Effect of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) on Conduction System Disease

Thomas A. Dewland, MD; Elsayed Z. Soliman, MD, MSc, MS; Barry R. Davis, MD, PhD; Jared W. Magnani, MD, MSc; Jose-Miguel Yamal, PhD; Linda B. Piller, MD, MPH; L. Julian Haywood, MD; Alvaro Alonso, MD, PhD; Christine M. Albert, MD, MPH; Gregory M. Marcus, MD, MAS; for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Collaborative Research Group

IMPORTANCE Cardiac conduction abnormalities are associated with an increased risk for morbidity and mortality, and understanding factors that accelerate or delay conduction system disease could help to identify preventive and therapeutic strategies. Antifibrotic and anti-inflammatory properties of angiotensin-converting enzyme inhibitors and treatment for hyperlipidemia may reduce the risk for incident conduction system disease.

OBJECTIVE To identify the effect of pharmacologic therapy randomization and clinical risk factors on the incidence of conduction system disease.

DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) investigation acquired data from 623 North American centers. A total of 21 004 ambulatory individuals 55 years or older with hypertension and at least 1 other cardiac risk factor were included in the analysis.

INTERVENTIONS Participants were randomly assigned to receive amlodipine besylate, lisinopril, or chlorthalidone. Individuals with elevated fasting low-density lipoprotein cholesterol levels were also randomized to pravastatin sodium vs usual care.

MAIN OUTCOMES AND MEASURES An electrocardiogram (ECG) was obtained at study enrollment and every 2 years of follow-up. The development of incident first-degree atrioventricular block, left anterior fascicular block, incomplete left bundle branch block (LBBB), LBBB, incomplete right bundle branch block (RBBB), RBBB, or intraventricular conduction delay was assessed by serial ECGs.

RESULTS The 21 004 participants (11 758 men [56.0%]; 9246 women [44.0%]; mean [SD] age, 66.5 [7.3] years) underwent a mean (SD) follow-up of 5.0 (1.2) years. Among the 1114 participants who developed any conduction defect, 389 developed LBBB, 570 developed RBBB, and 155 developed intraventricular conduction delay. Compared with chlorthalidone, randomization to lisinopril was associated with a significant 19% reduction in conduction abnormalities (hazard ratio [HR], 0.81; 95% CI, 0.69-0.95; P = .01). Treatment with amlodipine, however, was not associated with a significant difference in conduction outcome events (HR, 0.94; 95% CI, 0.81-1.09; P = .42). Similarly, pravastatin treatment was not associated with a reduced adjusted risk for incident disease compared with usual hyperlipidemia treatment (HR, 1.13; 95% CI, 0.95-1.35; P = .18). Increased age (HR, 1.47; 95% CI, 1.34-1.63; P < .001), male sex (HR, 0.59; 95% CI, 0.50-0.73; P < .001), white race (HR, 0.59; 95% CI, 0.50-0.70; P < .001), diabetes (HR, 1.23; 95% CI, 1.07-1.42; P = .003), and left ventricular hypertrophy (HR, 3.20; 95% CI, 2.61-3.94; P < .001) were also independently associated with increased risk for conduction system disease.

CONCLUSIONS AND RELEVANCE Incident conduction system disease is significantly reduced by lisinopril therapy and is independently associated with multiple clinical factors. Further studies are warranted to determine whether pharmacologic treatment affects conduction abnormality outcomes, including pacemaker implantation.

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Multiple studies have characterized the prevalence and prognosis of conduction system disease as identified on the surface 12-lead electrocardiogram (ECG). Right and left bundle branch block (RBBB and LBBB, respectively) have been associated with heightened cardiovascular morbidity and mortality in multiple populations. Growing evidence suggests that less severe ECG abnormalities, including left anterior fascicular block and first-degree atrioventricular block, are also associated with poor outcomes.

