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Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Rafael Diaz, M.D., Denis Xavier, M.D., Karen Sliwa, M.D., Ph.D., Antonio Dans, M.D., Alvaro Avezum, M.D., Ph.D., Leopoldo S. Piegas, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Alexander Parkhomenko, M.D., Ph.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Lawrence A. Leiter, M.D., Dora I. Molina, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Joanne Wilkinson, B.A., Hyejung Jung, M.Sc., Gilles Dagenais, M.D., and Salim Yusuf, M.B., B.S., D.Phil., for the HOPE-3 Investigators†

ABSTRACT

BACKGROUND

Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.

METHODS

In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.

RESULTS

The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI, 0.81 to 1.11; P=0.51). In one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had significantly lower rates of the first and second coprimary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P=0.02 and P=0.009, respectively, for trend in the two outcomes).

CONCLUSIONS

Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Lonn at the Population Health Research Institute and Hamilton Health Sciences, 237 Barton St. E., Hamilton ON L8L 2X2, Canada, or at eva.lonn@phri.ca.

*Deceased.

†A complete list of the Heart Outcomes Prevention Evaluation (HOPE)–3 trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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High blood pressure is the leading risk factor for cardiovascular disease globally[1] and affects more than 1 billion adults worldwide.[2] Observational studies involving persons without cardiovascular disease show a graded increase in risk at systolic blood-pressure levels above 115 mm Hg.[3] It has been suggested that lowering blood pressure at any level above this value will reduce the risk of cardiovascular events.[4] Antihypertensive therapy has been clearly shown to reduce the risk of cardiovascular disease among people with vascular or renal disease, diabetes, or hypertension with end-organ damage or, in the absence of these conditions, among persons with a systolic blood pressure of 160 mm Hg or higher.[5-8] However, the role of therapy in persons at intermediate risk (defined as an annual risk of major cardiovascular events of approximately 1%) who do not have vascular disease and who have a systolic blood pressure of less than 160 mm Hg (who represent the majority of middle-aged and older persons) remains less clear. We evaluated this question in the Heart Outcomes Prevention Evaluation (HOPE)–3 trial.

Methods

Trial Design

We conducted this double-blind, randomized, placebo-controlled trial at 228 centers in 21 countries, using a 2-by-2 factorial design. The trial evaluated blood-pressure–lowering therapy with a fixed-dose combination of an angiotensin-receptor blocker (ARB) and a thiazide diuretic, cholesterol-lowering therapy with a statin, and the combination of both interventions in persons at intermediate cardiovascular risk (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[9] The results of the cholesterol-lowering analysis and the analysis of the combination of blood-pressure lowering and cholesterol lowering are reported in accompanying articles in the *Journal*.[10,11]

The trial was designed by an international steering committee of academic investigators and sponsored by AstraZeneca and the Canadian Institutes of Health Research. AstraZeneca provided the trial drug, served as a single voting member on the 24-member steering committee, and had no other role in the trial. The Population Health Research Institute, McMaster University, Canada, coordinated data collection and monitoring and conducted all statistical analyses independent of the sponsors. Ethical approval was obtained at all centers, and all the participants provided written informed consent. An event-adjudication committee whose members were unaware of the trial-group assignments reviewed primary and secondary outcome events and deaths. An independent data and safety monitoring board reviewed the accumulating data. The authors vouch for the accuracy and completeness of the data and all the analyses, as well as for the fidelity of this report to the trial protocol (available at NEJM.org). The first author drafted the manuscript, and all the authors made the decision, with approval from the steering committee, to submit the manuscript for publication.

Trial Population

The trial included men 55 years of age or older and women 65 years of age or older who had at least one of the following cardiovascular risk factors: elevated waist-to-hip ratio, history of low concentration of high-density lipoprotein cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary disease, and mild renal dysfunction; details of the eligibility criteria are provided in Table S2 in the Supplementary Appendix. We also included women 60 years of age or older who had at least two such risk factors.[9] We excluded persons with known cardiovascular disease, clear indications or contraindications to the trial drugs or angiotensin-converting–enzyme (ACE) inhibitors, moderate or advanced renal dysfunction, or symptomatic hypotension.

