had a 5-year fixed duration of follow-up, but a proportion of the participants was treated as long as 6.7 years. Data collected were 1) total and cause-specific mortality and 2) post-trial treatment status and BP control in Stepped Care (SC) and Referred Care (RC). The post-trial use of antihypertensive medications declined in SC and increased in RC participants so that by the end of the post-trial period there was little difference in percentages of SC and RC participants taking medication. Control of DBP was slightly better for SC than for RC participants. The total mortality advantage found at 6.7 years persisted and increased throughout the post-trial period of follow-up despite discontinuation of the formal SC program. In MRFIT, a mortality follow-up (total and cause-specific) of 12,866 men was conducted 16 years after randomization to Special Intervention (SI) or Usual Care (UC) to address long-term effects of CV risk factor intervention on CHD, CVD, and total mortality. Information on levels of risk factors was obtained on participants at 4 of 22 clinical centers at ~ 3 years after the trial ended. Virtually no difference existed between the study groups in the proportion of men using antihypertensive medication while some difference in DBP persisted. In both trials these may have reflected acquisition of better adherence behavior in the SI (MRFIT) and SC (HDFP) groups during in-trial care at study sites. Similar to HDFP, differences between SI and UC in mortality rates from MI, CHD, and all causes were greater during the post-trial compared to in-trial period.

Since ALLHAT compared 4 active treatment regimens with the same BP goal across treatment groups, and because the achieved BP levels were similar, the follow-up outcomes will in part reflect long-term effects of medications with the small observed BP level differences being a part of an overall "drug package." This is different from HDFP and MRFIT where in-trial outcome differences were primarily driven by differential BP control, though in MRFIT differences within the class of thiazide/thiazide-like diuretics were engaged.^{9, 10}

In the LLT, we expect that following the trial's closeout most patients in both arms were treated with statins, maybe with the exception of those without CHD and $LDL < 130$ mg/dL. It is likely that in the PV group, the majority continued on pravastatin while in the UC, the majority was treated with other statins or life-style approaches as during the trial investigators were asked to avoid using pravastatin in participants assigned to PV. Recently, two clinical trials of lipid-lowering with statins in patients with CHD--the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) and the Scandinavian Simvastatin Survival Study (4S)--have reported results of their extended follow-ups.^{11, 12} In LIPID, following an early termination of the placebo-controlled trial ($n=9104$) due to efficacy, all patients without contraindications were offered an open-label pravastatin irrespective of their original therapy and were invited to participate in a long-term follow-up. Mortality and morbidity as well as total and LDL-cholesterol levels were assessed over an additional 2 years of follow-up. During the follow-up period ($n=7680$), patients originally assigned pravastatin had almost identical cholesterol concentrations to those assigned placebo, but lower risk of death from all-causes, CHD death, and CHD death or non-fatal MI. When the entire period was considered, the risk of stroke was also lower. In 4S ($n=4444$), patients were also followed for an additional 2 years (median overall follow-up 7.4 years). All patients were advised to take simvastatin, but no medication was provided. Cholesterol levels and use of lipid-lowering drugs were ascertained through questionnaires sent to all participants. Slightly, though statistically significantly, fewer patients were taking cholesterol-lowering drugs (mainly simvastatin) in

the placebo compared to the simvastatin group 3.4 years after study closure. Cholesterol levels were also slightly lower in the original statin group. At the end of the extended follow-up, there were fewer deaths in the simvastatin group, mainly due to fewer CHD deaths. Non-cardiovascular mortality did not differ.

Participants in the Lipid Research Clinics Coronary Primary Prevention Trial, a randomized, cholesterol-lowering trial comparing cholestyramine ($n=1907$) with placebo ($n=1899$) treatment in asymptomatic men conducted between 1973 and 1983 (7.4 years, mean follow-up), were followed up annually (by mail, phone or in-person) from 1985 until 1989 (a total of additional 6 years).¹³ Post-trial treatment was not provided. Similar increasing proportions of cholestyramine and placebo participants reported use of cholesterol-lowering drugs post-trial (25-55%). The difference in the mean lipid levels disappeared after the double-blind was broken and drug intervention ceased despite the persistence of slightly higher use of drugs (mainly resins) in the original cholestyramine group. Notably, use of diet was slightly higher in the original placebo group. While the cumulative mortality in the placebo group tended to exceed that in the intervention group throughout the period of follow-up, it has never reached statistical significance. The statistically significant in-trial reduction in CHD incidence rates in the cholestyramine group did not continue after cessation of the study intervention. Cancer incidence rates were similar, except for GI tumors which were non-significantly increased in the original intervention arm.

The following specific research questions will be considered (also see Table 3):

a.1 AHT: Will the observed advantages of diuretics over comparator drugs continue?

i. Amlodipine versus Chlorthalidone

In the amlodipine comparison with chlorthalidone, there was no difference in cardiovascular mortality (6-year rate 8.5% in the amlodipine arm versus 8.0% in the chlorthalidone arm; $p=0.76$). Non-cardiovascular mortality was lower in the amlodipine arm (6-year rate 8.0% versus 8.9% in the chlorthalidone; $p=0.04$) with unintentional injury/homicide/suicide being statistically significant ($p=0.005$). As a result, the all-cause mortality slightly, though not significantly, favored amlodipine (6-year rate 17.3% versus 16.8%; $p=0.20$).

Across CVD endpoints (fatal or non-fatal), the only statistically significant difference between chlorthalidone and amlodipine was a 38% highly statistically significant increased risk of incident HF in the amlodipine group ($p<.001$). The combined CVD occurrence non-significantly favored chlorthalidone (RR=1.04; $p=0.12$); the RR for PAD (hospitalized or treated) was 0.87, $p=0.06$ and for stroke 0.93, $p=.28$. Consequently, the most important research question in the extended follow-up is whether the substantial increase in the incidence of HF in the amlodipine arm will continue (see **a.5**) and whether it will result in an increased CVD morbidity and/or mortality.

ii. Lisinopril versus Chlorthalidone

In the lisinopril comparison with chlorthalidone, there were no differences in either cardiovascular or non-cardiovascular mortality (6-year rate 8.5% and 8.6% in the lisinopril arm compared with 8.0% and 8.9% in the chlorthalidone arm, $p=0.39$ and 0.57 for CVD and non-CVD mortality, respectively). Consequently, there was no difference in total mortality (6-year rates 17.3% in the chlorthalidone arm versus 17.2% in the lisinopril arm, $p=0.90$).

