# Online Supplemental Materials

## Characteristics and outcomes in patients with treatment resistant hypertension randomized to angiotensin converting enzyme inhibitor vs. calcium channel blocker vs. diuretic

Sripal Bangalore, MD, MHA, Barry R. Davis, MD, PhD, William C. Cushman, MD, Sara L. Pressel, MS, Paul M. Muntner, PhD, David A. Calhoun, MD, John B. Kostis, MD, Paul K. Whelton, MD, Jeffrey L. Probstfield, MD, Mahboob Rahman, MD, Henry R. Black, MD, for the ALLHAT Collaborative Research Group (see *JAMA* 2000;283:1973-1975).

*Affiliations: New York University School of Medicine, New York, NY [SB, HB]; The University of Texas School of Public Health, Houston, Tx [BRD, SP]; Memphis Veterans Affairs Medical Center, University of Tennessee College of Medicine, Memphis, TN [WCC]; University of Alabama, Birmingham, AL [PM, DAC]; University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick, NJ [JBK]; The University of Washington Medical Center, Seattle, WA [JLP]; Tulane University School of Public Health and Tropical Medicine, New Orleans, LA [PKW]; Case Western Reserve University, Cleveland, OH [MR]*

Corresponding author:
Barry R. Davis, M.D., Ph.D.
Director, Coordinating Center for Clinical Trials
The University of Texas School of Public Health
1200 Pressler St. W-916
Houston, TX 77030
Phone 713-500-9515
Fax 713-500-9530
E-mail barry.r.davis@uth.tmc.edu

**eTable 1.** Sensitivity analysis: clinical outcomes in the antihypertensive treatment groups in patients with aTRH* associated with taking ≥ 3 classes of antihypertensive medication with uncontrolled blood pressure

| | Chlorthalidone | Amlodipine | Lisinopril | Amlodipine vs. Chlorthalidone | | Lisinopril vs. Chlorthalidone | |
|---|---|---|---|---|---|---|---|
| | No. of events (%) | No. of events (%) | No. of events (%) | HR (95% CI) | P-Value | HR (95% CI) | P-Value |
| Primary outcome CHD† | 46 (7.5) | 33 (8.4) | 53 (7.9) | | | | |
| Model 1 | | | | 1.06 (0.68-1.67) | 0.78 | 1.02 (0.69-1.51) | 0.93 |
| Model 2 | | | | 1.07 (0.68-1.68) | 0.76 | 1.06 (0.71-1.58) | 0.77 |
| Model 3 | | | | 1.03 (0.65-1.65) | 0.89 | 1.09 (0.72-1.63) | 0.69 |
| Model 4 | | | | 0.90 (0.54-1.52) | 0.70 | 1.12 (0.72-1.72) | 0.62 |
| Secondary outcomes | | | | | | | |
| All-cause mortality | 76 (12.4) | 56 (14.1) | 88 (12.9) | | | | |
| Model 1 | | | | 1.08 (0.76-1.52) | 0.67 | 1.01 (0.74-1.37) | 0.97 |
| Model 2 | | | | 1.12 (0.79-1.58) | 0.53 | 1.07 (0.79-1.46) | 0.66 |
| Model 3 | | | | 1.10 (0.77-1.56) | 0.62 | 1.06 (0.77-1.45) | 0.74 |
| Model 4 | | | | 1.02 (0.69-1.51) | 0.92 | 1.11 (0.79-1.56) | 0.53 |
| Combined CHD‡ | 92 (15.1) | 62 (15.8) | 84 (12.6) | | | | |
| Model 1 | | | | 1.01 (0.73-1.39) | 0.96 | 0.79 (0.59-1.07) | 0.13 |
| Model 2 | | | | 1.01 (0.73-1.39) | 0.96 | 0.82 (0.61-1.10) | 0.18 |
| Model 3 | | | | 1.05 (0.75-1.47) | 0.77 | 0.84 (0.62-1.14) | 0.26 |
| Model 4 | | | | 1.02 (0.70-1.49) | 0.91 | 0.93 (0.67-1.31) | 0.69 |
| Stroke | 20 (3.3) | 24 (6.1) | 29 (4.4) | | | | |
| Model 1 | | | | 1.81 (1.00-3.27) | 0.05 | 1.28 (0.72-2.25) | 0.40 |
| Model 2 | | | | **1.88 (1.03-3.41)** | **0.04** | 1.34 (0.75-2.37) | 0.32 |
| Model 3 | | | | **1.87 (1.01-3.43)** | **0.04** | 1.31 (0.73-2.36) | 0.37 |
| Model 4 | | | | 1.84 (0.94-3.58) | 0.07 | 1.45 (0.77-2.75) | 0.25 |
| Combined CVD§ | 148 (24.3) | 108 (27.5) | 141 (21.0) | | | | |
| Model 1 | | | | 1.10 (0.86-1.41) | 0.44 | 0.83 (0.66-1.04) | 0.11 |
| Model 2 | | | | 1.10 (0.86-1.41) | 0.47 | 0.85 (0.67-1.07) | 0.15 |
| Model 3 | | | | 1.14 (0.88-1.48) | 0.31 | 0.86 (0.68-1.10) | 0.23 |
| Model 4 | | | | 1.18 (0.89-1.57) | 0.26 | 0.94 (0.72-1.22) | 0.63 |
| End-stage renal disease | 12 (2.0) | 7 (1.8) | 8 (1.2) | | | | |
| Model 1 | | | | 0.88 (0.35-2.24) | 0.79 | 0.58 (0.24-1.42) | 0.23 |
| Model 2 | | | | 0.90 (0.35-2.31) | 0.83 | 0.53 (0.21-1.30) | 0.16 |
| Model 3 | | | | 1.30 (0.47-3.59) | 0.61 | 0.69 (0.26-1.81) | 0.45 |
| Model 4 | | | | 1.60 (0.52-4.91) | 0.41 | 1.05 (0.36-3.07) | 0.93 |
| Cancer | 37 (6.1) | 20 (5.2) | 43 (6.5) | | | | |
| Model 1 | | | | 0.82 (0.48-1.42) | 0.48 | 1.02 (0.65-1.58) | 0.95 |