Fasting lipid, glucose, and creatinine levels and blood pressure were measured before enrollment. However, participants were not selected on the basis of history of either hypertension or hyperlipidemia, and the trial did not mandate strict blood-pressure or lipid levels for entry. Persons with a history of hypertension could be enrolled if the blood pressure was adequately controlled (in the assessment of the recruiting physician) with lifestyle or drugs other than an ARB, ACE inhibitor, or thiazides. Recruiting physicians were informed about local guidelines regarding the prevention of cardiovascular disease (including guidelines for the management of hypertension and dyslipidemia), and they used local standards as an additional guide to determine trial eligibility, on the basis of the uncertainty principle.[12]

TRIAL PROCEDURES

Eligible participants entered a single-blind run-in phase, during which they received both active treatments (for blood-pressure lowering and for cholesterol lowering) for 4 weeks. Serum creatinine, potassium, creatine kinase, and alanine aminotransferase (or aspartate aminotransferase) levels were measured at 3 weeks. Participants who adhered to the regimen (taking ≥80% of the tablets) and who did not have an unacceptable level of adverse events underwent randomization with the use of a central concealed randomization procedure, stratified according to center. Participants were randomly assigned to the daily administration of either a fixed-dose combination of candesartan at a dose of 16 mg and hydrochlorothiazide at a dose of 12.5 mg or placebo; participants were also randomly assigned to receive either rosuvastatin at a dose of 10 mg or placebo.

All the participants received individualized structured lifestyle advice, according to identified needs. Follow-up visits occurred at 6 weeks and 6 months after randomization and every 6 months thereafter. Adherence to the regimen (as measured by pill count), safety, and trial outcomes were evaluated at each visit. The blood pressure was measured at each visit during the first year and annually thereafter (average of two measurements after 5 minutes of quiet rest) with the use of a standardized protocol (see the Supplementary Appendix) and an automated measurement system (Omron model HEM-711DLXCAN). Fasting blood samples were obtained at baseline from all the participants and during follow-up from 10 to 20% of the participants (with representation across geographic and racial and ethnic subgroups), and the samples were shipped for central storage and analyses of lipid levels and additional markers (see the Supplementary Appendix).

TRIAL OUTCOMES

The two prespecified coprimary efficacy outcomes were the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke and the composite of these events plus resuscitated cardiac arrest, heart failure, or revascularization. There were two secondary outcomes: the composite of events comprising the second coprimary outcome plus angina with evidence of ischemia, and for the comparison of blood-pressure lowering, fatal or nonfatal stroke. The secondary outcomes were modified from the original trial protocol and were formally adopted by the steering committee without a protocol amendment on July 15, 2015, before unblinding on November 3, 2015.

Additional prespecified outcomes were total mortality, the components of the coprimary and secondary outcomes (stroke was a component of the coprimary outcomes and also a distinct secondary outcome for the comparison of blood-pressure lowering), new-onset diabetes, cognitive function (in participants ≥70 years of age), and erectile dysfunction in men. The latter two outcomes are not reported here. Event definitions are provided in the Supplementary Appendix.

Renal dysfunction was a tertiary outcome in the original trial protocol and was removed because of limitations of statistical power. The main safety outcomes included cancer, myopathy, rhabdomyolysis, and hospitalization. In addition, we collected data on adverse events leading to temporary or permanent discontinuation of the trial regimens and on suspected unexpected serious adverse reactions. Safety monitoring is summarized in the Supplementary Appendix.

STATISTICAL ANALYSIS

With an expected annual event rate of 1% for the first coprimary outcome in the dual-placebo group (i.e., the group of participants assigned to placebo in both the comparison of blood-pressure lowering and the comparison of cholesterol lowering), an average duration of follow-up of 5.5 years, cumulative nonadherence rates of 23%, drop-in rates of 11% (participants who were projected to use open-label ARBs, ACE inhibitors, thiazides, or statins), and rates of loss to follow-up of less than 1%, we estimated that a sample of 12,700 participants would provide the trial with 80% power to detect a risk with candesartan plus hydrochlorothiazide that was at least 22.5% lower than the risk with placebo, after the occurrence of at least 500 first and 600 second coprimary outcomes.[9]

The main analyses were performed according to the intention-to-treat principle. Survival curves were computed with the use of the Kaplan–Meier procedure. A Cox proportional-hazards model, stratified according to the opposite group of the factorial design, was used to estimate treatment effects and possible interactions and to evaluate effects in subgroups. No significant interaction between the two factorial treatments was ob-