Previous investigations of predictors of incident conduction system disease have largely focused on specific conduction defects in noncontemporary and racially homogeneous populations. In these studies, age and hypertension were consistently identified as strong predictors of bundle branch block. Improved recognition of characteristics associated with incident conduction system disease is necessary to identify at-risk patients and to develop preventive interventions. In addition, a subset of individuals with conduction system disease will ultimately develop complete heart block, which necessitates lifelong implantable cardiovascular device therapy. Understanding factors that prevent or delay conduction system disease could shift the treatment paradigm of this disorder, potentially reducing the likelihood of pacemaker implantation among certain high-risk patients.

Given the known mechanistic links among hypertension, inflammation, fibrosis, and conduction abnormalities, we examined whether randomized assignment to antihypertensives and/or therapy to lower lipid levels might affect the development of incident conduction system disease in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). We also studied the effect of other clinical characteristics on the development of incident conduction abnormalities in this large, contemporary population of at-risk individuals with hypertension.

### Methods

**ALLHAT Design**

ALLHAT was a double-blind, randomized clinical trial sponsored by the National Heart, Lung, and Blood Institute. Eligibility, enrollment, and follow-up protocols have been published previously.

Briefly, 42,418 individuals 55 or older with hypertension and at least 1 other cardiac risk factor were eligible for enrollment. Participants with a history of hospitalization for heart failure, treatment for symptomatic heart failure, or severe systolic dysfunction (ejection fraction ≤35%) were excluded. Certification to use deidentified ALLHAT data was obtained from the committee on human research of the University of California, San Francisco. All participants provided written informed consent on enrollment.

After undergoing a baseline physical examination and ECG, participants were randomized to treatment with chlortalidone, amlodipine besylate, lisinopril, or doxazosin mesylate. In addition to antihypertensive randomization, 10,355 participants with elevated fasting levels of low-density lipoprotein cholesterol (120-189 mg/dL or 100-129 mg/dL if known atherosclerotic coronary heart disease was present; to convert to millimoles per liter, multiply by 0.0259) were also randomized in a nonblinded fashion to pravastatin sodium or usual care.

Participants randomized to the antihypertensive arm were followed up for all-cause mortality. Those in the lipid level-lowering arm were followed up for the combined primary end points of fatal coronary heart disease or nonfatal myocardial infarction. Follow-up ECGs were obtained every 2 years.

**Study Cohort**

Study data were collected from February 23, 1994, to March 31, 2002 (completion of follow-up). The ALLHAT doxazosin treatment arm was terminated early because of a very low likelihood of finding a significant difference for the primary outcome and owing to increased cardiovascular disease events especially heart failure) compared with chlortalidone. As such, participants randomized to doxazosin treatment (n = 9061) were not included in the present investigation. All individuals randomized to chlortalidone, amlodipine, or lisinopril without prevalent conduction system disease on the baseline ECG, without a paced rhythm on the baseline ECG, and with at least 1 follow-up ECG were included in incident analyses (Figure 1).

**Treatment**

Participants were treated with escalating doses of antihypertensives according to their treatment randomization group to achieve a goal blood pressure of less than 140/90 mm Hg. Maximal allowable doses were 25 mg/d for chlortalidone, 10 mg/d for amlodipine besylate, and 40 mg/d for lisinopril. In the lipid level-lowering arm, participants randomized to pravastatin sodium were initially treated with 20 mg/d, followed by a dosage increase to 40 mg/d as needed to lower low-density lipoprotein cholesterol levels by at least 25%. This strategy was amended after the first 1000 participants were enrolled; a standardized pravastatin sodium dosage of 40 mg/d was used thereafter.

**Covariate Assessment**

Clinical variables potentially associated with conduction system disease and assessed during ALLHAT enrollment were
identified before analysis. Race or ethnicity, smoking status, and medical history were recorded using a standardized form on study enrollment. For the present analysis, non-Hispanic white participants were categorized as white; Hispanic white participants, as Hispanic; and black participants, as black regardless of Hispanic ethnicity status. Participants who did not identify as white, black, or Hispanic were included in the race category of other. Definitions of comorbid conditions, including coronary heart disease, diabetes, and smoking status, are described in eTable 1 in the Supplement. Left ventricular hypertrophy was diagnosed by ECG using the Cornell voltage criteria. Serum potassium, creatinine, glucose, and lipid profiles were obtained in a fasting state at the baseline visit.

