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Research Article

Electrocardiographic measures of left ventricular hypertrophy in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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Abstract

Left ventricular hypertrophy (LVH) predicts cardiovascular risk in hypertensive patients. We analyzed baseline/follow-up electrocardiographies in 26,376 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial participants randomized to amlodipine (A), lisinopril (L), or chlorthalidone (C). Prevalent/incident LVH was examined using continuous and categorical classifications of Cornell voltage. At 2 and 4 years, prevalence of LVH in the C group (5.57%; 6.14%) was not statistically different from A group (2 years: 5.47%; $P = .806$, 4 years: 6.54%; $P = .857$) or L group (2 years: 5.64%; $P = .857$, 4 years: 6.50%; $P = .430$). Incident LVH followed similarly, with no difference at 2 years for C (2.99%) compared to A (2.57%; $P = .173$) or L (3.16%; $P = .605$) and at 4 years (C = 3.52%, A = 3.29%, L = 3.71%; $P = .521$ C vs. A,

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P = .618 C vs. L). Mean Cornell voltage decreased comparably across treatment groups (Δ baseline, 2 years = +3 to −27 μV, analysis of variance P = .8612; 4 years = +10 to −17 μV, analysis of variance P = .9692). We conclude that risk reductions associated with C treatment in secondary end points of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial cannot be attributed to differential improvements in electrocardiography LVH. J Am Soc Hypertens 2016;10(12):930–938.

Keywords: Amlodipine; chlorthalidone; electrocardiography; lisinopril.

Introduction

Electrocardiography (ECG) is a useful modality to identify the presence of left ventricular hypertrophy (LVH), a common manifestation of preclinical cardiovascular disease that predicts cardiovascular morbidity and mortality.[1,2] ECG LVH is correlated with blood pressure control, and regression of LVH is associated with a reduction in the risk for cardiovascular events.[3–5]

Chlorthalidone, a long-acting thiazide diuretic, has demonstrated benefit in reducing cardiovascular events compared with other drugs in several major clinical trials, including the secondary end points of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[6] These findings occurred in spite of small differences in blood pressure reduction between groups which may not fully account for differences observed in clinical end points. In a retrospective analysis from another large study, the Multiple Risk Factor Intervention Trial, favorable reductions in ECG measures of LVH were observed in men prescribed chlorthalidone compared to those prescribed hydrochlorothiazide.[7]

The purpose of this study was to examine the prevalence and incidence of ECG LVH over time in ALLHAT participants and to determine whether these findings paralleled the blood pressure changes and major clinical end points reported in the main analysis of the trial. Further, we sought to determine whether the lower risk with chlorthalidone found in secondary end points of ALLHAT could be related to differential effects of the three treatment groups on ECG LVH.

Methods

Study Population

Details about ALLHAT and its principal findings have been extensively published and disseminated.[6,8] Briefly, ALLHAT was a multicenter, randomized, controlled trial in 42,418 high-risk hypertensive individuals aged 55 years and older comparing the risk for cardiovascular and renal events (primary end point: fatal coronary heart disease or nonfatal myocardial infarction) with amlodipine, lisinopril, or doxazosin-based treatments, compared to chlorthalidone. Follow-up visits were conducted at intervals of 1, 3, 6, 9, and 12 months, followed by every 4 months thereafter.

For this analysis, all participants randomized to amlodipine, lisinopril, or chlorthalidone and with ECG data available at baseline, and either 2 and/or 4 years of follow-up were included. Participants with LVH at baseline were included to allow for examination of regression of LVH over time.

ECGs from individuals randomized to doxazosin were excluded due to shorter follow-up since this arm of the study was terminated early after the finding of an increased risk of cardiovascular events, particularly heart failure.[9] ECGs were also excluded if they had one of the following Minnesota codes (Online Supplemental Appendix Table 1): 7.1× (complete left bundle branch block), 7.2× (complete right bundle branch block), 7.4 (nonspecific intraventricular conduction delay QRS $\geq$ 120 ms), 7.8 (concomitant presence of 7.2 and 7.7 [left anterior fascicular block]), 6.6 (aberrant AV conduction which includes QRS $\geq$ 120 ms as part of the definition), 6.4× (Wolff-Parkinson-White Syndrome), or 6.8 (pacemaker). These exclusions are based on ECG interpretation guidelines which recommend caution in interpreting ECG in the presence of major intraventricular conduction defects[10]; in addition, LVH detection is suppressed in the presence of the exclusion codes listed.

ECG Coding and Ascertainment of LVH

The ALLHAT protocol called for standard 12-lead ECG measurements to be conducted at baseline, 2, and 4-year follow-up visits, recorded at clinical sites using standardized procedures. Individual ECG tracings were forwarded to the core ECG Reading Center (University of Minnesota, Minneapolis), where cross-sectional and serial coding of multiple variables was performed manually by reviewers blinded to treatment assignment. These readings were obtained from 1994 to 2002.

Current ECG interpretation guidelines do not advocate a preferred criteria set for assessing LVH, as long as an established criteria set is used and named explicitly.[10] We determined LVH using Cornell voltage, defined as the sum of the voltages of the R wave in lead aVL and the S wave in lead V_3 (ie, RaVL + SV_3 = Cornell voltage, in μV). LVH was considered present when Cornell voltage exceeded 2200 μV (22 mm) in women and 2800 μV (28 mm) in men (where 1 mm = 100 μV).[11,12] Cornell product, another common criteria set for examining LVH, was not calculated because the ALLHAT ECG data set does not include other