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Candesartan + Hydrochlorothiazide (N = 6356)	Placebo (N = 6349)
Age — yr	65.7±6.4	65.8±6.4
Female sex — no. (%)	2910 (45.8)	2964 (46.7)
Cardiovascular risk factor — no. (%)		
Elevated waist-to-hip ratio	5511 (86.7)	5523 (87.0)
Recent or current smoking	1782 (28.0)	1742 (27.4)
Low concentration of HDL cholesterol	2297 (36.1)	2291 (36.1)
Impaired fasting glucose or impaired glucose tolerance	799 (12.6)	817 (12.9)
Early diabetes mellitus	386 (6.1)	345 (5.4)
Family history of premature coronary heart disease	1668 (26.2)	1667 (26.3)
Early renal dysfunction	184 (2.9)	166 (2.6)
Hypertension	2398 (37.7)	2416 (38.1)
Blood pressure — mm Hg		
Systolic	138.2±14.7	137.9±14.8
Diastolic	82.0±9.4	81.8±9.3
Heart rate — beats/min	72.9±10.2	72.5±10.2
Body-mass index	27.1±4.8	27.1±4.7
Waist-to-hip ratio	0.94±0.08	0.94±0.08
Total cholesterol — mg/dl†	201.4±42.6	201.5±41.7
LDL cholesterol — mg/dl†	127.4±36.5	128.3±35.6
HDL cholesterol — mg/dl†	44.9±13.9	44.8±13.7
Triglycerides — mg/dl†		
Median	127.4	128.3
Interquartile range	92.9–180.5	92.9–175.2
Fasting plasma glucose — mg/dl		
Median	95.4	95.4
Interquartile range	87.0–106.2	86.4–106.0
High-sensitivity C-reactive protein — mg/liter†		
Median	2.0	2.0
Interquartile range	1.0–4.1	1.0–3.9
Serum creatinine — mg/dl	0.9±0.2	0.9±0.2
INTERHEART Risk Score‡	14.5±5.2	14.4±5.2
Race or ethnic group — no. (%)§		
Chinese	1844 (29.0)	1847 (29.1)
Hispanic	1739 (27.4)	1757 (27.7)
White	1284 (20.2)	1262 (19.9)
South Asian	932 (14.7)	922 (14.5)
Other Asian	342 (5.4)	354 (5.6)
Black	116 (1.8)	109 (1.7)
Other	99 (1.6)	98 (1.5)

Table 1. (Continued.)

Characteristic	Candesartan + Hydrochlorothiazide (N = 6356)	Placebo (N = 6349)
Medication use — no. (%)		
Aspirin	739 (11.6)	654 (10.3)
Beta-blocker	524 (8.2)	496 (7.8)
Calcium-channel blocker	928 (14.6)	957 (15.1)
Alpha-blocker	72 (1.1)	69 (1.1)
Nonthiazide diuretic	36 (0.6)	29 (0.5)
Aldosterone antagonist	6 (0.1)	11 (0.2)
Any blood-pressure-lowering drug	1388 (21.8)	1395 (22.0)
Oral hypoglycemic agent	176 (2.8)	161 (2.5)

* Plus–minus values are means ±SD. There were no significant between-group differences, except for heart rate (P=0.03) and the use of aspirin (P=0.02). Definitions for the cardiovascular risk factors are provided in Table S2 in the Supplementary Appendix. Data on blood pressure were missing for 2 participants in the placebo group, and data on central core laboratory measurements of low-density lipoprotein (LDL) cholesterol concentration for 649 in the active-treatment group and for 658 in the placebo group. Data on age and sex were complete. Data on other characteristics were available for 99.7% or more of the trial participants, except that some laboratory variables measured at the central core laboratory had rates of missing data similar to that for LDL cholesterol concentration. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for cholesterol to millimoles per liter, multiply by 0.0259. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for creatinine to micromoles per liter, multiply by 88.4. HDL denotes high-density lipoprotein.

† The measurements were made at the central core laboratory.

‡ The scale for the INTERHEART Risk Score[14] ranges from 0 to 49; low cardiovascular risk corresponds to a score of 9 or less, medium risk to a score of 10 to 15, and high risk to a score of 16 or higher.

§ Race and ethnic group were self-reported.

served. Prespecified hypothesis-based subgroup analyses were conducted according to thirds of baseline cardiovascular risk, of systolic blood pressure, and of low-density lipoprotein (LDL) cholesterol concentration (with P values for trend), with additional confirmatory prespecified subgroup analyses according to age, sex, diastolic blood pressure, waist-to-hip ratio, additional lipid measurements, and race or ethnic group. A post hoc recurrent-events analysis was performed with the use of proportional-means models to describe the effect on the risk of total cardiovascular events.[13]

To preserve an overall type I error rate of 5%, the first coprimary outcome was tested at a P value of 0.04 and the second at a P value of 0.02 (considering an 80% overlap between the coprimary outcomes). A nominal P value of less than 0.05 was used for all other analyses. Further details are provided in the Supplementary Appendix.

RESULTS

PARTICIPANTS, FOLLOW-UP, AND MEDICATION USE

From April 2007 through November 2010, a total of 14,682 participants entered the run-in phase (Fig. S1 in the Supplementary Appendix). Of these, 12,705 participants (86.5%) underwent randomization; 6356 participants were randomly assigned to candesartan plus hydrochlorothiazide, and 6349 to placebo. The main reasons that participants did not undergo randomization were an unwillingness to continue in the trial, an adherence to the regimen of less than 80%, and side effects, the most common of which were abnormal laboratory values and hypotension.