While the primary outcome did not differ between the treatment groups (RR=0.99, $p=0.81$), the CCVD rates were higher in the lisinopril compared to the chlorthalidone arm (RR=1.10; $p<0.001$). The RR; p -value for stroke were 1.15; $p=0.02$, for HF (hospitalized or treated without hospitalization) 1.19; $p=0.001$ and for angina (hospitalized or treated without hospitalization) 1.11; $p=0.01$. Notably, there was a statistically significant outcome by race interaction (black versus non-black) for stroke and for CCVD, but not for other outcomes. Of note is also an age by outcome interaction for a combined CHD outcome with increased risk in those 65+. The interaction was statistically significant only for the pre-specified dichotomous age subgroups (<65 versus 65+) but not when age was modeled as a continuous variable. The increased risk of combined CHD may become more pronounced as the ALLHAT population ages and may even affect the CVD outcome.

The extended follow-up will have a potential to determine whether these differences persist and result in a difference in CVD mortality, especially in Blacks and those 65+.

iii. Doxazosin versus chlorthalidone

The doxazosin arm was terminated early due to an observed 25% increased risk of CCVD (with risk of HF nearly doubled) and futility of observing a statistically significant difference in the primary endpoint by the scheduled end of the trial. The final report was based on data through February 15, 2000. No difference in the all-cause mortality was observed. However, CVD mortality favored chlorthalidone (RR; 95% CI=1.15; 1.01-1.32) and included a 39% increased stroke mortality ($p=0.03$). In addition, relative to chlorthalidone, the doxazosin group experienced an 80% greater risk of HF (fatal, hospitalized, or treated, $p<0.001$), a 26% greater risk of stroke ($p<0.001$), and a 13% greater risk of angina (with or without hospitalization, $p=0.01$). Thus, the most important research question for the extended follow-up will be whether these higher risks will contribute to further divergence in the CVD mortality curves for the two groups.

a.2 AHT: Will the observed lack of differences across randomized comparisons with respect to CHD (AHT primary endpoint) persist?

The better metabolic profiles of the newer drugs did not translate into a superior CHD outcome in any of the comparisons. Notably, BP control was superior in the chlorthalidone group, especially in comparison with the doxazosin and the lisinopril arms. The observed lack of advantage of the amlodipine-, lisinopril-, and doxazosin-based treatments over the chlorthalidone-based strategy for CHD (CHD mortality and non-fatal MI), including in those with diabetes at baseline, will be explored to especially

address concerns about potential long-term effects of the diuretic-induced dysglycemia and resulting incident diabetes on progression of atherosclerosis (see a.4). The stroke outcome will also be evaluated.

a.3 AHT: Will the observed lack of difference across randomized comparisons with respect to total mortality persist?

During ALLHAT active follow-up, non-CVD mortality constituted about half of the total mortality. The ratio of non-CVD to total mortality may even become larger as the ALLHAT population (55+ at the time of enrollment) ages. Since ALLHAT interventions did not aim to improve non-CVD morbidity, we would not expect any changes in non-CVD mortality except for a small shift resulting from competing risks of death if CVD deaths are prevented. During the trial, no statistically significant differences in total mortality were observed.

Notably, during the active phase of the trial, the amlodipine group had lower incidence of non-CVD mortality primarily due to a lower incidence of accidental deaths (unintentional injury/homicide/suicide). This finding was most likely due to chance as it was not seen in previous studies and it has no known biological explanation. In addition, prior to ALLHAT there were concerns about gastrointestinal bleeding and cancer being potential adverse effects of amlodipine – findings not confirmed in ALLHAT. In contrast, cancer mortality trended lower in the amlodipine group (6-year rate per 100 = 4.3 versus 3.8; $p=0.31$).

Another surprising outcome, though not statistically significant, was a trend towards higher incidence of hospitalizations for gastrointestinal bleeding (RR=1.11; $p=0.07$) in the lisinopril group.

These findings will be explored in the context of total mortality and its components. Cancer mortality is of special interest as it is known to take longer to emerge.

a.4 AHT: Will diuretic-induced dysglycemia result in adverse clinical outcomes?

In light of the well documented lower incidence of diabetes, especially in patients treated with ACE-inhibitors and alpha-blockers compared to those treated with thiazide diuretics, an important research question for the ALLHAT extension is whether the difference in the CCVD outcome will be maintained over the longer period of follow-up, especially in participants with a history of diabetes at baseline or in those who developed diabetes during active follow-up, and whether the observed difference in the CCVD outcome will result in a difference in CVD mortality over the longer period of observation. CCVD components of special interest are the primary endpoint (no difference), HF (difference in favor of chlorthalidone), and stroke (difference in favor of chlorthalidone in Blacks).

Data related to the long-term effects of incident diabetes are crucial to the interpretation of ALLHAT's findings. Such hypotheses for total mortality and CVD mortality were addressed in SHEP by the SHEP extension study.⁴ In addition to the SHEP-extension-

type hypotheses, we also intend to analyze CVD events. In the ALLHAT diabetes incidence paper for the A/L/C comparison, which related CVD outcomes to incident diabetes occurring during the trial in a time-dependent manner, participants assigned to chlorthalidone had a higher rate of incident diabetes than did participants assigned to amlodipine or to lisinopril.¹⁴ There was no significant association of fasting glucose change at 2 years with subsequent CHD, stroke, CVD, total mortality, or ESRD. There was no significant association of incident diabetes at 2 years with clinical outcomes, except for CHD (RR=1.64, $p=0.006$), but RR was lower and non-significant in the chlorthalidone group. The extended follow-up will allow for a total 6-7 years of observation following incident diabetes compared to about 3 years in the published data.

For the doxazosin comparison with chlorthalidone, only diabetes status at baseline was analyzed (known diabetes and newly diagnosed). While there was no difference in the primary endpoint or total mortality, HF rates were higher in those treated with doxazosin in both those with known and newly diagnosed diabetes at baseline (RR; 95% CI= 1.85; 1.56- 2.19 and 1.63; 1.05- 2.55, respectively).