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|---|---|---|---|---|---|---|---|
| Model 2 | | | | 0.84 (0.48-1.44) | 0.52 | 1.03 (0.66-1.61) | 0.89 |
| Model 3 | | | | 0.83 (0.48-1.45) | 0.52 | 1.00 (0.64-1.56) | 0.99 |
| Model 4 | | | | 0.94 (0.52-1.68) | 0.83 | 1.04 (0.64-1.70) | 0.86 |
| Hospitalized for gastrointestinal bleeding | 29 (6.0) | 17 (5.6) | 31 (6.1) | | | | |
| Model 1 | | | | 0.90 (0.50-1.65) | 0.74 | 0.98 (0.59-1.63) | 0.94 |
| Model 2 | | | | 0.90 (0.50-1.65) | 0.74 | 0.98 (0.59-1.63) | 0.94 |
| Model 3 | | | | 1.03 (0.55-1.91) | 0.93 | 1.14 (0.67-1.94) | 0.64 |
| Model 4 | | | | 0.97 (0.49-1.92) | 0.93 | 1.25 (0.70-2.22) | 0.45 |
| Components of secondary outcomes | | | | | | | |
| Heart failure | 42 (6.9) | 41 (10.5) | 37 (5.6) | | | | |
| Model 1 | | | | 1.50 (0.97-2.30) | 0.07 | 0.78 (0.50-1.21) | 0.26 |
| Model 2 | | | | 1.52 (0.99-2.34) | 0.06 | 0.84 (0.54-1.31) | 0.44 |
| Model 3 | | | | 1.41 (0.90-2.20) | 0.13 | 0.82 (0.52-1.29) | 0.39 |
| Model 4 | | | | 1.52 (0.95-2.44) | 0.08 | 0.88 (0.55-1.42) | 0.61 |
| Hospitalized/fatal heart failure | 36 (5.9) | 31 (7.9) | 26 (3.9) | | | | |
| Model 1 | | | | 1.32 (0.82-2.13) | 0.26 | 0.63 (0.38-1.04) | 0.07 |
| Model 2 | | | | 1.36 (0.84-2.20) | 0.22 | 0.69 (0.41-1.14) | 0.15 |
| Model 3 | | | | 1.30 (0.79-2.13) | 0.30 | 0.67 (0.40-1.13) | 0.13 |
| Model 4 | | | | 1.43 (0.84-2.44) | 0.19 | 0.77 (0.45-1.34) | 0.36 |
| Angina (hospitalized or treated) | 50 (8.2) | 32 (8.2) | 41 (6.2) | | | | |
| Model 1 | | | | 0.97 (0.62-1.50) | 0.88 | 0.72 (0.48-1.09) | 0.12 |
| Model 2 | | | | 0.95 (0.61-1.48) | 0.81 | 0.70 (0.46-1.06) | 0.09 |
| Model 3 | | | | 1.10 (0.69-1.74) | 0.69 | 0.72 (0.47-1.12) | 0.15 |
| Model 4 | | | | 1.08 (0.64-1.82) | 0.77 | 0.79 (0.49-1.29) | 0.35 |
| Angina (hospitalized) | 40 (6.6) | 23 (5.9) | 28 (4.2) | | | | |
| Model 1 | | | | 0.86 (0.52-1.44) | 0.58 | **0.61 (0.38-0.99)** | **0.04** |
| Model 2 | | | | 0.86 (0.51-1.44) | 0.56 | **0.60 (0.37-0.98)** | **0.04** |
| Model 3 | | | | 0.94 (0.56-1.60) | 0.83 | **0.61 (0.37-1.00)** | **0.05** |
| Model 4 | | | | 0.92 (0.50-1.70) | 0.79 | 0.68 (0.39-1.21) | 0.19 |
| Coronary revascularizations | 40 (6.6) | 35 (8.9) | 29 (4.4) | | | | |
| Model 1 | | | | 1.35 (0.85-2.12) | 0.20 | 0.63 (0.39-1.02) | 0.06 |
| Model 2 | | | | 1.38 (0.88-2.18) | 0.16 | 0.67 (0.41-1.08) | 0.10 |
| Model 3 | | | | 1.55 (0.97-2.49) | 0.07 | 0.71 (0.43-1.17) | 0.18 |
| Model 4 | | | | **1.82 (1.04-3.17)** | **0.04** | 0.90 (0.51-1.59) | 0.73 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Peripheral arterial disease (hospitalized or treated) | 25 (4.1) | 9 (2.3) | 12 (1.8) | | | | |
| Model 1 | | | | 0.54 (0.25-1.16) | 0.12 | **0.42 (0.21-0.85)** | **0.01** |
| Model 2 | | | | 0.53 (0.25-1.13) | 0.10 | **0.44 (0.22-0.88)** | **0.02** |
| Model 3 | | | | 0.53 (0.24-1.16) | 0.11 | **0.46 (0.22-0.92)** | **0.03** |
| Model 4 | | | | 0.65 (0.27-1.54) | 0.33 | 0.45 (0.20-1.04) | 0.06 |