Conduction System Disease Ascertainment
Conduction system disease was assessed using standard 12-lead ECGs obtained in the supine position at 0, 24, 48, 72, and 96 months of follow-up. Abnormal findings on the ECGs were classified using the Minnesota code classification system for electrocardiographic findings in a core laboratory at the University of Minnesota. Criteria used to define incident conduction system disease are described in eTable 2 in the Supplement. Any conduction system disease was defined as first-degree atrioventricular block, left anterior fascicular block, incomplete LBBB, LBBB, incomplete RBBB, RBBB, or intraventricular conduction delay.

Statistical Analysis
Data were analyzed from June 28, 2014, to March 17, 2016. Continuous variables are presented as mean (SD) and compared using 2-sample t tests. The association between categorical variables was determined using the Pearson χ² test. Cox proportional hazards models were used to determine the association between baseline covariates and incident conduction system disease before and after controlling for hypothesized confounders. Participants were censored at the time of their ECG-diagnosed conduction abnormality or at the time of their last study ECG, whichever came first. Additional analyses examining the clinical predictors of incident isolated RBBB and LBBB were also performed. Interaction analyses were performed to determine whether the association between antihypertensive treatment assignment and conduction system disease differed with respect to race or baseline left ventricular hypertrophy. Cumulative event rates were calculated using the Kaplan-Meier method. We used an intention-to-treat analysis to quantify the association between drug assignment and conduction outcomes. Data were analyzed using STATA (version 12; StataCorp). A 2-tailed P < .05 was considered statistically significant.

Results
Among the 33357 ALLHAT participants randomized to chlorthalidone, amlodipine, or lisinopril, 1537 demonstrated prevalent conduction system disease (including 461 individuals with LBBB and 892 with RBBB), 125 were excluded secondary to a paced rhythm on the baseline ECG, and 10691 did not have a baseline or at least 1 follow-up ECG (Figure 1). ALLHAT participants with serial ECGs were more likely to be men and white, not to have diabetes, and to be treated with aspirin (eTable 3 in the Supplement) compared with individuals without serial ECGs. Individuals with serial ECGs were less likely to have left ventricular hypertrophy. Other differences in baseline characteristics between included and excluded participants, although statistically significant, were not clinically substantial.

The remaining cohort of 21004 participants (11758 men [56.0%]; 9246 women [44.0%]; mean [SD] age, 66.5 [7.3] years) was followed for a mean (SD) 5.0 [1.2] years. Individuals treated with lisinopril had significantly higher systolic and diastolic blood pressure compared with individuals treated with chlorthalidone or amlodipine at nearly all points (eTable 4 in the Supplement). A total of 1114 participants developed incident conduction system disease during this period, including 570 with RBBB and 389 with LBBB (Figure 2); the remaining 155 participants had intraventricular conduction delay. No individuals demonstrated incident first-degree atrioventricular block, left anterior fascicular block, or incomplete bundle branch block. The overall incidence was 13.0 (95% CI, 12.2-13.7) per 1000 person-years for any conduction abnormality, 4.5 (95% CI, 4.1-5.0) per 1000 person-years for LBBB, and 6.6 (95% CI, 6.1-7.2) per 1000 person-years for RBBB. Participants who developed incident conduction system disease were
older and more likely to be white and male and had more co-
morbidities, including diabetes, coronary artery disease, and left ventricular hypertrophy (Table).