- a.5 AHT: Will the differences in heart failure (HF) incidence observed during the trial continue over a longer period of follow-up? Will the sustained advantage for C vs A continue? Will the similar HF rates for C and L after the first year of follow-up become an advantage for L? Will the mortality and hospitalization burden associated with HF remain similar, increase or decrease?**

ALLHAT extended follow-up will also provide an opportunity to assess the incidence of hospitalized HF over a longer period of time as well as the case-fatality and mortality associated with incident HF events. The average duration of follow-up post-hospitalized HF will be 6-7 years. Mortality associated with HF events with preserved and impaired ejection fraction will also be evaluated. Assessment of a burden of hospitalizations following incident HF events may also be included.

- a.6 AHT: Will the observed lack of superiority for kidney outcomes of lisinopril over chlorthalidone persist and/or will the observed higher estimated glomerular filtration rate (e-GFR) in the amlodipine group translate into lower incidence of ESRD (initiation of chronic renal dialysis or kidney transplant)? Will the advantage of chlorthalidone on CVD outcomes across the renal function spectrum at baseline persist?**

Given the morbidity, mortality and costs associated with progressive kidney disease, it is important to establish the long term renal outcomes associated with antihypertensive drug therapy. Further, given the increase in CVD risk associated with impaired renal function, long-term CVD outcomes by renal functions at baseline are also of interest.

i. Amlodipine versus Chlorthalidone

At baseline, eGFR was similar between ALLHAT participants assigned to amlodipine and chlorthalidone.¹⁵ However, at the end of the study participants assigned to

amlodipine had a significantly higher eGFR than those on chlorthalidone.¹⁵ This may suggest a “renoprotective” effect of amlodipine compared to chlorthalidone. However, the incidence of end stage renal disease did not differ between the groups. If the elevated GFR reflects preservation of renal function, it would be expected that over a longer follow-up period, the amlodipine arm will have a lower ESRD rate than chlorthalidone. We hypothesize that the high GFR with amlodipine is a manifestation of the effect of amlodipine on renal microcirculation; amlodipine causes afferent vasodilatation that results in increased intraglomerular pressure.¹⁶ While this results in a transient elevation in GFR, long term elevation in intraglomerular pressure may promote glomerulosclerosis and actually accelerate decline in renal function. This physiologic concept is supported by data from ALLHAT which shows an early increase in GFR in participants assigned to amlodipine. Similarly, in the AASK study which compared amlodipine with ramipril, GFR was initially higher in participants on amlodipine, but clinical renal events were lower with ramipril.¹⁷

Patients with impaired renal functions are at increased risk for CVD events. Across eGFR strata (≥ 90 ; 60- 89; and <60 mL/min per 1.73 m²) at baseline, outcomes across treatment groups were similar to those for the entire cohort (see **a.1**). An important question is whether the observed superiority of chlorthalidone over amlodipine will persist over a longer period of follow-up.

ii. Lisinopril versus Chlorthalidone

The lack of added benefit in the lisinopril arm with respect to ESRD was rather surprising, and it will be important to determine whether a difference will emerge over a longer period of follow-up. CVD outcomes across the spectrum of renal functions, which were similar to those in the entire cohort, will also be of interest.

iii. Doxazosin versus chlorthalidone

ESRD and CVD outcomes will be assessed for the overall cohort and by e-GFR strata.

a.7 AHT: Will the observed lack of statistically significant difference in hospitalizations for gastrointestinal bleeding continue?

Hospitalization for gastrointestinal bleeding was one of two major safety outcomes which were prespecified in the ALLHAT original protocol; the other one was angioedema. Prior to ALLHAT results, a body of literature based on observational studies and secondary CHD prevention trials of short-acting CCBs has suggested that CCBs, especially DHP-CCBs, may increase the risk of gastrointestinal bleeding, cancer, and all-cause mortality. The results of ALLHAT did not support these findings. Unexpectedly, the mortality from all-causes was significantly lower in the amlodipine group, primarily due to lower incidence of accidental deaths. Notably, the incidence of hospitalizations for gastrointestinal bleeding did not differ between the amlodipine and the diuretic arms (RR, 95% CI=0.92; 0.82- 1.03). However, for L versus C this RR, 95% CI was 1.11,

0.99- 1.24. The extended follow-up will allow addressing these interesting findings with respect to an important safety concern over a longer period of observation.

a.8 LLT: Will the small observed difference in cholesterol levels favoring pravastatin result in improved CHD and/or stroke outcomes without affecting cancer or total mortality?

The ALLHAT lipid component was an open-label comparison of pravastatin (PV) versus usual care (UC). The drop-in rate in the control group was nearly 20% by year 4 and nearly 30% by year 6, resulting in a lower than anticipated difference in the achieved lipid levels between the randomized treatment groups (9% for total cholesterol and 14% for LDL cholesterol). As the investigators were asked to avoid treating the UC group participants with pravastatin, it is likely that other statins were predominantly used in the UC group (information not collected during the trial).

At the end of the ALLHAT active follow-up, there was no difference between treatment groups in the all-cause mortality (6-year rate 19.9 in PV and 15.3 in UC; RR=0.99, $p=0.88$) – the LLT primary endpoint. The RRs for the CVD and non-CVD mortality were 0.99 and 1.01, respectively. The fatal CHD and non-fatal MI endpoint was slightly, but not significantly, lower in the PV group (RR; 95% CI = 0.91; 0.79- 1.04) and similarly was fatal and non-fatal stroke (RR; 95% CI= 0.91; 0.75- 1.09). For both the stroke and the CHD endpoints, there was a significant heterogeneity by race. For the CHD event, RR (95% CI) was 0.73 (0.58-0.92) for Blacks and 1.02 (0.86-1.21) for non-blacks (interaction $p = 0.03$). For stroke, the RR (95% CI) were 1.12 (0.86-1.48) in Blacks versus 0.74 (0.57-0.96) in non-Blacks (interaction $p = 0.03$).

Cancer mortality was non-significantly higher in the PV group compared to UC (1.11; 0.89-1.30); the RR (95% CI) for a composite of fatal and non-fatal cancer was 1.03 (0.89- 1.19).

