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ORIGINAL ARTICLE

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

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ABSTRACT

BACKGROUND

Elevated blood pressure and elevated low-density lipoprotein (LDL) cholesterol increase the risk of cardiovascular disease. Lowering both should reduce the risk of cardiovascular events substantially.

METHODS

In a trial with 2-by-2 factorial design, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to rosuvastatin (10 mg per day) or placebo and to candesartan (16 mg per day) plus hydrochlorothiazide (12.5 mg per day) or placebo. In the analyses reported here, we compared the 3180 participants assigned to combined therapy (with rosuvastatin and the two antihypertensive agents) with the 3168 participants assigned to dual placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included heart failure, cardiac arrest, or revascularization. The median follow-up was 5.6 years.

RESULTS

The decrease in the LDL cholesterol level was 33.7 mg per deciliter (0.87 mmol per liter) greater in the combined-therapy group than in the dual-placebo group, and the decrease in systolic blood pressure was 6.2 mm Hg greater with combined therapy than with dual placebo. The first coprimary outcome occurred in 113 participants (3.6%) in the combined-therapy group and in 157 (5.0%) in the dual-placebo group (hazard ratio, 0.71; 95% confidence interval [CI], 0.56 to 0.90; P=0.005). The second coprimary outcome occurred in 136 participants (4.3%) and 187 participants (5.9%), respectively (hazard ratio, 0.72; 95% CI, 0.57 to 0.89; P=0.003). Muscle weakness and dizziness were more common in the combined-therapy group than in the dual-placebo group, but the overall rate of discontinuation of the trial regimen was similar in the two groups.

CONCLUSIONS

The combination of rosuvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) was associated with a significantly lower rate of cardiovascular events than dual 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 HEART OUTCOMES PREVENTION EVALUATION

(HOPE)–3 Trial

BACKGROUND

- Cardiovascular diseases are major causes of death and illness worldwide.
- Systolic blood pressure and low density lipoprotein (LDL) cholesterol show graded associations with cardiovascular disease.
- Account for two thirds of the population-attributable risk of cardiovascular disease.

Roth GA, et al. N Engl J Med 2015; 372: 1333-41.
Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

BACKGROUND

- Combined lowering of LDL-C and BP has significant role in reducing CV events than either intervention alone.
- Majority of CV events occur in persons at average risk with no previous CV disease.
- Strategy of broad population-based treatment of LDL cholesterol and BP could be more effective than targeting only high-risk persons.

Roth GA, et al. N Engl J Med 2015; 372: 1333-41.
Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

OBJECTIVE

Investigators evaluated the effects of:

- Moderate Dose of a Potent Statin ***vs*** Placebo
- Fixed Combination of Moderate Doses of ARB, Diuretic ***vs*** Placebo
- Combination of both treatments ***vs*** dual placebo on the prevention of major CV events.

Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

METHODOLOGY

STUDY DESIGN

Multicenter, long-term, international, double-blind, randomized, placebo-controlled trial , 2-by-2 factorial design.

ELIGIBILITY

Table S2: HOPE-3 Eligibility Criteria

Inclusion Criteria
Women aged ≥ 65 years* and men aged ≥ 55 years
At least one of the following additional CV risk factors:
Waist/hip ratio ≥ 0.85 in women and ≥ 0.90 in men
History of current or recent smoking (regular tobacco use within 5 years)
Low HDL-C (HDL-C < 1.0 mmol/L in men and <1.3 mmol/L in women)
Dysglycemia (impaired fasting glucose, impaired glucose tolerance or uncomplicated diabetes treated with diet only)†
Early renal dysfunction‡
Family history of premature coronary heart disease in first degree relatives (men < 55 years or women <65 years)
Provision of informed consent
Exclusion Criteria
Documented clinically manifest atherothrombotic CVD
Indication for statin and/or ARB, ACE inhibitor or thiazide diuretics
Contraindications for statin and/or ARB or thiazide diuretics[1]
Symptomatic hypotension
Chronic liver disease (cirrhosis or persistent hepatitis) or abnormal liver function (ALT or AST > 3 x ULN)
Inflammatory muscle disease (such as dermatomyositis or polymyositis) or creatine kinase (CK > 3 x ULN)
Moderate renal dysfunction defined as serum creatinine > 2.0 mg/dL (180µmol/L) or eGFR <45ml/min/1.73m²
Treatment with cyclosporine or fibrates
Other serious condition(s) likely to interfere with study participation or with the ability to complete the trial
Concurrent use of any experimental pharmacological agent