Abbreviations: aTRH, apparent treatment resistant hypertension; HR indicates Hazard Ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease.
*aTRH was defined as having uncontrolled hypertension despite the use of antihypertensive medications from 3 or more classes or the use of 4 or more antihypertensive medication classes to achieve blood pressure control.
†CHD includes nonfatal myocardial infarction (MI) and fatal CHD; end-stage renal disease: kidney disease death, kidney transplant, or start of chronic renal dialysis; and heart failure: fatal, nonfatal hospitalized, or treated.
‡Combined CHD indicates CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina.
§Combined CVD indicates CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).
Model 1: unadjusted;
Model 2: adjusted for age, sex, race/ethnicity and region of residence;
Model 3: adjusted for variables in model 2 plus practice setting, education level, smoking status and body mass index (BMI);
Model 4: adjusted for variables in model 2 and 3 along with estimated glomerular filtration rate (eGFR), diabetes, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, history of CHD, left ventricular hypertrophy (LVH), and taking blood pressure medications prior to randomization

**eTable 2.** Sensitivity analysis: clinical outcomes in the antihypertensive treatment groups in patients with aTRH* associated with taking ≥ 4 classes of antihypertensive medication with controlled blood pressure

| | Chlorthalidone | Amlodipine | Lisinopril | Amlodipine vs. Chlorthalidone | | Lisinopril vs. Chlorthalidone | |
|---|---|---|---|---|---|---|---|
| | No. of events (%) | No. of events (%) | No. of events (%) | HR (95% CI) | P-Value | HR (95% CI) | P-Value |
| Primary outcome CHD† | 9 (15.5) | 3 (7.1) | 4 (5.2) | | | | |
| Model 1 | | | | 0.38 (0.10-1.40) | 0.15 | **0.28 (0.09-0.93)** | **0.04** |
| Model 2 | | | | 0.42 (0.11-1.56) | 0.19 | 0.30 (0.09-1.05) | 0.06 |
| Model 3 | | | | 0.60 (0.13-2.82) | 0.51 | 0.50 (0.11-2.18) | 0.35 |
| Model 4 | | | | 1.19 (0.13-10.66) | 0.87 | 1.33 (0.13-13.94) | 0.81 |
| Secondary outcomes | | | | | | | |
| All-cause mortality | 5 (8.6) | 4 (9.3) | 4 (5.2) | | | | |
| Model 1 | | | | 0.94 (0.25-3.52) | 0.93 | 0.55 (0.15-2.04) | 0.37 |
| Model 2 | | | | 1.61 (0.38-6.87) | 0.52 | 0.59 (0.13-2.62) | 0.49 |
| Model 3 | | | | 8.49 (0.82-87.95) | 0.07 | 3.77 (0.36-39.09) | 0.27 |
| Model 4 | | | | - | - | - | - |
| Combined CHD‡ | 10 (17.2) | 9 (21.4) | 9 (11.7) | | | | |
| Model 1 | | | | 1.24 (0.50-3.06) | 0.64 | 0.61 (0.25-1.50) | 0.28 |
| Model 2 | | | | 1.35 (0.54-3.36) | 0.52 | 0.65 (0.26-1.63) | 0.35 |
| Model 3 | | | | 1.93 (0.65-5.73) | 0.23 | 1.04 (0.35-3.09) | 0.95 |
| Model 4 | | | | **6.09 (1.20-30.98)** | **0.03** | 3.18 (0.75-13.46) | 0.12 |
| Stroke | 3 (5.3) | 0 (0.0) | 1 (1.3) | | | | |
| Model 1 | | | | - | - | 0.25 (0.03-2.36) | 0.22 |
| Model 2 | | | | - | - | 0.23 (0.02-2.92) | 0.26 |
| Model 3 | | | | - | - | - | - |
| Model 4 | | | | - | - | - | - |
| Combined CVD§ | 14 (24.1) | 12 (28.6) | 13 (16.9) | | | | |
| Model 1 | | | | 1.20 (0.55-2.60) | 0.64 | 0.62 (0.29-1.33) | 0.22 |
| Model 2 | | | | 1.39 (0.63-3.07) | 0.41 | 0.72 (0.33-1.56) | 0.40 |
| Model 3 | | | | 2.15 (0.87-5.32) | 0.10 | 1.01 (0.40-2.57) | 0.98 |
| Model 4 | | | | **3.62 (1.04-12.65)** | **0.04** | 1.61 (0.50-5.22) | 0.43 |
| End-stage renal disease | 1 (1.8) | 0 (0.0) | 1 (1.4) | | | | |
| Model 1 | | | | - | - | 0.64 (0.04-10.37) | 0.76 |
| Model 2 | | | | - | - | 1.31 (0.08-21.77) | 0.85 |
| Model 3 | | | | - | - | - | - |
| Model 4 | | | | - | - | - | - |
| Cancer | 2 (3.5) | 1 (2.4) | 1 (1.4) | | | | |
| Model 1 | | | | 0.67 (0.06-7.39) | 0.74 | 0.39 (0.04-4.27) | 0.44 |
| Model 2 | | | | 0.68 (0.05-9.99) | 0.78 | 0.36 (0.03-4.17) | 0.41 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Model 3 | | | | 0.24 (0.01-11.66) | 0.47 | 0.28 (0.01-7.07) | 0.44 |
| Model 4 | | | | - | - | - | - |
| Hospitalized for gastrointestinal bleeding | 3 (6.0) | 2 (6.1) | 4 (8.2) | | | | |
| Model 1 | | | | 0.84 (0.14-5.02) | 0.85 | 1.16 (0.26-5.20) | 0.85 |
| Model 2 | | | | 0.87 (0.13-5.61) | 0.88 | 1.09 (0.22-5.36) | 0.91 |
| Model 3 | | | | 0.94 (0.10-8.74) | 0.96 | 0.82 (0.07-9.85) | 0.87 |
| Model 4 | | | | - | - | - | - |
| Components of secondary outcomes | | | | | | | |
| Heart failure | 5 (8.6) | 2 (4.8) | 2 (2.6) | | | | |
| Model 1 | | | | 0.44 (0.08-2.28) | 0.33 | 0.26 (0.05-1.34) | 0.11 |
| Model 2 | | | | 0.38 (0.07-2.20) | 0.28 | 0.35 (0.06-1.94) | 0.23 |
| Model 3 | | | | 0.29 (0.03-2.49) | 0.26 | 0.28 (0.02-3.46) | 0.32 |
| Model 4 | | | | - | - | - | - |
| Hospitalized/fatal heart failure | 5 (8.6) | 2 (4.8) | 2 (2.6) | | | | |
| Model 1 | | | | 0.42 (0.08-2.18) | 0.30 | 0.24 (0.05-1.27) | 0.09 |
| Model 2 | | | | 0.38 (0.07-2.20) | 0.28 | 0.31 (0.05-1.80) | 0.19 |
| Model 3 | | | | 0.30 (0.04-2.37) | 0.25 | 0.23 (0.02-3.23) | 0.28 |
| Model 4 | | | | - | - | - | - |
| Angina (hospitalized or treated) | 0 (0.0) | 9 (21.4) | 5 (6.7) | | | | |
| Model 1 | | | | - | - | - | - |
| Model 2 | | | | - | - | - | - |
| Model 3 | | | | - | - | - | - |
| Model 4 | | | | - | - | - | - |
| Angina (hospitalized) | 0 (0.0) | 8 (19.0) | 4 (5.3) | | | | |
| Model 1 | | | | - | - | - | - |
| Model 2 | | | | - | - | - | - |
| Model 3 | | | | - | - | - | - |
| Model 4 | | | | - | - | - | - |
| Coronary revascularizations | 4 (7.0) | 6 (14.3) | 3 (3.9) | | | | |
| Model 1 | | | | 1.93 (0.54-6.85) | 0.31 | 0.50 (0.11-2.26) | 0.37 |
| Model 2 | | | | 2.00 (0.55-7.27) | 0.29 | 0.53 (0.12-2.43) | 0.41 |
| Model 3 | | | | 2.07 (0.43-9.93) | 0.37 | 0.81 (0.12-5.34) | 0.83 |
| Model 4 | | | | 229 (0.49-107816) | 0.08 | 0.88 (0.02-46.66) | 0.95 |
| Peripheral arterial | 2 (3.5) | 0 (0.0) | 2 (2.7) | | | | |

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|---|---|---|---|---|
| disease (hospitalized or treated) | | | | |
| Model 1 | - | - | 0.72 (0.10-5.11) | 0.74 |
| Model 2 | - | - | 1.48 (0.15-14.07) | 0.74 |
| Model 3 | - | - | - | - |
| Model 4 | - | - | - | - |

Abbreviations: aTRH, apparent treatment resistant hypertension; HR indicates Hazard Ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease.
*aTRH was defined as having uncontrolled hypertension despite the use of antihypertensive medications from 3 or more classes or the use of 4 or more antihypertensive medication classes to achieve blood pressure control.
†CHD includes nonfatal myocardial infarction (MI) and fatal CHD; end-stage renal disease: kidney disease death, kidney transplant, or start of chronic renal dialysis; and heart failure: fatal, nonfatal hospitalized, or treated.
‡Combined CHD indicates CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina.
§Combined CVD indicates CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).
Model 1: unadjusted;
Model 2: adjusted for age, sex, race/ethnicity and region of residence;
Model 3: adjusted for variables in model 2 plus practice setting, education level, smoking status and body mass index (BMI);
Model 4: adjusted for variables in model 2 and 3 along with estimated glomerular filtration rate (eGFR), diabetes, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, history of CHD, left ventricular hypertrophy (LVH), and taking blood pressure medications prior to randomization