ALLHAT enrolled older individuals with no history of CHD, including those with LDL<130 mg/dL. While evidence on long-term safety of statins has accumulated over the past decade, there is still some uncertainty about long-term outcomes, CHD benefit versus non-CHD risk (especially cancer) in this relatively low-CHD risk subgroup. At the end of the active follow-up, we reported for this post-hoc subgroup a non-significantly higher risk of total mortality (1.18; 0.90-1.56) and also a non-significantly lower risk of a composite endpoint of CHD deaths and non-fatal MI (0.73; 0.49- 1.07). Cancer incidence and cancer mortality risks in this subgroup were not significantly different in PV compared to UC (0.92; 0.64-1.33 and 1.69; 0.95-3.01, respectively). Consequently, both total and CVD mortality over extended period of time will be of great interest as well as CHD mortality and morbidity and cancer mortality and morbidity.

Given the paucity of information on renal outcomes, long-term effects on ESRD should be evaluated. Also of potential interest are the effects on HF incidence and re-hospitalizations – in light of the recent approval of a statin for prevention of HF hospitalizations.¹⁸

In interpreting the results of the ALLHAT-LLT, consideration should be given to the substantial drop-in rate of patients likely treated with statins other than pravastatin.

IV. Hypotheses

Table 3 presents the specific hypotheses for various outcomes with accompanying estimates of event rates and power. The estimated 9-year and 10-year rates for cardiovascular disease (CVD) mortality and total mortality, CHD, stroke, HF, CVD, and ESRD in the chlorthalidone and usual care groups are based on the observed results in the original study extended through 9 and 10 years of follow-up. Cancer mortality and HF mortality rate estimates are based upon the proportion of total mortality that these outcomes represented at the end of the main trial for the chlorthalidone and usual care groups. HF case-fatality rates are also based on those seen within the trial at present but extended into the post-trial follow-up period for the chlorthalidone and usual care groups. Since the average follow-up time to first HF hospitalization was 2.9 years, the case-fatality rate projections will be for 6 and 7 years rather than 9 and 10 years. The effect sizes for the comparisons are based on the achieved sample size and the use of 90% power.

The comparisons within subgroups are also based on the observed in-trial rates and the achieved sample size within these subgroups. The CHD, stroke, and HF non-fatal outcomes associated with hospitalization will be based upon 82% of the total cohort which we estimate captures those individuals available to be followed by databases – VA, Health Care Financing Administration (now the Centers for Medicare and Medicaid Services [CMS]), etc. In the Cardiovascular Health Study (CHS), the agreement rate between HCFA and CHS was high for MI; 84.8% of HCFA-eligible incident MI's were ascertained by both CHS and HCFA. These results for other endpoints include 84.8% for angina, 84.0% for HF, 80.0% for PVD, and 81.0% for stroke.¹⁹ About 15.8% of all HCFA-eligible incident events were ascertained by CHS but not by HCFA. We believe that these agreement rates are high enough to allow for meaningful comparisons across treatment groups using only events ascertained through database searches.

It should be noted that silent MI (a component of the CHD endpoint) cannot be determined during extended follow-up.

Hypotheses regarding the effect of in-trial and post-trial occurrences of hospitalized nonfatal heart failure (Hypotheses 20-23) on subsequent events will be analyzed using time-dependent covariate analyses. Post-trial new nonfatal hospitalized HF will be ascertained through searches of the HCFA/VA databases.

Hypotheses regarding the effect of incident diabetes at 2 years (Hypotheses 17-19) on subsequent events will be analyzed using Cox regression models beginning at 2 years.

There are several factors that relate some of the hypotheses:

- Over time, ALLHAT participants develop diabetes, which is an important risk factor for CHD and HF.
- Over time, ALLHAT participants develop CHD, which is an important risk factor for HF.

- HF and stroke both have high case fatality rates and are important risk factors for CVD and total mortality.

These possible relationships will be explored as time-dependent variables in the context of evaluating risk factors for CHD, HF, and total mortality.

V. Methods

a. Sources of outcome data

All-cause mortality, mortality by cause, and specific nonfatal events as listed previously will be the outcomes of interest for our analysis. Table 4 lists the sources of outcome data.

All-cause mortality will be ascertained from the National Death Index (NDI). Data on all-cause mortality will be obtained from the National Death Index using Social Security number, name, sex, and date of birth as matching criteria, and cause of death will be ascertained from the NDI Plus database.

Nonfatal events will be ascertained from Centers for Medicare and Medicaid Services (CMS [formerly HCFA]) and the VA databases. These outcome data are only available for participants with valid Medicare numbers and/or who have data available from the VA (82% of all participants). Renal endpoints will be ascertained from the US Renal Data System database.

Due to the lack of access to a Canadian database that would provide outcome information, and lack of identifying information (i.e., a health system number) for Canadian participants, participants randomized in Canada will not be included in post-trial analyses.

b. Definitions

A death identified through passive surveillance is defined as a possible match through NDI or Social Security that is verified at the CTC after receipt of a death certificate from the state. Death certificates are used only for verification of participant identity. Causes of death are obtained from NDI Plus. However, if a cause of death is not available from NDI, the death certificate will be coded by a nosologist using the ICD10 coding scheme. Causes of death will be classified using the ICD10 code, translated to ICD9 and classified as specified in Table 3.

Nonfatal events will be identified through CMS and VA data using the provided ICD9 codes from those sources and classified as in Table 3. Renal endpoints will be determined from CMS and the VA as well as from the US Renal Data System.

c. Statistical Analyses

The proposed analyses will include evaluation of the effect of treatment group on the risk for the primary and secondary outcomes using Cox regression. The follow-up period includes both the randomized trial (mean duration of follow-up, 4.9 years) and subsequent follow-up during the extension period. Refer to table 3 to see the projected percent reduction using this data for each hypotheses proposed. Death will be censored as a competing event in the analyses that include non-fatal events. All

analyses will be performed on an intention-to-treat basis, i.e., participants are analyzed according to their original randomized treatment group. Hazard ratios will be adjusted for baseline factors based on analyses showing which factors were independently associated with the events of interest. Finally, the proportional hazards assumption of the Cox regression models will be checked. Pre-specified tests for interactions will be conducted to determine whether the effects of the treatment intervention differ between subgroups, defined by age, race, sex, or diabetes status.

Time-dependent Cox regression will be used to estimate the hazard ratios associated with the treatment intervention separately for the trial period and the post-trial follow-up period.

