ALLHAT and its implications in the diabetic population

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The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is the largest hypertension study ever conducted. It included a large number of diabetic patients, representing nearly a third of its entire cohort of 42,448 participants. Furthermore, the study showed a significant increase in the number of incident diabetes cases with the use of chlorothalidone throughout the trial. In this report we discuss the major ALLHAT results with emphasis on the diabetic population, a particularly high-risk group for cardiovascular events, the primary outcome for the trial.

Diabetes is a major public health problem that is currently approaching epidemic proportions. It is projected that the number of diabetic patients will increase from 171 million in the year 2000, to 366 million in the year 2030 [1]. Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with diabetes and insulin resistance [2]. Hypertension is one of the most important risk factors for CVD and accounts for nearly 80% of excess CVD risk in diabetic patients [2–4]. In Type 2 diabetes, hypertension is usually a component of the metabolic syndrome and is associated with other CVD risk factors such as central obesity, insulin resistance, microalbuminuria, endothelial dysfunction, dyslipidemia and increased inflammatory and procoagulant state [2–4] (**Box 1**). Furthermore, patients with hypertension are more prone to develop diabetes than are normotensive patients [3,4].

Clinical characteristics of hypertension associated with diabetes

Hypertension in patients with diabetes compared with those without is usually associated with clinical characteristics (**Box 2**), including salt sensitivity and volume expansion, isolated systolic hypertension, loss of nocturnal decline in blood pressure (BP), miroalbuminuria and orthostatic hypotension [3,4]. These clinical aspects must be taken into account when prescribing antihypertensive therapy for this high-risk population. For example, loss of nocturnal dipping conveys excess stroke and myocardial infarction. Therefore optimum-dosing strategies with drugs that provide 24 h BP control would be advantageous [5].

Hypertension in patients with diabetes is difficult to control and usually requires three medications, on average, in order to achieve BP goal [6]. For example, in a study by our group [6], which included 1372 diabetic patients from four academic centers across two US cities, the rate of BP and other CVD risk factors was largely suboptimal [6]. Less than a third of the diabetic population achieved a BP goal of 130/80 mmHg [6].

Currently recommended BP treatment goals for diabetic patients

The currently recommended BP goal for patients with diabetes is 130/80 mmHg [7,8]. These recommendations are continuously revised based on the results of randomized controlled trials in hypertension. These trials help to establish an optimum basis for therapeutic decisions and serve as tools for evidence-based guidelines.

The ALLHAT trial

Historical perspectives

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), the largest hypertension trial in history involving 42,448 high-risk patients with hypertension, was US-based and sponsored by the US National Institute of Health (NIH) [9]. The study was conceived in the 1980s, when another NIH-sponsored study, the Multiple Risk Factor Intervention Trial (MRFIT) [10,11], challenged the notion that prevention of CVD could be achieved solely via control of BP, regardless of the medication used [10]. This study created a dilemma regarding the management of hypertension in the 1980s, particularly regarding the use of diuretics [12].

Keywords:
ALLHAT, cardiovascular disease, diabetes, hypertension

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Box 1. Cardiovascular risk factors associated with diabetes.

- Hypertension
- Central obesity
- Insulin resistance/ hyperinsulinemia
- Microalbuminuria
- Endothelial dysfunction
- Small, dense LDL-C particles
- Low serum HDL-C levels
- High serum triglyceride levels
- Increased serum apolipoprotein B levels
- Increased PAI/PA ratio
- Increased serum fibrinogen levels
- Increased serum C-reactive protein levels
- Increased production of TNF-α
- Increased production of interleukin-6
- Increased blood viscosity
- Increased systolic and pulse pressure
- Left ventricular hypertrophy

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; PAI/PA: Plasminogen activator inhibitor/plasminogen activator; TNF-α: Tumor necrosis factor α.

Research questions & primary outcomes

The ALLHAT trial was designed to determine whether the treatment of hypertension with newer agents (newer at the time of the study initiation in 1993), such as dihydropyridine calcium channel blockers (CCBs) (amlodipine), angiotensin-converting enzyme (ACE) inhibitor (lisinopril) or α-blocker (doxazosin, Cardura®, Pfizer Inc.), would lower the incidence of coronary heart disease (CHD) or other CVD events compared with treatment with a thiazide-type diuretic (chlorothalidone), in use in the USA since 1957 [9].