**eTable 3.** As-treated analysis: Clinical outcomes in patients with aTRH*, on diuretics vs. not on diuretics at 2 years

| | On diuretics (n=616) No. of events (%) | Not on diuretics (n=1254) No. of events (%) | P-value | On diuretics vs. not on diuretics HR (95% CI) | P-Value |
|---|---|---|---|---|---|
| Primary outcome CHD† | 55 (9.0) | 93 (7.5) | 0.250 | | |
| Model 1 | | | | 1.20 (0.86 – 1.68) | 0.28 |
| Model 2 | | | | 1.19 (0.85 – 1.67) | 0.30 |
| Model 3 | | | | 1.14 (0.80 – 1.61) | 0.48 |
| Model 4 | | | | 1.02 (0.69 – 1.50) | 0.94 |
| Secondary outcomes | | | | | |
| All-cause mortality | 84 (13.6) | 149 (11.9) | 0.280 | | |
| Model 1 | | | | 1.13 (0.87 – 1.48) | 0.36 |
| Model 2 | | | | 1.15 (0.88 – 1.51) | 0.29 |
| Model 3 | | | | 1.17 (0.89 – 1.55) | 0.27 |
| Model 4 | | | | 1.10 (0.81 – 1.49) | 0.54 |
| Combined CHD‡ | 94 (15.5) | 172 (13.9) | 0.360 | | |
| Model 1 | | | | 1.12 (0.87 – 1.44) | 0.39 |
| Model 2 | | | | 1.12 (0.87 – 1.44) | 0.38 |
| Model 3 | | | | 1.09 (0.84 – 1.43) | 0.51 |
| Model 4 | | | | 1.13 (0.84 – 1.52) | 0.41 |
| Stroke | 31 (5.1) | 46 (3.7) | 0.158 | | |
| Model 1 | | | | 1.37 (0.87 – 2.15) | 0.18 |
| Model 2 | | | | 1.33 (0.84 – 2.11) | 0.22 |
| Model 3 | | | | 1.29 (0.80 – 2.08) | 0.30 |
| Model 4 | | | | 1.10 (0.65 – 1.86) | 0.73 |
| Combined CVD§ | 155 (25.5) | 281 (22.6) | 0.172 | | |
| Model 1 | | | | 1.13 (0.93 – 1.38) | 0.22 |
| Model 2 | | | | 1.11 (0.91 – 1.35) | 0.30 |
| Model 3 | | | | 1.08 (0.88 – 1.32) | 0.47 |
| Model 4 | | | | 1.02 (0.81 – 1.28) | 0.88 |
| End-stage renal disease | 11 (1.8) | 18 (1.5) | 0.562 | | |
| Model 1 | | | | 1.23 (0.58 – 2.60) | 0.59 |
| Model 2 | | | | 1.17 (0.55 – 2.49) | 0.69 |
| Model 3 | | | | 1.48 (0.67 – 3.30) | 0.33 |
| Model 4 | | | | 1.51 (0.60 – 3.80) | 0.38 |
| Cancer | 26 (4.4) | 78 (6.4) | 0.085 | | |
| Model 1 | | | | 0.67 (0.43 – 1.05) | 0.08 |
| Model 2 | | | | 0.69 (0.44 – 1.07) | 0.10 |
| Model 3 | | | | 0.73 (0.47 – 1.15) | 0.18 |
| Model 4 | | | | 0.85 (0.53 – 1.37) | 0.51 |

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| Hospitalized for gastrointestinal bleeding | 45 (9.5) | 41 (4.3) | <0.001 | | |
| Model 1 | | | | 2.25 (1.47 – 3.43) | <0.01 |
| Model 2 | | | | 2.39 (1.56 – 3.66) | <0.01 |
| Model 3 | | | | 2.27 (1.46 - 3.55) | <0.01 |
| Model 4 | | | | 2.55 (1.57 – 4.14) | <0.01 |
| Components of secondary outcomes | | | | | |
| Heart failure | 47 (7.7) | 82 (6.6) | 0.381 | | |
| Model 1 | | | | 1.16 (0.81 – 1.66) | 0.41 |
| Model 2 | | | | 1.10 (0.77 – 1.59) | 0.59 |
| Model 3 | | | | 0.95 (0.66 – 1.39) | 0.81 |
| Model 4 | | | | 0.89 (0.60 – 1.33) | 0.56 |
| Hospitalized/fatal heart failure | 40 (6.6) | 62 (5.0) | 0.165 | | |
| Model 1 | | | | 1.31 (0.88 – 1.95) | 0.18 |
| Model 2 | | | | 1.26 (0.85 – 1.88) | 0.25 |
| Model 3 | | | | 1.07 (0.71 – 1.62) | 0.75 |
| Model 4 | | | | 1.03 (0.66 – 1.61) | 0.89 |
| Angina (hospitalized or treated) | 49 (8.1) | 88 (7.1) | 0.458 | | |
| Model 1 | | | | 1.13 (0.79 – 1.60) | 0.51 |
| Model 2 | | | | 1.16 (0.81 – 1.65) | 0.41 |
| Model 3 | | | | 1.24 (0.86 – 1.79) | 0.24 |
| Model 4 | | | | 1.26 (0.83 – 1.91) | 0.27 |
| Angina (hospitalized) | 37 (6.1) | 66 (5.3) | 0.501 | | |
| Model 1 | | | | 1.13 (0.76 – 1.69) | 0.55 |
| Model 2 | | | | 1.18 (0.79 – 1.77) | 0.43 |
| Model 3 | | | | 1.20 (0.79 – 1.82) | 0.40 |
| Model 4 | | | | 1.25 (0.77 – 2.03) | 0.36 |
| Coronary revascularizations | 40 (6.6) | 77 (6.2) | 0.766 | | |
| Model 1 | | | | 1.06 (0.72 – 1.55) | 0.78 |
| Model 2 | | | | 1.06 (0.72 – 1.56) | 0.75 |
| Model 3 | | | | 0.98 (0.65 – 1.46) | 0.91 |
| Model 4 | | | | 1.04 (0.66 – 1.64) | 0.86 |
| Peripheral arterial disease (hospitalized or treated) | 17 (2.8) | 33 (2.7) | 0.864 | | |