VI. Operations

a. Long-Term Follow-up (2002–2006) of the ALLHAT Study

The investigational review board (IRB) of The University of Texas Health Science Center approved the long-term follow-up study. Several databases will be pursued as described in Table 4.

- National Death Index (NDI)
- Social Security Administration (SSA)
- Centers for Medicare and Medicaid Services (CMS)
- Veterans' Administration (VA)
- USRDS

b. Timeline

The average follow-up time in ALLHAT was 4.9 years (4.8 in LLT). Table 4 describes the additional follow-up expected from the databases described above. Follow-up through the NDI and SSA through 2006 will provide an additional 4.75 years of follow-up for a total of 9.65 years average follow-up. The timeline in Figure 1 shows how the additional follow-up data fit into ALLHAT as a whole, and also shows the activities related to obtaining and verifying the additional data (e.g., obtaining death certificates and causes of death), and completion of papers and presentations.

During the main trial, the Clinical Trials Center received possible matches from the NDI and SSA and sent requests to various states for death certificates. The purpose of this was to verify that the decedent was, in fact, the matched ALLHAT participant. Only those with their identities thus verified by death certificate review were counted as deaths for the antihypertensive and lipid-lowering final papers; the cause of death was from NDI Plus. Those potentially matched through NDI or SSA, but for whom death certificates were not received, were not counted as dead, but were counted in a separate category of “dead pending confirmation” (so as to not be counted as lost to follow-up). Many participants who were “dead pending confirmation” at the time of the final papers have since been confirmed. The Clinical Trials Center will continue to request death certificates from the states for participants who are potential SSA or NDI matches during the extension. Death certificates are used for verification of participant identity as described in Section V.b. However, it is anticipated that by the time of the final extension data lock (December 31, 2008), over half of the 2006 death certificates will still be missing (along with some with earlier dates of death). For those without death certificates as of the data lock, we will count those as deceased in the final extension results. It is expected that out of these “unconfirmed” deaths, 94-96% would eventually be confirmed to be the matched ALLHAT

participant, with no difference expected across treatment groups. Causes of death will be obtained from NDI Plus.

c. Papers and presentations

Although the final decision regarding presenting and publishing data from the extended follow-up belong with the Editorial Subcommittee and Steering Committee, it is suggested that we consider presenting the 10-year results of the AHT and LLT at the American College of Cardiology meeting in March 2009, with simultaneous publication.

V. References

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Table 1 – ALLHAT Outcomes

1. Death
 - a. Definite myocardial infarction
 - b. Definite coronary heart disease
 - c. Possible coronary heart disease
 - d. Stroke
 - e. Congestive heart failure
 - f. Other cardiovascular disease
 - g. Cancer
 - h. Accident, suicide, or homicide
 - i. Other noncardiovascular cause
 - j. Unknown cause
 2. Myocardial infarction
 3. Stroke
 4. Angina (hospitalized or treated)
 5. Heart failure (hospitalized or treated)
 6. Peripheral arterial disease (hospitalized or treated)
 7. New cancer diagnosis (hospitalized or treated)
 8. Accident or attempted suicide (hospitalized or treated)
 9. Left ventricular hypertrophy (biennial study, electrocardiogram)
 10. Renal function
 - a. Slope of the reciprocal of serum creatinine level versus time
 - b. End-stage renal disease (initiation of chronic renal dialysis or kidney transplant)
 11. Quality of life
 12. Medical care use
-

Table 2 – Secondary Hypotheses for the ALLHAT Trial Components

Antihypertensive Trial—The following endpoints (or their incidence) will be reduced in patients randomized to receive amlodipine, lisinopril, or doxazosin relative to those receiving chlorthalidone:

1. All-cause mortality
2. Combined coronary heart disease (CHD or revascularization procedures or hospitalized angina)
3. Stroke
4. Combined cardiovascular disease (CHD or stroke or coronary revascularization procedures or angina [hospitalized or medically treated] or HF [hospitalized or medically treated] or peripheral arterial disease [hospitalized or outpatient revascularization procedure]),
5. Left ventricular hypertrophy by ECG
6. Renal disease
 - a. Slope and reciprocal of serum creatinine
 - b. End-stage renal disease (initiation of chronic renal dialysis or kidney transplant)
7. Health-related quality of life
8. Major costs of medical care

Lipid-Lowering Trial—The following endpoints (or their incidence) will be reduced in patients randomized to receive pravastatin relative to those receiving usual care:

1. The combined incidence of CHD death and nonfatal myocardial infarction, especially in certain subgroups, e.g., blacks, patients over age 65 (the original Cholesterol Reduction in Seniors Program [CRISP] hypothesis²⁰), type 2 diabetics, and women
2. Changes in the biennial study ECG indicative of myocardial infarction
3. Cause-specific mortality (e.g., cancer, trauma)
4. Total and site-specific cancer incidence
5. Health-related quality of life
6. Major costs of medical care

CHD, coronary heart disease; HF, heart failure; ECG, electrocardiogram.

Table 3. Percent Reductions from Comparator Treatment for 90% Power
(The general null hypothesis is that there is no difference in event rates at an average of 9-10 years of follow-up.)

Statement of hypothesis	Primary outcome variable	9 Years		10 Years	
		Estimated rate of outcome	Relative Risk Reduction	Estimated rate of outcome	Relative Risk Reduction
Antihypertensive Trial					
1. CVD Mortality					
Is there a CVD mortality difference at an average of 9 or 10 years of follow-up?					
1a – amlodipine vs chlorthalidone 1b – lisinopril vs chlorthalidone 1c – doxazosin vs chlorthalidone	CVD mortality ¹	14%	11.9%	16%	11.0%
2. Total Mortality / Non-CVD mortality / Cancer mortality / Other causes					
Is there a total mortality difference at an average of 9 or 10 years of follow-up?					
2a – amlodipine vs chlorthalidone 2b – lisinopril vs chlorthalidone 2c – doxazosin vs chlorthalidone	Total mortality Cancer mortality ³	29% 6.5%	7.6% 17.8%	33% 7.4%	6.9% 16.7%
3. CVD Endpoint (CVD mortality or hospitalized non-fatal MI or hospitalized non-fatal HF or hospitalized non-fatal stroke)					
Is there a CVD endpoint difference at an average of 9 or 10 years of follow-up?					
3a – amlodipine vs chlorthalidone 3b – lisinopril vs chlorthalidone 3c – doxazosin vs chlorthalidone	CVD endpoint ⁴	30.0%	8.1%	33.0%	7.6%
4. CHD Endpoint (CHD death or hospitalized non-fatal MI)					
Is there a CHD endpoint difference at an average of 9 or 10 years of follow-up?					
4a – amlodipine vs chlorthalidone 4b – lisinopril vs chlorthalidone 4c – doxazosin vs chlorthalidone	CHD ⁴	18%	11.2%	20%	10.6%