Secondary outcomes

Secondary outcomes of the study included all-cause mortality, stroke, combined CHD and CVD events (including heart failure). Incident diabetes, however, was not a pre-specified secondary outcome, it was reported in the primary paper, given the importance in diabetes as a major disease associated with CVD [9,13].

Study design

The study was a double-blinded randomized, active control trial of 42,448 high-risk hypertensive participants, aged 55 years or more, conducted in 623 North American Centers in medical office-based settings [14].

For all participants the goal BP was less than 140/90 mmHg. If the BP goal was not achieved using first-step, blinded therapy, treating physicians had the choice of open-label S = step 2 medications (reserpine, clonidine or atenolol).

The study had a large enough sample size to capture treatment differences among heterogeneous groups of patients. Of the 42,448 participants in ALLHAT, 47% were women, 35% African-Americans and 36% were diabetic.

The diabetic cohort

The ALLHAT was neither designed to prospectively assess the treatment effect in the diabetic patients, nor was incident diabetes a prespecified secondary outcome. However, the diabetic cohort was pre-designed for subgroup analysis [9,13,14]. *Post hoc* power analysis revealed a lower degree of confidence for detection of a difference between the chlorothalidone and other treatment arms for the primary outcome of the study (fatal and nonfatal CHD). This analysis, however, showed a higher power for detection of a difference in the secondary outcome of the study (combined CVD) among the diabetic subgroup [9,13–15].

Of the 42,448 patients, 15,297 (36%) were diabetic with a mean age of 66.6 years. Of these. 50% were women and 40% were African-Americans. The mean follow up of the study groups was 4.9 years [9,13–15].

5535 of the diabetic cohort were randomized to chlorothalidone, 3220 to doxazocin, 3327 to amlodipine and 3217 to lisinopril [15]. Doxazosin arm was discontinued when interim analysis of the data showed a 25% increase in the combined CVD events, primarily CHF, in the doxazosin group compared with chlorothalidone-randomized patients [16].

Box 2. Clinical characteristics of hypertension associated with diabetes.

1. Salt sensitivity
2. Volume expansion
3. Orthostatic hypotension
4. Loss of nocturnal decline of blood pressure (nondipping)
5. Isolated systolic hypertension
6. Microalbuminuria

Major study results [9,13–17]

- There were no significant treatment differences in the primary outcome (fatal and nonfatal CHD) or in all-cause mortality between the different treatment groups
- There was a significantly higher 6-year rate of heart failure with amlodipine compared with chlorothalidone (10.2 versus 7.7% respectively)
- The lisinopril group had a higher 6-year rate of combined CVD (stroke and CHF), compared with chlorothalidone (33.3 versus 30.9% respectively)
- Mean systolic BP averaged approximately 2 mmHg higher in the lisinopril group compared with the chlorothalidone group. This difference was even higher, 4 mmHg, for African-Americans
- Serum potassium levels less than 3.5 μmol/L were 6–8% higher in the chlorothalidone group
- Fasting glucose was 0.17 μmol/L (3 mg/dl) and 0.28 μmol/L (5 mg/dl) higher in the chlorothalidone group compared with the amlodipine and lisinopril group respectively
- New-onset diabetes (fasting glucose of ≥7 μmol/L, 126 mg/dL), was 1.8 and 3.5% higher in the chlorothalidone group compared with the amlodipine and lisinopril group respectively
- All outcomes were consistent among different populations including diabetic patients and those of different age, gender and racial backgrounds. However, greater reduction in stroke was seen in African-Americans in the chlorothalidone group, consistent with a significantly lower BP

Discussion

The ALLHAT showed that diuretics are comparable with CCBs and ACE inhibitors in preventing fatal and nonfatal CHD and all-cause mortality in high-risk populations [9]. Being less expensive, diuretics have been advocated as a first-line therapy for individuals with hypertension [9]. However, considering patients with diabetes, several points should be made in interpreting the ALLHAT results and putting them into perspective.