The characteristics at baseline were similar in the two trial groups (Table 1). The population was racially and ethnically diverse, and the mean age of the participants was 65.7 years. A total of 46.2% of the participants were women, 37.9% reported a history of hypertension, and 21.9%

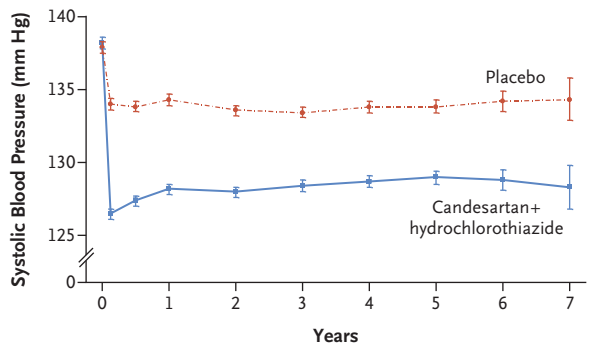
were taking antihypertensive agents (other than ARBs, ACE inhibitors, or thiazides).

The median follow-up was 5.6 years (interquartile range, 5.2 to 6.2). Vital status was ascertained in 12,587 participants (99.1%) at the end of the trial (Fig. S1 in the Supplementary Appendix). Among participants randomly assigned to active therapy, 88.2% were taking the assigned regimen at 1 year, 83.6% at 3 years, 75.0% at 5 years, and 76.8% at the end of the trial; the corresponding rates in the placebo group were 87.9%, 83.4%, 74.5%, and 75.7%. Data on open-label use of ARBs, ACE inhibitors, thiazides, and other blood-pressure-lowering drugs are provided in Table S3 in the Supplementary Appendix.

BLOOD PRESSURE

At baseline, the mean blood pressure in the entire trial population was 138.1/81.9 mm Hg. The mean (±SD) systolic blood pressure was 138.2±14.7 mm Hg in the active-treatment group and 137.9±14.8 mm Hg in the placebo group. The mean decreases from baseline during the trial were 10.0±13.1 mm Hg in the active-treatment group and 4.0±12.9 mm Hg in the placebo group (Fig. 1), and the average difference between the groups was 6.0±13.0 mm Hg.

The mean diastolic blood pressure at baseline was 82.0±9.4 mm Hg in the active-treatment group and 81.8±9.3 mm Hg in the placebo group. The mean decreases from baseline during the trial were 5.7±8.2 mm Hg in the active-treatment group and 2.7±7.9 mm Hg in the placebo group (Fig. S4 in the Supplementary Appendix), and the average difference between the groups was 3.0±8.0 mm Hg.



No. at Risk

Candesartan+hydrochlorothiazide	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

Figure 1. Systolic Blood Pressure over the Course of the Trial, According to Trial Group.

I bars represent 95% confidence intervals.

CLINICAL OUTCOMES

There were no significant differences between the active-treatment group and the placebo group in the incidence of the first coprimary outcome (260 [4.1%] and 279 [4.4%], respectively; hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40) or the second coprimary outcome (312 [4.9%] and 328 [5.2%], respectively; hazard ratio, 0.95; 95% CI, 0.81 to 1.11; P=0.51). There were also no significant between-group differences in the incidence of the secondary outcomes and the components of the coprimary outcomes, in total mortality, in the incidence of new-onset diabetes, or in the post hoc outcome of total cardiovascular events (Table 2 and Fig. 2, and Figs. S5 and S6 in the Supplementary Appendix).

In one of three prespecified hypothesis-based subgroups, there were significant differences in the prespecified subgroup analysis according to thirds of baseline systolic blood pressure for the two coprimary outcomes and the first secondary outcome (P=0.02 for trend for the first coprimary outcome, P=0.009 for trend for the second coprimary outcome, and P=0.005 for trend for the first secondary outcome) but not for the second secondary outcome of stroke (P=0.22 for trend) (Fig. 3, and Fig. S11 in the Supplementary Appendix). Participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg; mean, 154.1±8.9 mm Hg) who were in the active-treatment group had nominally significantly lower rates than those in the placebo group with respect to the first coprimary outcome (hazard ratio, 0.73; 95% CI, 0.56 to 0.94), the second coprimary outcome (hazard ratio, 0.76; 95% CI, 0.60 to 0.96), and the first secondary outcome (hazard ratio, 0.72; 95% CI, 0.57 to 0.90). There were no significant interactions among the other prespecified subgroups, including those according to thirds of baseline risk, LDL cholesterol concentration, or diastolic blood pressure (Figs. S12 and S13 in the Supplementary Appendix).