Participants randomized to treatment with lisinopril were significantly less likely to develop incident conduction system disease compared with those randomized to chlorthalidone therapy (HR, 0.81; 95% CI, 0.69-0.95; \( P = .01 \)) (Figure 3). Treatment with amlodipine, however, was not associated with a significant difference in conduction outcome events (HR, 0.94; 95% CI, 0.81-1.09; \( P = .42 \)). Similarly, randomization to pravastatin was not associated with a reduced adjusted risk for incident disease compared with usual hyperlipidemia treatment (HR, 1.13; 95% CI, 0.95-1.35; \( P = .18 \)). When amlodipine was used as the reference antihypertensive treatment assignment, randomization to chlorthalidone did not result in a significantly different risk for conduction system disease (HR, 1.06; 95% CI, 0.91-1.24; \( P = .42 \)). Compared with amlodipine, lisinopril randomization was associated with a reduction in incident conduction system disease (HR, 0.86; 95% CI, 0.72-1.03), although this was not statistically significant (\( P = .10 \)).

Although treatment with lisinopril vs chlorthalidone resulted in a greater reduction in the risk for incident conduction system disease among white (HR 0.72; 95% CI, 0.59-0.89) compared with black (HR, 0.95; 95% CI, 0.67-1.34) participants, no statistically significant interaction was detected (\( P = .16 \)). No statistically significant interaction was found between baseline left ventricular hypertrophy and antihypertensive treatment randomization.

The table and figure below provide a detailed analysis of the baseline characteristics of ALLHAT participants with and without incident conduction system disease.

### Table. Baseline Characteristics of ALLHAT Participants With and Without Incident Conduction System Disease*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Population, No. (%)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>66.3 (7.3) vs 68.3 (7.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>8892 (45.2) vs 354 (31.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>10 221 (52.0) vs 712 (63.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White Hispanic</td>
<td>2606 (13.3) vs 127 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>6491 (33.0) vs 264 (23.7)</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>348 (1.8) vs 11 (1.0)</td>
<td></td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>29.8 (6.1) vs 29.8 (5.9)</td>
<td>.85</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4264 (21.7) vs 230 (20.6)</td>
<td>.75</td>
</tr>
<tr>
<td>Prior antihypertensive treatment</td>
<td>17 782 (90.4) vs 1021 (91.7)</td>
<td>.39</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>7407 (38.0) vs 494 (44.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7312 (39.4) vs 447 (43.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>4832 (24.8) vs 375 (34.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>1077 (5.5) vs 134 (12.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GFR, mean (SD), mL/min/1.73 m²</td>
<td>78.0 (18.8) vs 76.3 (19.3)</td>
<td>.002</td>
</tr>
<tr>
<td>Serum potassium level, mean (SD), mEq/L</td>
<td>4.30 (0.50) vs 4.35 (.49)</td>
<td>.005</td>
</tr>
<tr>
<td>Cholesterol level, mean (SD), mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>216.0 (42.3) vs 213.4 (41.3)</td>
<td>.03</td>
</tr>
<tr>
<td>HDL</td>
<td>46.6 (14.7) vs 44.3 (13.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL</td>
<td>135.9 (36.5) vs 134.0 (35.0)</td>
<td>.03</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

* Calculated for comparison of the indicated characteristic in participants with vs without incident conduction system disease.

† Participants who did not identify as white, black, or Hispanic were included. Individuals with missing data were omitted from the proportion calculations for the missing variable.
When the conduction system disease outcome was restricted to incident LBBB, the magnitude of LBBB risk reduction with lisinopril was similar to that observed for all conduction abnormalities, although not of statistical significance (adjusted HR vs chlorthalidone, 0.77; 95% CI, 0.60-1.00; \( P = .05 \)). In a similar analysis that examined the association between antihypertensive treatment and incident RBBB, lisinopril was associated with a nonsignificant reduced risk for disease (adjusted HR vs chlorthalidone, 0.88; 95% CI, 0.71-1.09; \( P = .23 \)).