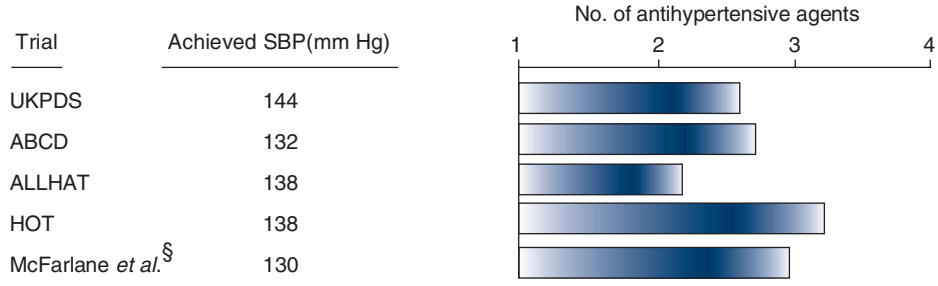
First, optimal control of BP in people with diabetes is difficult to achieve and requires multiple medications [18,19] (**Figure 1**).

Data from our group [6] demonstrated that in a large diabetic cohort with a mean age of 64.5 years, comparable with the ALLHAT mean age of 66.6 years in the diabetic subgroup [15], a BP goal of 130/80 was achieved in only 25% of the patients. Furthermore, an average of 3.1 medications were required to achieve such a BP goal [6]. These data are consistent with the results of major trials such as the UK prospective diabetes study (UKPDS) [20], Appropriate Blood Pressure Control in Diabetes (ABCD) trial [21] and the Hypertension Optimal Treatment (HOT) study [22]. The ALLHAT trial, however, illustrates the importance of BP lowering in order to control the CVD risk. Therefore, efforts should be directed towards improving BP control that is largely suboptimal in diabetic patients [6,18,19].

Second, the ALLHAT results have raised several questions:

- The study did not explain the lack of difference in the primary outcome (fatal CHD or nonfatal myocardial infarction) among the different treatment arms, although BP reduction was in favor of the diuretic group
- There has been an increased incidence in newly diagnosed diabetes in the chlorothalidone group compared with other treatment arms. This is consistent with the well-known adverse metabolic effects of the thiazide-type diuretics on glucose metabolism [23,24]. In fact, the ALLHAT study showed a significant 43 to 65% higher risk of new-onset diabetes with chlorthalidone compared with amlodipine (30%) and lisinopril (18%) [25]
- The follow-up period of the ALLHAT study was not long enough to examine the effect of diuretics on incident diabetes and the long-term effects on CVD morbidity and mortality. Therefore, justification provided by the investigators that the greater incidence of diabetes did not translate into more cardiovascular events is largely unfounded
- While the cost of medication is an important consideration in disease management, the ALLHAT, which advocates the use of chlorothalidone as a first line drug, did not address the cost of management of the excess cases of new-onset diabetes and the cost of potassium replacement and monitoring of serum potassium and other metabolic parameters
- Despite the higher incidence of CHF with CCB compared with diuretic (which is a therapeutic agent for CHF), CCB remains to be a viable option in the multi-drug therapy required to control BP in diabetic patients [26]

Figure 1. Multiple antihypertensive agents are needed to achieve target BP in diabetic patients.



§:McFarlane *et al.* [6]. ABCD: Appropriate Blood Pressure Control in Diabetes; ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; HOT: Hypertension Optimal Treatment; SBP: Systolic blood pressure; UKPDS: UK prospective diabetes study.

- The trial did not provide information on the antihypertensive medication use, prior to the initiation of the study. Further, there was no washout period for treated patients

Finally, the ALLHAT, with its simple office-based design, did not offer information that is particularly relevant for the diabetic population, such as the use of anti-diabetic agents, glucose control, or microalbuminuria. Therefore, medications that have been shown, in randomized controlled trials to have renoprotective effects and favorable effects on glucose metabolism including reduction of new-onset diabetes, might be preferred as a first-line therapy in patients with diabetes or kidney disease [27–29].

Given the fact that diabetic patients would need multiple medications to achieve optimum BP control, the issue regarding which medication to start with in treating hypertension associated with diabetes is moot and irrelevant.

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