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Candesartan + Hydrochlorothiazide (N = 6356)	Placebo (N = 6349)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	260 (4.1)	279 (4.4)	0.93 (0.79–1.10)	0.40
Second coprimary outcome	312 (4.9)	328 (5.2)	0.95 (0.81–1.11)	0.51
Secondary outcomes — no. (%)				
First secondary outcome†	335 (5.3)	364 (5.7)	0.92 (0.79–1.06)	0.26
Fatal or nonfatal stroke	75 (1.2)	94 (1.5)	0.80 (0.59–1.08)	0.14
Components of the coprimary and secondary outcomes — no. (%)				
Death from cardiovascular causes	155 (2.4)	170 (2.7)	0.91 (0.73–1.13)	0.40
Fatal or nonfatal myocardial infarction	52 (0.8)	62 (1.0)	0.84 (0.58–1.21)	0.34
Resuscitated cardiac arrest	2 (<0.1)	6 (0.1)	0.33 (0.07–1.65)	0.18
Heart failure	21 (0.3)	29 (0.5)	0.72 (0.41–1.27)	0.26
Revascularization‡	64 (1.0)	74 (1.2)	0.86 (0.62–1.21)	0.39
Angina with objective evidence of ischemia†	51 (0.8)	69 (1.1)	0.74 (0.51–1.06)	0.10
Other outcomes				
Death from any cause — no. (%)	342 (5.4)	349 (5.5)	0.98 (0.84–1.14)	0.78
New diagnosis of diabetes — no./total no. (%)	236/5970 (4.0)	222/6004 (3.7)	1.07 (0.89–1.29)	0.46
Hospitalization for cardiovascular causes — no. (%)§	319 (5.0)	331 (5.2)	0.96 (0.83–1.12)	0.63
First and recurrent events of the second coprimary outcome¶				
No. of participants with ≥1 event	312	328	—	—
No. of participants with ≥2 events	59	98	—	—
No. of participants with ≥3 events	5	17	—	—
Total no. of events	380	446	0.87 (0.74–1.02)	0.09

* The first coprimary outcome was the composite of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke; the second coprimary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, or revascularization; and the first secondary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization, or angina with objective evidence of ischemia.
† This outcome was not specified in the trial protocol but was adopted by the steering committee before unblinding.
‡ Revascularization included coronary, cerebrovascular, and peripheral arterial revascularization.
§ Hospitalization for cardiovascular causes was a prespecified safety outcome.
¶ The analysis of recurrent events of the second coprimary outcome was a post hoc analysis that used a proportional-means model. The second coprimary outcome is shown because it comprises all events that were included in the first coprimary outcome as well as resuscitated cardiac arrest, heart failure, and revascularization.

SAFETY

There were no differences between the active-treatment group and the placebo group in the rates of cancer, hospitalization for cardiovascular causes, hospitalization for noncardiovascular causes, or death from noncardiovascular causes (Tables S6, S7, and S8 in the Supplementary Appendix). Permanent discontinuation of the trial regimen occurred in 1552 participants (24.4%) in the active-therapy group and in 1598 (25.2%) in the placebo group (P=0.33) and was more common in the active-therapy group than in the placebo group owing to symptomatic hypotension, dizziness, or light-headedness (217 participants [3.4%] vs. 130 [2.0%], P<0.001) but not owing to syncope (7 [0.1%] vs. 4 [0.1%], P=0.55) or renal dysfunction or abnormalities in the serum potassium level (32 [0.5%] vs. 20 [0.3%], P=0.13) (Table S9 in the Supplementary Appendix). The results for temporary discontinuation of the trial