| | | |
|---|---|---|
| Model 1 | 1.04 (0.58 – 1.86) | 0.90 |
| Model 2 | 1.04 (0.58 – 1.87) | 0.90 |
| Model 3 | 1.01 (0.55 – 1.86) | 0.97 |
| Model 4 | 0.87 (0.41 – 1.84) | 0.71 |

Abbreviations: aTRH, apparent treatment resistant hypertension; HR indicates Hazard Ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease.
[*]aTRH was defined as having uncontrolled hypertension despite the use of antihypertensive medications from 3 or more classes or the use of 4 or more antihypertensive medication classes to achieve blood pressure control.
[†]CHD includes nonfatal myocardial infarction (MI) and fatal CHD; end-stage renal disease: kidney disease death, kidney transplant, or start of chronic renal dialysis; and heart failure: fatal, nonfatal hospitalized, or treated.
[‡]Combined CHD indicates CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina.
[§]Combined CVD indicates CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).
Model 1: unadjusted;
Model 2: adjusted for age, sex, race/ethnicity and region of residence;
Model 3: adjusted for variables in model 2 plus practice setting, education level, smoking status and body mass index (BMI);
Model 4: adjusted for variables in model 2 and 3 along with estimated glomerular filtration rate (eGFR), diabetes, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, history of CHD, left ventricular hypertrophy (LVH), and taking blood pressure medications prior to randomization