In multivariable models that adjusted for antihypertensive treatment, statin treatment, and the variables described in the Table, increased age (HR, 1.47; 95% CI, 1.34-1.63; \( P < .001 \)), male sex (HR, 0.59; 95% CI, 0.50-0.73; \( P < .001 \)), increased body mass index (HR, 1.07; 95% CI, 1.00-1.13; \( P = .04 \)), tobacco use (HR, 1.29; 95% CI, 1.09-1.52; \( P = .003 \)), diabetes (HR, 1.23; 95% CI, 1.07-1.42; \( P = .003 \)), coronary heart disease (HR, 1.25; 95% CI, 1.08-1.44; \( P = .003 \)), and left ventricular hypertrophy (HR, 3.20; 95% CI, 2.61-3.94; \( P < .001 \)) were each significantly associated with an increased risk for incident conduction system disease (Figure 4). Black participants, on the other hand, demonstrated a significantly reduced adjusted risk for conduction system disease compared with non-Hispanic white participants (HR, 0.59; 95% CI, 0.50-0.70; \( P < .001 \)).

### Discussion

In a large cohort of older individuals with hypertension randomized to antihypertensive treatment and followed up with serial ECGs, we found that randomization to lisinopril therapy resulted in a 19% reduction in the overall risk for incident conduction system disease compared with chlorthalidone. In addition, several clinical factors were associated with the development of incident conduction system disease. Increasing age, male sex, and left ventricular hypertrophy were among the strongest predictors of incident disease, whereas black individuals had significantly less conduction system disease compared with white individuals.

The randomized ALLHAT study design allowed us to calculate an unbiased association between pharmacologic treatment assignment and incident conduction system disease. Although angiotensin-converting enzyme (ACE) inhibitors and statins have been proposed as treatments for the primary prevention of atrial fibrillation owing to their antifibrotic and anti-inflammatory properties,28,29 data from ALLHAT suggest that incident atrial fibrillation is not reduced with lisinopril vs chlorthalidone therapy.20 Nevertheless, we hypothesized that ACE inhibitors and statin medications could reduce the likelihood of incident conduction system disease via mechanisms similar to those considered for atrial fibrillation prevention. Although our results exclude a clinically substantial benefit of pravastatin therapy compared with usual care, treatment with lisinopril resulted in a significant reduction in conduction system disease events compared with chlorthalidone. Systolic and diastolic blood pressures were higher in the lisinopril treatment group compared with the chlorthalidone or amlodipine group (eTable 4 in the Supplement). As a result, the significant reduction in conduction system disease attributed to lisinopril treatment cannot be fully explained by the antihypertensive effects of this medication.

Although studies investigating the association between antihypertensive treatment and regression of left ventricular mass have not reached uniform conclusions,31,32 some evidence suggests that ACE inhibitors may be superior to diuretics and calcium channel blockers for improvement in this variable.23 Furthermore, the reduction in ventricular hypertrophy with ACE inhibition may occur independently of antihypertensive effects. In light of the established association between left-sided conduction abnormalities and subsequent systolic heart failure4 and in conjunction with data suggesting that the reversal of LBBB-induced dyssynchrony can improve left ventricular systolic function,25,26 we may speculate whether the benefit of ACE inhibition in the treatment of patients with chronic heart failure is partially explained by the prevention of conduction system disease. On the other hand, prior ALLHAT data27 suggest that lisinopril is not superior to chlorthalidone for the long-term prevention of incident diagnoses of heart failure.