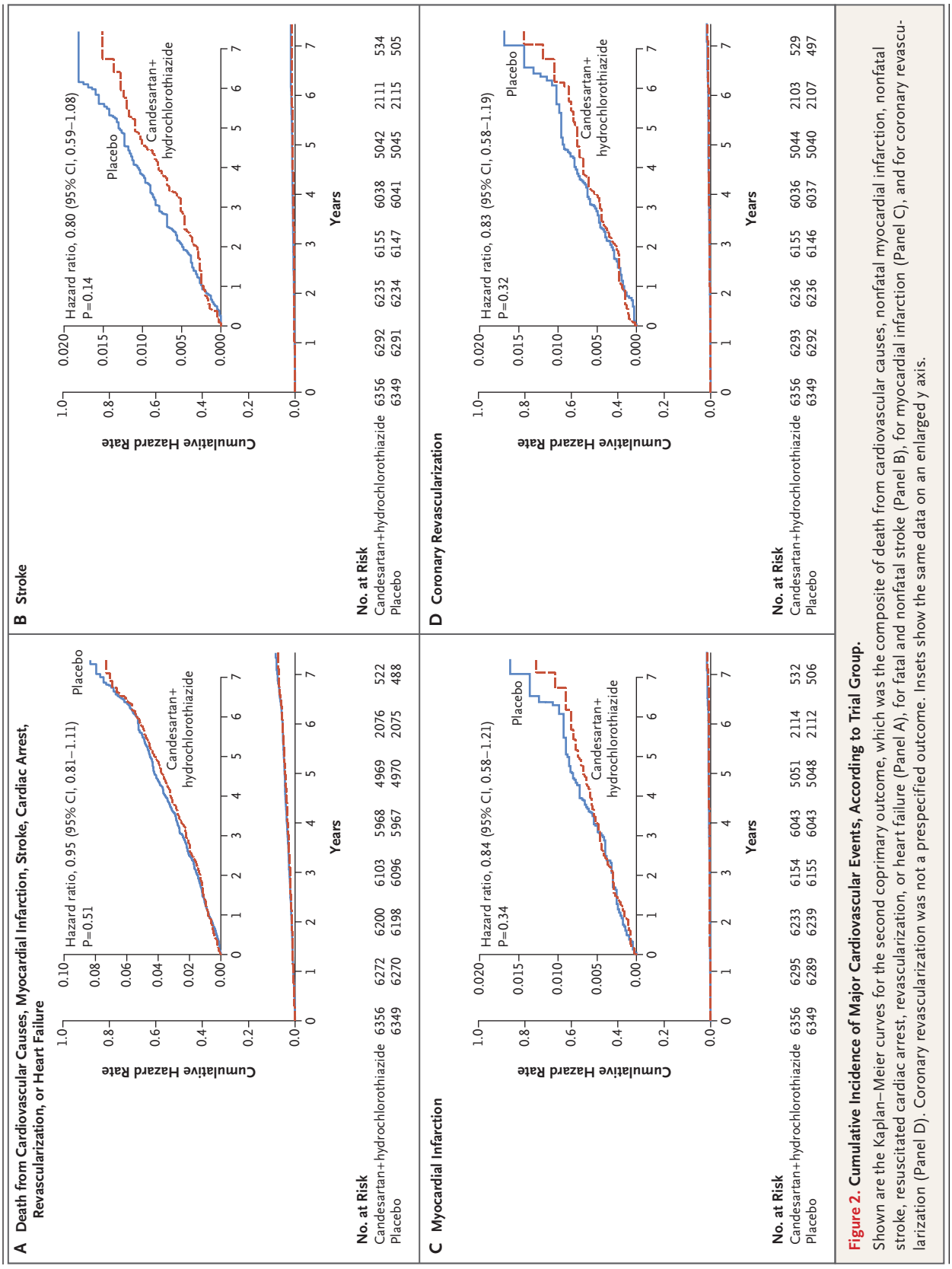
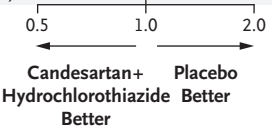


Figure 2. Cumulative Incidence of Major Cardiovascular Events, According to Trial Group.

Shown are the Kaplan–Meier curves for the second coprimary outcome, which was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, revascularization, or heart failure (Panel A), for fatal and nonfatal stroke (Panel B), for myocardial infarction (Panel C), and for coronary revascularization (Panel D). Coronary revascularization was not a prespecified outcome. Insets show the same data on an enlarged y axis.

A First Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	260/6356 (4.1)	279/6349 (4.4)	0.93 (0.79–1.10)	—
Systolic blood pressure						0.02
≤131.5 mm Hg	122.2	6.1/3.1	70/2080 (3.4)	62/2122 (2.9)	1.16 (0.82–1.63)	
131.6–143.5 mm Hg	137.6	5.6/2.7	87/2120 (4.1)	81/2141 (3.8)	1.08 (0.80–1.46)	
>143.5 mm Hg	154.1	5.8/3.0	103/2156 (4.8)	136/2084 (6.5)	0.73 (0.56–0.94)	



B Second Coprimary Outcome

Subgroup	Mean Systolic Blood Pressure	Difference in Blood Pressure	Candesartan+ Hydrochlorothiazide	Placebo	Hazard Ratio (95% CI)	P Value for Trend
	mm Hg		*no. of events/total no. of participants (%)*			
Overall	138.1	6.0/3.0	312/6356 (4.9)	328/6349 (5.2)	0.95 (0.81–1.11)	—
Systolic blood pressure						0.009
≤131.5 mm Hg	122.2	6.1/3.1	90/2080 (4.3)	74/2122 (3.5)	1.25 (0.92–1.70)	
131.6–143.5 mm Hg	137.6	5.6/2.7	99/2120 (4.7)	98/2141 (4.6)	1.02 (0.77–1.34)	
>143.5 mm Hg	154.1	5.8/3.0	123/2156 (5.7)	156/2084 (7.5)	0.76 (0.60–0.96)	

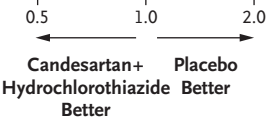


Figure 3. Forest Plots, According to Subgroup of Systolic Blood Pressure for the Coprimary Outcomes.