5. Hospitalized or fatal stroke					
Is there a difference in hospitalized stroke at an average of 9 or 10 years of follow-up?					
5a – amlodipine vs chlorthalidone 5b – lisinopril vs chlorthalidone 5c – doxazosin vs chlorthalidone	Stroke ⁴	8.0%	17.5%	9.0%	16.5%
6. Hospitalized heart failure					
Is there a difference in hospitalized heart failure at an average of 9 or 10 years of follow-up?					
6a – amlodipine vs chlorthalidone 6b – lisinopril vs chlorthalidone 6c – doxazosin vs chlorthalidone	Hospitalized/fatal HF ⁴	10.5%	15.2%	12%	14.1%
7. Hospitalized GI bleeding					
Is there a difference in hospitalized GI bleeding at an average of 9 or 10 years of follow-up?					
7a – amlodipine vs chlorthalidone 7b – lisinopril vs chlorthalidone 7c – doxazosin vs chlorthalidone	Hospitalized GI bleed ⁴	13.0%	13.5%	15.0%	18.7%
8. ESRD (initiation of chronic renal dialysis or kidney transplant)					
Is there a difference in ESRD at an average of 9 or 10 years of follow-up?					
8a – amlodipine vs chlorthalidone 8b – lisinopril vs chlorthalidone 8c – doxazosin vs chlorthalidone	ESRD through USRDS ⁴	3.2%	27.5%	3.7%	25.7%
9. AHT Subgroups					
Are there mortality or morbidity differences seen in the above comparisons in the pre-specified subgroups - [age (<65, 65+), sex, race (Black, non-Black), and history of diabetes (yes/no)] at an average of 10 years of follow-up? 9a – amlodipine vs chlorthalidone 9b – lisinopril vs chlorthalidone 9c – doxazosin vs chlorthalidone	Total mortality (Blacks)	30.4%	12.2%	34.3%	11.2%
	CVD mortality ¹ (Blacks)	13.8%	19.7%	15.5%	18.5%
	Hospitalized/fatal HF ⁴ (Blacks)	10.5%	24.9%	12%	23.2%

Lipid-Lowering Trial					
10. Total Mortality					
Is there a total mortality difference between pravastatin and usual care at an average of 9 or 10 years of follow-up?	Total mortality	28%	10.4%	32% ⁵	9.3%
11. CVD Mortality					
Is there a CVD mortality difference between pravastatin and usual care at an average of 9 or 10 years of follow-up?	CVD mortality ¹	13%	16.2%	15%	14.9%
12. CHD Endpoint (CHD death or hospitalized non-fatal MI)					
Is there a CHD endpoint difference between pravastatin and usual care at an average of 9 or 10 years of follow-up?	CHD ⁴	16.5%	15.5%	18.5%	14.5%
13. Hospitalized or fatal stroke					
Is there a difference in hospitalized stroke between pravastatin and usual care at an average of 9 or 10 years of follow-up?	Stroke ⁴	8.5%	22.2%	9.5%	20.9%
14. Cause-specific mortality (especially cancer)					
Are there differences in CVD and cancer mortality between pravastatin and usual care at an average of 9 or 10 years of follow-up?	CVD mortality ¹ Cancer mortality ³	13% 6.3%	16.2% 23.7%	15% 7.2%	14.9% 22.1%
15. ESRD (initiation of chronic renal dialysis or kidney transplant), total and by eGFR at baseline.					
Are there differences in ESRD between pravastatin and usual care at an average of 9 or 10 years of follow-up?	ESRD through USRDS ⁴	3.2%	35.9%	3.8%	33.1%
16. LLT Subgroups					
Are there mortality or morbidity differences seen in the above comparisons in the pre-specified subgroups - [age (<65, 65+), sex, race (Black, non-Black), and history of diabetes (yes/no)] at an average of 10 years of follow-up?	Total mortality (Blacks)	30.5%	15.5%	35.5%	13.9%
	CVD mortality ¹ (Blacks)	13.9%	24.8%	16.1%	22.8%

Additional Hypotheses Regarding Diabetes					
17. Total Mortality					
Does long term total mortality differ by diabetes status (no diabetes, diabetes at baseline, new onset diabetes, at 2 years during ALLHAT) 17a – amlodipine vs chlorthalidone 17b – lisinopril vs chlorthalidone 17c – doxazosin vs chlorthalidone	Total mortality no diabetes	16.1%	23.6%	22.5%	19.4%
	diabetes at baseline	18.8%	26.2%	26.4%	21.4%
	new onset diabetes	15.7%	78.1%	21.8%	67.7%
18. CVD Mortality					
Does long term CVD mortality differ by diabetes status (no diabetes, diabetes at baseline, new onset diabetes, at 2 years during ALLHAT) 18a – amlodipine vs chlorthalidone 18b – lisinopril vs chlorthalidone 18c – doxazosin vs chlorthalidone	CVD mortality ¹ no diabetes	7.1%	35.9%	9.9%	30.5%
	diabetes at baseline	9.2%	38.0%	12.9%	32.1%
	new onset diabetes	7.4%	>99%	10.3%	91.5%
19. CVD Endpoint (CVD mortality or hospitalized non-fatal MI or hospitalized non-fatal HF or hospitalized non-fatal stroke)					
Does long term CVD events differ by diabetes status (no diabetes, diabetes at baseline, new onset diabetes, at 2 years during ALLHAT) 19a – amlodipine vs chlorthalidone 19b – lisinopril vs chlorthalidone 19c – doxazosin vs chlorthalidone	CVD endpoint ⁴ no diabetes	17.3%	24.5%	20.3%	22.4%
	diabetes at baseline	23.9%	24.8%	28.3%	22.3%
	new onset diabetes	21.4%	72.9%	25.6%	67.2%