Most prior investigations examining conduction system disease have focused on the association between prevalent conduction abnormalities and clinical outcomes. Various studies have found associations of LBBB, RBBB,1,2,6,11,31,33 intraventricular conduction delay,5 left anterior fascicular block,4 and first-degree atrioventricular block5,6 with worsened outcomes. The mechanisms underlying these associations are poorly understood. For instance,
whether the conduction abnormality acts as a primary cause of pathogenesis or is instead a secondary consequence of another pathologic myocardial process, such as infarction or fibrosis, remains unknown. Previous histologic analyses using autopsy specimens have identified fibrosis as the driver of conduction system abnormalities, but why certain individuals develop clinically apparent disease remains unclear. Because treatment with lisinopril (vs chlorthalidone) was associated with an increased risk for cardiovascular disease and stroke end points in the primary ALLHAT investigation, the superiority of lisinopril for the prevention of incident conduction system disease is not readily explained by reduced development of comorbid cardiovascular conditions during study follow-up.12

The association between clinical variables and incident conduction system disease has primarily been limited to single conduction abnormalities in noncontemporary and racially homogeneous cohorts. In these studies, hypertension and advanced age emerged as common risk factors for incident LBBB and RBBB. Our study cohort, which consisted of older (≥55 years) adults with hypertension, represented an ideal, high-risk population for further study of conduction system disease risk factors. We found that several comorbidities beyond age are associated with the risk for a conduction abnormality, indicating that multiple mechanisms likely coalesce into a final pathologic pathway that results in manifestation of clinical disease. Many of the risk factors associated with conduction system disease, including smoking, increased body mass index, diabetes, and left ventricular hypertrophy, are preventable or treatable. The aging of the United States population and the projected future increase in prevalence of many chronic diseases, including diabetes, suggests the burden of conduction system disease will similarly rise.

The reduction in the adjusted risk for incident conduction system disease among black compared with white participants was an unanticipated finding. Our results add to a recent investigation from the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) cohorts that observed a reduced likelihood of sick sinus syndrome among black vs white participants. These results are of further interest in light of the growing literature demonstrating a reduced incidence of atrial fibrillation among black compared with white participants. While speculative, these findings raise the possibility that a singular mechanism (eg, accelerated myocardial fibrosis) could explain the heightened propensity for atrial fibrillation and conduction system disease observed in white compared with black populations.

Limitations of this study should be acknowledged. The current investigation is a secondary analysis of a randomized clinical trial designed to determine the effects of pharmacological...
logic therapy on coronary artery disease events and other major cardiovascular and renal outcomes. However, because the primary outcome of the present study was assessed using prospectively collected ECGs (the criterion standard for identifying conduction system disease) analyzed according to a standardized protocol in a core laboratory, we do not believe that this investigative approach should meaningfully bias our results or weaken our conclusions. Because the ALLHAT trial enrolled participants 55 years or older with hypertension and other cardiac risk factors, generalizability of the current findings to younger individuals or those without cardiovascular risk factors may be limited. In addition, participant crossover between antihypertensive treatment arms occurred, and an intention-to-treat analysis was used to define the association between treatment randomization and incident conduction system disease. However, crossover or treatment with multiple classes of antihypertensives would tend to bias the results toward the null hypothesis and is therefore unlikely to explain our positive findings with respect to ACE inhibition.

Baseline and follow-up ECGs were not obtained on all participants, and we found statistically significant differences in the proportion of individuals with serial ECGs between the randomized antihypertensive treatment arms (eTable 3 in the Supplement). Although the proportion of participants treated with lisinopril was lower in the included cohort (compared with individuals excluded owing to lack of serial ECGs), this difference would only underestimate the observed lisinopril treatment effect. Because renin-angiotensin-aldosterone system activity was not specifically assessed in ALLHAT participants, the observed benefit of lisinopril may have actually been secondary to enhanced fibrosis caused by chlorthalidone-induced renin-angiotensin-aldosterone system activation.

Finally, the association between clinical variables and conduction system abnormalities could be biased by unmeasured or incompletely characterized factors important to disease pathogenesis. Because antihypertensive and statin treatments were randomized, residual confounding is unlikely to explain the association between ACE inhibitor treatment assignment and conduction outcomes.

Conclusions

The risk for incident conduction system disease is significantly reduced by lisinopril compared with chlorthalidone therapy and is independently associated with multiple clinical factors. Further studies are warranted to determine whether pharmacologic treatment can affect clinical conduction abnormality outcomes, including pacemaker implantation.