The difference in blood pressure refers to the average difference of the systolic and diastolic blood pressures between the two groups during the trial, with the active-treatment group having lower mean values. The first coprimary outcome (Panel A) was the composite of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke; the second coprimary outcome (Panel B) was the composite of these events plus resuscitated cardiac arrest, heart failure, or revascularization. Measurements of the systolic blood pressure at baseline were missing for two participants in the placebo group. The size of each square is proportional to the number of events.

regimen were similar to those for permanent discontinuation (Table S10 in the Supplementary Appendix). There were also no significant differences in the rates of serious unexpected suspected adverse reactions (Table S11 in the Supplementary Appendix).

DISCUSSION

In the HOPE-3 trial, treatment with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day over a period of 5.6 years lowered blood pressure by 6.0/3.0 mm Hg from baseline but did not result in a significantly lower risk, as compared with placebo, of major cardiovascular events in an intermediate-risk population without cardiovascular disease and with very low rates of diabetes (5.8%) and mild renal dysfunction (2.8%). The average blood pressure of the participants at baseline was 138.1/81.9 mm Hg, approximately one third of the participants had a history of hypertension, and approximately 22% were taking antihypertensive agents. As compared with placebo, active treatment was associated with a slightly higher risk of symptomatic hypotension, dizziness and light-headedness but not syncope, renal dysfunction, or other adverse events.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Systolic Blood Pressure Intervention (SPRINT) trials[15,16] are similar to the HOPE-3 trial in that they also included participants with an average systolic blood pressure that was considered to be in the high-normal

range. However, the participants' risk was much higher in these two trials by design (yearly event rates in the control group of 2.1% in the ACCORD trial and 2.2% in the SPRINT trial vs. 0.8% for the first coprimary outcome and 0.9% for the second coprimary outcome in the HOPE-3 trial). These trials used complex treat-to-target approaches, which resulted in greater lowering of blood pressure than was observed in the HOPE-3 trial but also in higher rates of adverse events.

Given the data from the ACCORD and SPRINT trials,[15,16] we cannot fully exclude the possibility that greater reduction in blood pressure might have been more effective in the HOPE-3 trial. However, the Blood Pressure Lowering Treatment Trialists' Collaboration reported an 18% lower risk of major cardiovascular events among persons at comparable baseline risk (5-year event rate in the placebo group, 6.5%) with a reduction in blood pressure of 4.6/3.0 mm Hg from baseline but with a systolic blood pressure of 155±21 mm Hg at baseline.[8] Thus, a higher systolic blood pressure at baseline may be decisive in determining whether small reductions in blood pressure reduce risk.

There were significant trends toward a lower risk of events at higher baseline systolic blood pressure for the two coprimary outcomes and for the first secondary outcome, with risks that were nominally significantly lower by 24 to 28% in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg; mean, 154.1±8.9 mm Hg). By contrast, no benefit was observed in participants who had a baseline systolic blood pressure of 143.5 mm Hg or less and a suggestion of harm for those in the lower-third subgroup (≤131.5 mm Hg; mean, 122.2±7.5 mm Hg). The pattern for stroke differed, with no heterogeneity in the three subgroups that were defined according to baseline systolic blood pressure. Blood-pressure differences between the trial groups were similar across the three subgroups of baseline systolic blood pressure. Therefore, the observed subgroup findings are not related to differences in the magnitude of blood-pressure lowering but rather to a differential effect in participants at different baseline blood-pressure levels. Although any subgroup analysis should be interpreted with caution, the analysis according to thirds of systolic blood pressure was hypothesis-driven and prespecified, and the benefits were consistent across prespecified outcomes and appear to be plausible in the context of previously reported data.

Our findings contradict the "lower is better" hypothesis that has been derived from epidemiologic studies,[3] and our findings support the concept that a J-curve phenomenon exists for major cardiovascular events, other than for stroke, in this population. After correction for time-dependent regression dilution by averaging of all blood-pressure measurements in the placebo group over the first year, the mean "usual" systolic blood pressure thus calculated was 140.9±11.9 mm Hg in the upper-third subgroup and 127.1±11.1 mm Hg in the lower-third subgroup. Therefore, our data are compatible with the hypothesis that treating persons without cardiovascular disease who have a systolic blood pressure above approximately 140 mm Hg appears to be beneficial, but treatment would not be of benefit and may be even harmful in persons with lower systolic blood-pressure levels.