Additional Hypotheses Regarding Heart Failure					
20. Case Fatality					
Does the case fatality rate differ by treatment group for those who develop hospitalized HF in ALLHAT? By subgroup? 20a – amlodipine vs chlorthalidone 20b – lisinopril vs chlorthalidone 20c – doxazosin vs chlorthalidone	HF case fatality	59% 59% (Blacks)	17.0% 29.3%	63% ⁷ 64% (Blacks)	15.8% 26.8%
21. Case Fatality by LV systolic function⁸					
Does the case fatality rate differ by treatment group for those who develop hospitalized HF with preserved/impaired/unknown left ventricular systolic function? 21a – amlodipine vs chlorthalidone 21b – lisinopril vs chlorthalidone 21c – doxazosin vs chlorthalidone	HF case fatality ⁸	Pending finalization and publication of relevant ALLHAT paper.			
22. Total Mortality by HF Status					
Does long term total mortality differ by HF status (no HF, new onset HF during ALLHAT) 22a – amlodipine vs chlorthalidone 22b – lisinopril vs chlorthalidone 22c – doxazosin vs chlorthalidone	Total mortality	57% (in HF Group)	8.1%	62% (HF Group)	7.3%
23. CVD Mortality by HF Status					
Does long term CVD mortality differ by HF status (no HF, new onset HF during ALLHAT) 23a – amlodipine vs chlorthalidone 23b – lisinopril vs chlorthalidone 23c – doxazosin vs chlorthalidone	CVD mortality ¹	40% (HF Group)	11.3%	44% (HF Group)	10.4%

Additional Hypotheses Regarding Renal Disease					
24. ESRD (initiation of chronic renal dialysis or kidney transplant) by eGFR					
Is there a difference in ESRD at an average of 9 or 10 years of follow-up across the spectrum of eGFR at baseline?					
24a – amlodipine vs chlorthalidone 24b – lisinopril vs chlorthalidone 24c – doxazosin vs chlorthalidone	ESRD through USRDS ⁴ GFR <60 GFR=60-89.9 GFR=90+	11.3% 1.6% 1.2%	34.1% 51.1% 79.0%	12.9% 1.8% 1.5%	31.9% 47.5% 71.9%
25. CVD Endpoint (CVD mortality or hospitalized non-fatal MI or hospitalized non-fatal HF or hospitalized non-fatal stroke) by eGFR					
Is there a difference in CVD endpoints at an average of 9 or 10 years of follow-up across the spectrum of eGFR at baseline?					
25a – amlodipine vs chlorthalidone 25b – lisinopril vs chlorthalidone 25c – doxazosin vs chlorthalidone	ESRD through USRDS ⁴ GFR <60 GFR=60-89.9 GFR=90+	41.5% 28.9% 23.7%	15.5% 11.3% 18.9%	45.3% 31.8% 26.2%	14.4% 10.6% 17.8%
Notes: ¹ CVD mortality is estimated at 40 - 49% of total mortality, depending on subgroup. ² The estimated mortality rate in the chlorthalidone group at 6 years is about 18%. ³ Cancer mortality is assumed 22.5% of total mortality. ⁴ Assumes follow-up on 82% of cohort. Silent MI is not available during extended follow-up. ⁵ The estimated mortality rate in the usual care group at 6 years is about 16%. ⁶ Incident diabetes is not available during extended follow-up. ⁷ The estimated case-fatality rates are for 6 and 7 years post HF hospitalization because the mean time to nonfatal HF event was 2.5 years. Likewise, the post-HF mortality and CVD mortality are restricted to 6 and 7 years post HF event. ⁸ The data for this hypothesis is currently being validated.					

TABLE 4
Assuming End Date 3/31/2009
ALLHAT EXTENSION
SUMMARY OF OUTSIDE DATABASE SEARCHES
FOR VITAL STATUS AND STUDY EVENTS

Database	Purpose	Status & plans
SSA	Dead, alive during benefits year	CTC has searches through September 2004 Submit search June 2007 for remainder of 2004 and for 2005 and 2006 status (Verified deaths will be “searched” through the NDI for death certificate information and causes of death)
NDI	Death, cause of death	CTC has NDI Plus through 2002 Planned searches: <ul style="list-style-type: none"> • June 2007 – 2003 through 2005 deaths & causes • May 2008 – 2006 deaths & causes • All searches include information to be verified from SSA searches
CMS	Hospitalized events	June 2007 – Request 2001-2006 events
VA	Hospitalized events	June 2007 – Request 2001-2006 events
USRDS	ESRD cases and related data; for several ALLHAT papers	July 2007 – Request 1994-2006 events

Table 5
COMPLETE LISTING OF ICD9 CODES MAPPED TO ALLHAT EVENTS
Revised March 28, 2002

INFECTIOUS / PARASITIC DISEASES 001-139

Nonfatal - Not applicable
 Fatal - Other noncardiovascular

NEOPLASMS 140-239

Codes	Description	Nonfatal	Fatal
140.x through 208.x	Malignant neoplasms	Cancer	Cancer
Except: 173.x - Skin neoplasm NEC, primary 196.x - Secondary cancers 197.x - Secondary cancers 198.x - Secondary cancers 199.x - Unspecified primary and secondary cancers		(Not applicable)	Cancer
209.x-229.x	Benign neoplasms	(Not applicable)	Other noncardiovascular
230.x through 234.x	In-situ cancers	Cancer	Cancer
Except: 232.x - In situ skin cancer		(Not applicable)	Cancer
235.x through 238.x (was 239.x)	Cancers of uncertain behavior	(Not applicable)	Cancer
239.x	Unspecified cancer	(Not applicable)	Cancer

ENDOCRINE, NUTRITIONAL, METABOLIC, IMMUNITY - 240-279

Nonfatal - Not applicable except as noted below
 Fatal - All codes are other noncardiovascular death

Codes	Description	Nonfatal	Fatal
250.7	Diabetes with peripheral circulatory disorders	Hospitalized lower extremity arterial disease	