**eTable 4.** Clinical outcomes in the antihypertensive treatment groups in patient with aTRH[*] at 1 year

| | Chlorthalidone (N=510) | Amlodipine (N=300) | Lisinopril (N=655) | Amlodipine vs. Chlorthalidone | | Lisinopril vs. Chlorthalidone | |
|---|---|---|---|---|---|---|---|
| | No. of events (%) | No. of events (%) | No. of events (%) | HR (95% CI) | P-Value | HR (95% CI) | P-Value |
| Primary outcome CHD[†] | 54 (10.7) | 27 (9.1) | 61 (9.5) | | | | |
| Model 1 | | | | 0.81 (0.51-1.29) | 0.38 | 0.82 (0.57-1.19) | 0.30 |
| Model 2 | | | | 0.79 (0.49-1.25) | 0.31 | 0.84 (0.58-1.21) | 0.35 |
| Model 3 | | | | 0.74 (0.46-1.21) | 0.23 | 0.84 (0.57-1.22) | 0.36 |
| Model 4 | | | | 0.73 (0.43-1.24) | 0.24 | 0.85 (0.56-1.28) | 0.44 |
| Model 5 | | | | 0.77 (0.45-1.32) | 0.34 | 0.84 (0.55-1.28) | 0.43 |
| Secondary outcomes | | | | | | | |
| All-cause mortality | 96 (18.8) | 38 (12.7) | 91 (13.9) | | | | |
| Model 1 | | | | **0.63 (0.44-0.92)** | **0.02** | **0.69 (0.51-0.91)** | **0.01** |
| Model 2 | | | | **0.61 (0.42-0.89)** | **0.01** | **0.67 (0.50-0.89)** | **0.01** |
| Model 3 | | | | **0.58 (0.40-0.86)** | **0.01** | **0.65 (0.49-0.87)** | **<0.01** |
| Model 4 | | | | **0.63 (0.42-0.96)** | **0.03** | 0.77 (0.56-1.06) | 0.11 |
| Model 5 | | | | 0.66 (0.44-1.01) | 0.06 | 0.75 (0.54-1.03) | 0.08 |
| Combined CHD[‡] | 83 (16.5) | 46 (15.4) | 105 (16.4) | | | | |
| Model 1 | | | | 0.91 (0.63-1.30) | 0.60 | 0.94 (0.71-1.26) | 0.69 |
| Model 2 | | | | 0.92 (0.64-1.32) | 0.65 | 0.97 (0.73-1.30) | 0.85 |
| Model 3 | | | | 0.89 (0.61-1.28) | 0.52 | 0.94 (0.70-1.26) | 0.67 |
| Model 4 | | | | 0.92 (0.61-1.38) | 0.68 | 1.01 (0.72-1.40) | 0.97 |
| Model 5 | | | | 0.98 (0.65-1.47) | 0.91 | 0.99 (0.71-1.37) | 0.93 |
| Stroke | 33 (6.6) | 10 (3.4) | 34 (5.3) | | | | |
| Model 1 | | | | 0.49 (0.24-1.00) | 0.05 | 0.77 (0.48-1.25) | 0.30 |
| Model 2 | | | | **0.48 (0.23-0.97)** | **0.04** | 0.76 (0.47-1.23) | 0.26 |
| Model 3 | | | | 0.49 (0.24-1.01) | 0.05 | 0.74 (0.45-1.21) | 0.23 |
| Model 4 | | | | 0.48 (0.23-1.03) | 0.06 | 0.65 (0.38-1.12) | 0.12 |
| Model 5 | | | | 0.50 (0.23-1.07) | 0.08 | 0.65 (0.38-1.13) | 0.13 |
| Combined CVD[§] | 157 (31.1) | 87 (29.2) | 179 (27.8) | | | | |
| Model 1 | | | | 0.92 (0.71-1.20) | 0.56 | 0.86 (0.69-1.07) | 0.17 |
| Model 2 | | | | 0.90 (0.69-1.18) | 0.45 | 0.87 (0.70-1.08) | 0.22 |
| Model 3 | | | | 0.89 (0.68-1.16) | 0.38 | 0.84 (0.67-1.05) | 0.13 |
| Model 4 | | | | 0.93 (0.69-1.25) | 0.63 | 0.87 (0.68-1.11) | 0.26 |
| Model 5 | | | | 0.97 (0.72-1.30) | 0.82 | 0.86 (0.67-1.10) | 0.24 |
| End-stage renal disease | 17 (3.4) | 7 (2.4) | 10 (1.6) | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Model 1 | | | | 0.74 (0.30-1.79) | 0.50 | 0.49 (0.21-1.10) | 0.09 |
| Model 2 | | | | 0.89 (0.36-2.18) | 0.79 | 0.54 (0.23-1.26) | 0.15 |
| Model 3 | | | | 0.67 (0.23-1.96) | 0.46 | 0.63 (0.25-1.60) | 0.33 |
| Model 4 | | | | 0.74 (0.17-3.18) | 0.69 | 1.04 (0.32-3.41) | 0.95 |
| Model 5 | | | | 0.79 (0.17-3.63) | 0.76 | 1.24 (0.34-4.56) | 0.74 |
| Cancer | 35 (7.0) | 21 (7.1) | 52 (8.2) | | | | |
| Model 1 | | | | 0.96 (0.56-1.64) | 0.87 | 1.09 (0.71-1.68) | 0.69 |
| Model 2 | | | | 0.93 (0.54-1.60) | 0.79 | 1.04 (0.68-1.61) | 0.85 |
| Model 3 | | | | 0.85 (0.49-1.48) | 0.56 | 0.97 (0.63-1.50) | 0.90 |