Several meta-analyses have shown similar reductions in relative risk across pretreatment systolic blood-pressure levels ranging from less than 130 mm Hg to more than 180 mm Hg with the use of various drugs, among persons with diabetes and those without diabetes, and across various levels of risk, largely on the basis of trials involving patients with vascular or renal disease, diabetes, or entry systolic blood-pressure levels of more than 150 mm Hg in primary prevention.[5-8,17] Other meta-analyses of trials involving patients with diabetes showed no reduction in the risk of major cardiovascular events (except possibly stroke) and a potential for harm in persons with a pretreatment systolic blood pressure of less than 140 mm Hg.[18,19]

There are insufficient data to guide decisions about blood-pressure levels for the initiation of antihypertensive agents in persons at low or moderate cardiovascular risk who have mild uncomplicated hypertension.[20] In previous trials, most participants were already receiving antihypertensive agents before randomization or their blood pressure was substantially higher than our current definitions of grade 1 hypertension[21-24]; previous meta-analyses are also inconclusive.[25,26] The uncertainty surrounding this important question is reflected in recent U.S. and European guidelines.[27,28]

This trial evaluated blood-pressure–lowering

therapy with a fixed-dose combination of an ARB and a thiazide, at relatively low doses, in persons at intermediate risk who did not have cardiovascular disease, among whom very few had diabetes or renal dysfunction and only approximately one fifth were receiving antihypertensive drugs before randomization. Our data indicate that in this population overall, there was no significant benefit of blood-pressure lowering with the tested treatment. However, in one of the three subgroups of participants with uncomplicated mild hypertension, such therapy significantly reduced the risk of cardiovascular events.

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APPENDIX

The authors' affiliations are as follows: the Population Health Research Institute, Hamilton Health Sciences (E.M.L., J.B., R.M., J.P., J.W., H.J., S.Y.), the Department of Medicine (E.M.L., R.M., S.Y.), the School of Rehabilitation Science (J.B.), and the Department of Clinical Epidemiology and Biostatistics (J.P.), McMaster University, Hamilton, ON, Li Ka Shing Knowledge Institute and Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.), and Institut Universitaire de Cardiologie et Pneumologie de Québec, Université Laval, Quebec, QC (G.D.) — all in Canada; Fundacion Oftalmológica de Santander and Instituto Masira, Medical School, Universidad de Santander, Bucaramanga (P.L.-J.), and University of Caldas and Institución Prestadora de Salud Internistas de Caldas, Manizales (D.I.M.S.) — both in Colombia; Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing (J.Z., L.L.); St. John's Research Institute (P.P., D.X.) and St. John's Medical College (D.X.), Bangalore, India; Instituto Cardiovascular de Rosario, Rosario, Argentina (R.D.); Hatter Institute for Cardiovascular Research in Africa, Department of Medicine, University of Cape Town, Soweto Cardiovascular Research Group, Cape Town, South Africa (K.S.); College of Medicine, University of the Philippines, Manila (A.D.); Dante Pazzanese Institute of Cardiology (A.A.) and HCor-Heart Hospital (L.S.P.) — both in São Paulo; Hungarian Institute of Cardiology, Semmelweis University, Budapest, Hungary (K. Keltai, M.K.); Institute of Clinical Cardiology in the Russian Cardiology Research Complex, Moscow (I.C.); the Department of Cardiology, Academic Medical Center, Amsterdam (R.J.G.P.); the Department of Medical Sciences, Cardiology, Clinical Research Center, Uppsala University, Uppsala, Sweden (C.H.); Universiti Teknologi Majlis Amansh Rakyat, Selayang, and University College Sedaya International University, Kuala Lumpur (K.Y.) — both in Malaysia; Lady Davis Carmel Medical Center, Ruth and Bruce Rappaport School of Medicine, Technion–Israel Institute of Technology, Haifa (B.S.L.); University Hospital Motol, Prague, Czech Republic (P.J.); Institute of Cardiology, Kiev, Ukraine (A.P.); Diabetes Research Centre (K. Khunti) and the Department of Cardiovascular Sciences (W.D.T.), University of Leicester, and the National Institute for Health Research, Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital (W.D.T.) — both in Leicester, United Kingdom; and Primary Care Diabetes and Vascular Medicine, Monash Centre of Cardiovascular Research and Education in Therapeutics (C.M.R.), and the Department of Epidemiology and Preventive Medicine (J.V.), Monash University, Melbourne, VIC, and the School of Public Health, Curtin University, Perth, WA (C.M.R.) — both in Australia.

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