BLOOD AND BLOOD-FORMING ORGANS - 280-289

Nonfatal: Not applicable
 Fatal: All codes are other noncardiovascular death

MENTAL DISORDERS - 290-319

Nonfatal: Not applicable

Fatal: All codes are other noncardiovascular death

DISEASES OF THE NERVOUS SYSTEM AND SENSE ORGANS - 320-389

Nonfatal: Not applicable

Fatal: All codes are other noncardiovascular death

DISEASE OF THE CIRCULATORY SYSTEM - 390-459

Codes	Description	Nonfatal	Fatal
402.01, 402.11, 402.91	HF	HF	HF
410.x	MI	MI	MI
411.1, 413.x	Angina	Hospitalized angina	Probable CHD
411.x, 412.x, 414.x			Probable CHD
415.0	HF	HF	HF
416.1			Other noncardiovascular
427.41, 427.42, 427.5			Probable CHD
428.x	HF	HF	HF
430.x-434.x, 436.x Please note that 435.9 was previously coded as stroke, but this is incorrect	Stroke	Stroke	Stroke
440.2x, 440.3x, 442.2, 442.3, 443.9, 444.22, 444.81	Peripheral vascular disease	Hospitalized lower extremity arterial disease?	Other cardiovascular
454.x, 455.0-8, 456.0-2, 458.x			Other cardiovascular
457.x, 455.9, 456.3- .8			Other noncardiovascular
459.0 - Intra- abdominal hemorrhage	GI bleed	GI bleed	Other cardiovascular
All other 390-459	Other cardiovascular		Other cardiovascular

DISEASES OF THE RESPIRATORY SYSTEM - 460-519
DISEASES OF THE DIGESTIVE SYSTEM - 529-579
DISEASES OF THE GENITOURINARY SYSTEM - 580-629
COMPLICATIONS OF PREGNANCY, CHILDBIRTH AND THE PUERPERIUM - 630-676
DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUES - 680-709
DISEASES OF THE MUSCULOSKELETAL SYSTEM & CONNECTIVE TISSUES - 710-739
CONGENITAL ABNORMALITY - 740-759
PERINATAL CONDITIONS - 760-779
SYMPTOMS, SIGNS, AND ILL-DEFINED CONDITIONS - 780-799

Nonfatal: Not applicable except as noted below

Fatal: Other noncardiovascular except as noted below

Codes	Description	Nonfatal	Fatal
578.x - (originally only 578.9)	GI hemorrhage	GI bleed	
531.0, 531.2, 531.4	Gastric ulcer - Acute with hemorrhage - Acute with hemorrhage and perforation - chronic or unspecified with hemorrhage	GI bleed	
531.6	Gastric ulcer, chronic or unspecified with hemorrhage and perforation	GI bleed	
532.0/2/4/6	Duodenal ulcer, acute or chronic or unspecified, with hemorrhage	GI bleed	
533.0/2/4/6	Peptic ulcer, site unspecified, acute or chronic or unspecified, with hemorrhage	GI bleed	
534.0/2/4/6	Gastrojejunal ulcer, acute or chronic or unspecified, with hemorrhage	GI bleed	
535.01, .11, .21, .31, .41, .51, .61	Gastritis/duodenitis with hemorrhage	GI bleed	
580-593			Kidney disease
745.2, 745.4, 745.9, 747.22, 746.x, 746.xx			Other cardiovascular
753.1, 753.3			Kidney disease
785.4	Gangrene of lower or upper extremity	Hospitalized lower extremity arterial disease?	Other cardiovascular
780.2 785.0/1/2/3, 785.51, 786.50/51/59, 796.2/3			Other cardiovascular
798.1, 798.2, 798.9, 799.1			Probable CHD

INJURY AND POISONING - 800-999

Nonfatal: Accident or attempted suicide, except as noted

Fatal: Accident, suicide, homicide, except as noted

Codes	Description	Nonfatal	Fatal
996.0x, 996.1, 996.61, 996.62, 996.72, 996.83, 997.1			Other cardiovascular
996.73, 996.81			Kidney disease
997.02		Stroke, GI bleed	Stroke, GI bleed
998.1, 998.11, 998.12		GI bleed	GI bleed
997.2, 997.6, 999.2		Hospitalized lower extremity arterial disease?	Other cardiovascular

SUPPLEMENTARY CLASSIFICATION OF FACTORS INFLUENCING HEALTH STATUS AND CONTACT WITH HEALTH SERVICES - V01-V82

Nonfatal: Not applicable

Fatal: Unknown cause of death

SUPPLEMENTARY CLASSIFICATION OF EXTERNAL CAUSES OF INJURY AND POISONING - E800-E999

Nonfatal: Accident or attempted suicide

Fatal: Accident, suicide or homicide

PROCEDURES

Codes	Description	Procedure
36.0x		PTCA
Other 36.xx	Operations on vessels of heart, coronary stent, atherectomy	CABG
38.08, .18, .38, .48, .68	Incision, excision, and occlusion of lower limb arteries	Lower extremity revascularization /bypass/ angioplasty
39.25	Aorta-femoral bypass	Lower extremity arterial revascularization/bypass/ angioplasty
39.29	Other peripheral vascular shunt or bypass	
39.95	Kidney dialysis	Kidney dialysis
55.6x	Kidney transplant	Kidney transplant
84.1x	Leg amputation	Hospitalized lower extremity arterial disease
99.03, 99.04, 99.05	Transfusion - general, packed red blood cells, platelets	GI bleed
99.10	Streptokinase	MI
99.20	Thrombolytic procedure	MI

**Figure 1
ALLHAT Timeline**

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
1994		1 st AHT rz		1 st LLT rz								
1998	Last AHT rz				Last LLT rz							
2000	Decision to end dox	Dox c/o begins		1 st dox paper	Dox c/o ends							
2001										Study c/o begins		
2002			Study c/o ends									AHT/LLT final papers
2003									Final dox paper			
2004												
2005												
2006												
2007						Request 2003-2005 NDI & 2004-2006 SSA files; request CMS 2001-6 & VA 2001-6; Identify conveners; Charge to writing groups	Request USRDS 1994-2006; start drafting final extension papers; Identify writing groups	Request 2003-2005 NDI & 2004-2006 SSA DC's through states; 1 st conference call of writing groups			Run 1 st post-trial analyses	
2008		Expect ½ of last round of requested NDI & SSA DC's; 2 nd draft of papers			NDI 2006		Request 2006 NDI DC's through states; run 2 nd round of post-trial analyses		3 rd draft of papers			EXTENSION DATA LOCK – 12/31/2008
2009	Final post-trial analyses	Final papers	ACC presentation. Submission of papers.									