| Model 4 | | | | 0.92 (0.51-1.65) | 0.79 | 1.09 (0.69-1.74) | 0.70 |
| Model 5 | | | | 0.91 (0.51-1.64) | 0.76 | 1.13 (0.71-1.80) | 0.62 |
| Hospitalized for gastrointestinal bleeding | 33 (8.3) | 16 (6.9) | 39 (8.0) | | | | |
| Model 1 | | | | 0.79 (0.44-1.44) | 0.44 | 0.92 (0.58-1.47) | 0.73 |
| Model 2 | | | | 0.74 (0.41-1.35) | 0.33 | 0.92 (0.58-1.47) | 0.72 |
| Model 3 | | | | 0.69 (0.37-1.28) | 0.23 | 0.85 (0.52-1.38) | 0.51 |
| Model 4 | | | | 0.76 (0.38-1.50) | 0.42 | 1.07 (0.63-1.84) | 0.80 |
| Model 5 | | | | 0.74 (0.37-1.47) | 0.39 | 1.01 (0.58-1.73) | 0.98 |
| Components of secondary outcomes | | | | | | | |
| Heart failure | 47 (9.3) | 36 (12.2) | 49 (7.7) | | | | |
| Model 1 | | | | 1.26 (0.82-1.95) | 0.30 | 0.76 (0.51-1.14) | 0.19 |
| Model 2 | | | | 1.21 (0.78-1.86) | 0.40 | 0.77 (0.52-1.16) | 0.21 |
| Model 3 | | | | 1.24 (0.80-1.92) | 0.35 | 0.77 (0.51-1.15) | 0.20 |
| Model 4 | | | | 1.18 (0.73-1.90) | 0.49 | 0.71 (0.46-1.11) | 0.13 |
| Model 5 | | | | 1.22 (0.75-1.97) | 0.43 | 0.71 (0.45-1.12) | 0.14 |
| Hospitalized/fatal heart failure | 42 (8.3) | 32 (10.8) | 39 (6.1) | | | | |
| Model 1 | | | | 1.25 (0.79-1.98) | 0.35 | 0.67 (0.43-1.04) | 0.07 |
| Model 2 | | | | 1.20 (0.76-1.91) | 0.43 | 0.69 (0.44-1.07) | 0.10 |
| Model 3 | | | | 1.23 (0.77-1.95) | 0.39 | 0.68 (0.43-1.06) | 0.09 |
| Model 4 | | | | 1.13 (0.68-1.88) | 0.63 | **0.59 (0.36-0.97)** | **0.04** |
| Model 5 | | | | 1.17 (0.70-1.95) | 0.55 | **0.59 (0.36-0.97)** | **0.04** |
| Angina (hospitalized or treated) | 44 (8.7) | 25 (8.4) | 61 (9.6) | | | | |
| Model 1 | | | | 0.92 (0.56-1.50) | 0.73 | 1.05 (0.71-1.55) | 0.79 |
| Model 2 | | | | 0.94 (0.57-1.54) | 0.80 | 1.10 (0.75-1.63) | 0.62 |
| Model 3 | | | | 0.88 (0.53-1.45) | 0.62 | 1.05 (0.71-1.56) | 0.81 |
| Model 4 | | | | 1.09 (0.62-1.93) | 0.75 | 1.40 (0.88-2.24) | 0.15 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Model 5 | | | | 1.14 (0.65-2.03) | 0.64 | 1.39 (0.87-2.23) | 0.16 |
| Angina (hospitalized) | 30 (6.0) | 18 (6.1) | 47 (7.4) | | | | |
| Model 1 | | | | 0.97 (0.54-1.74) | 0.92 | 1.19 (0.75-1.87) | 0.47 |
| Model 2 | | | | 1.02 (0.57-1.83) | 0.96 | 1.24 (0.78-1.96) | 0.37 |
| Model 3 | | | | 0.91 (0.50-1.66) | 0.76 | 1.15 (0.72-1.85) | 0.55 |
| Model 4 | | | | 1.08 (0.55-2.13) | 0.81 | 1.40 (0.81-2.42) | 0.23 |
| Model 5 | | | | 1.16 (0.58-2.29) | 0.68 | 1.38 (0.80-2.40) | 0.25 |
| Coronary revascularizations | 33 (6.5) | 26 (8.8) | 52 (8.1) | | | | |
| Model 1 | | | | 1.29 (0.77-2.16) | 0.33 | 1.18 (0.77-1.83) | 0.45 |
| Model 2 | | | | 1.33 (0.80-2.23) | 0.28 | 1.26 (0.81-1.96) | 0.30 |
| Model 3 | | | | 1.25 (0.74-2.11) | 0.41 | 1.19 (0.76-1.85) | 0.45 |
| Model 4 | | | | 1.16 (0.65-2.05) | 0.62 | 1.14 (0.70-1.85) | 0.60 |
| Model 5 | | | | 1.18 (0.66-2.10) | 0.58 | 1.12 (0.68-1.83) | 0.66 |
| Peripheral arterial disease (hospitalized or treated) | 27 (5.4) | 6 (2.0) | 19 (3.0) | | | | |
| Model 1 | | | | **0.36 (0.15-0.86)** | **0.02** | **0.53 (0.29-0.95)** | **0.03** |
| Model 2 | | | | **0.36 (0.15-0.88)** | **0.02** | **0.54 (0.30-0.97)** | **0.04** |
| Model 3 | | | | **0.35 (0.14-0.85)** | **0.02** | **0.51 (0.28-0.94)** | **0.03** |
| Model 4 | | | | 0.47 (0.18-1.20) | 0.12 | 0.64 (0.32-1.29) | 0.21 |
| Model 5 | | | | 0.51 (0.20-1.32) | 0.16 | 0.66 (0.32-1.35) | 0.26 |

Abbreviations: aTRH, apparent treatment resistant hypertension; HR indicates Hazard Ratio; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease.

[*]aTRH was defined as having uncontrolled hypertension despite the use of antihypertensive medications from 3 or more classes or the use of 4 or more antihypertensive medication classes to achieve blood pressure control.

[†]CHD includes nonfatal myocardial infarction (MI) and fatal CHD; end-stage renal disease: kidney disease death, kidney transplant, or start of chronic renal dialysis; and heart failure: fatal, nonfatal hospitalized, or treated.

[‡]Combined CHD indicates CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina.

[§]Combined CVD indicates CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).

Model 1: unadjusted;

Model 2: adjusted for age, sex, race/ethnicity and region of residence;

Model 3: adjusted for variables in model 2 plus practice setting, education level, smoking status and body mass index (BMI);

Model 4: adjusted for variables in model 2 and 3 along with estimated glomerular filtration rate (eGFR), diabetes, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, history of CHD, left ventricular hypertrophy (LVH), and taking blood pressure medications prior to randomization

Model 5: adjusted for variables in model 2, 3 and 4 along with baseline and year two blood pressure

**eTable 5.** Primary outcome CHD in the antihypertensive treatment groups in patients with aTRH at 2 years, using alternate cohort*

| | Chlorthalidone (N=838) No. events (%) | Amlodipine (N=557) No. events (%) | Lisinopril (N=964) No. events (%) | Amlodipine vs Chlorthalidone HR (95% CI) | *P*-value | Lisinopril vs Chlorthalidone HR (95% CI) | *P*-value |
|---|---|---|---|---|---|---|---|
| Total | 104 (12.41) | 75 (13.46) | 117 (12.14) | | | | |
| Model 1 | | | | 0.89 (0.63 – 1.26) | 0.50 | 0.84 (0.62 – 1.14) | 0.27 |
| Model 2 | | | | 0.90 (0.64 – 1.28) | 0.57 | 0.88 (0.64 – 1.19) | 0.40 |
| Model 3 | | | | 0.86 (0.60 – 1.24) | 0.41 | 0.90 (0.66 – 1.24) | 0.53 |
| Model 4 | | | | 0.81 (0.55 – 1.21) | 0.31 | 0.92 (0.66 – 1.29) | 0.64 |
| Model 5 | | | | 0.83 (0.55 – 1.26) | 0.38 | 0.95 (0.67 – 1.34) | 0.75 |

*Alternate cohort includes individuals for that had an event before 2 years (other than death) and missing 2 year values needed to determine aTRH were replaced by 20 month or 28 month values when available, with preference given to 20 month values.