* women ≥ 60 years with at least two additional risk factors were also eligible

Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

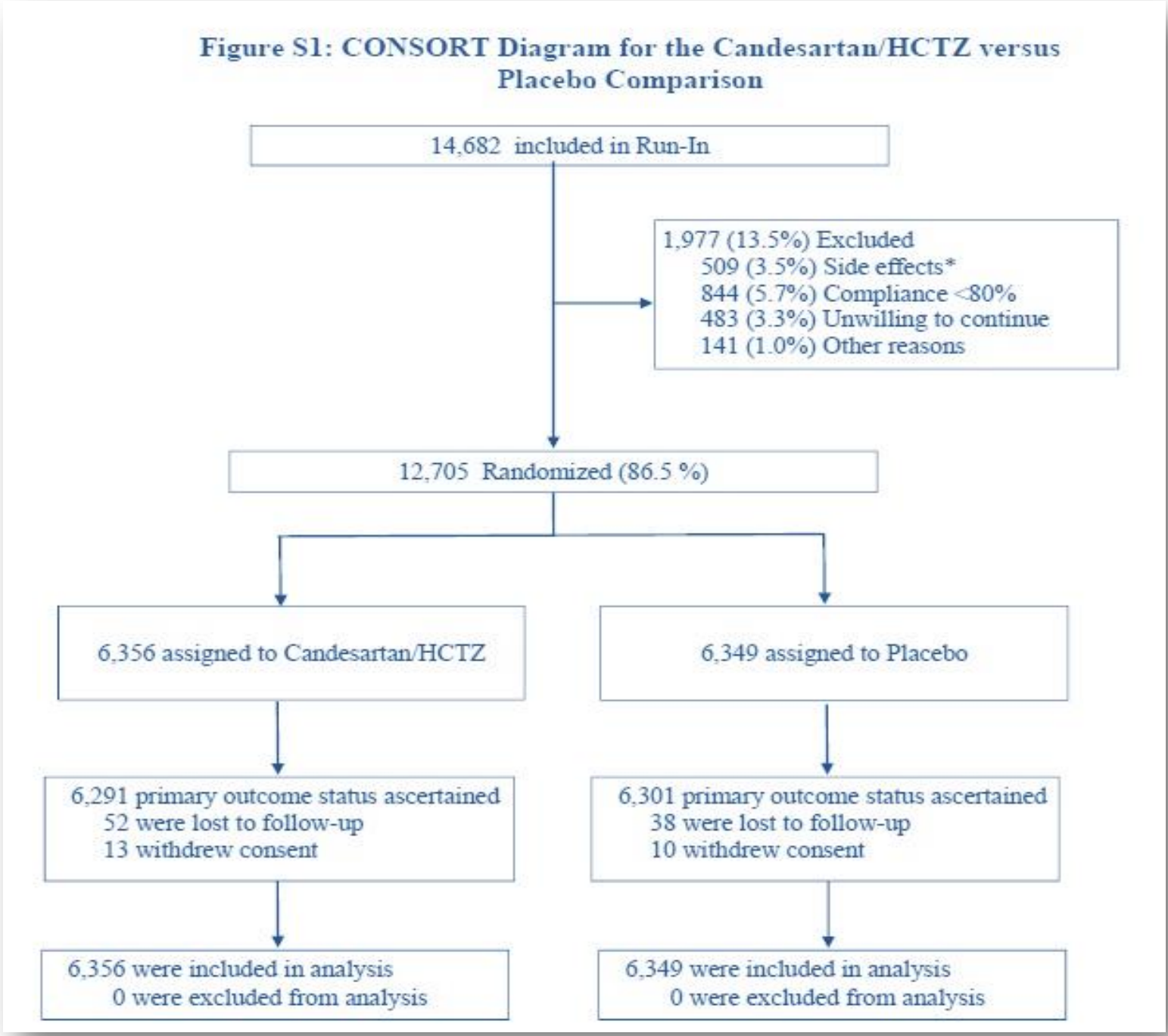

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Figure S2: CONSORT Diagram for the Rosuvastatin versus Placebo Comparison

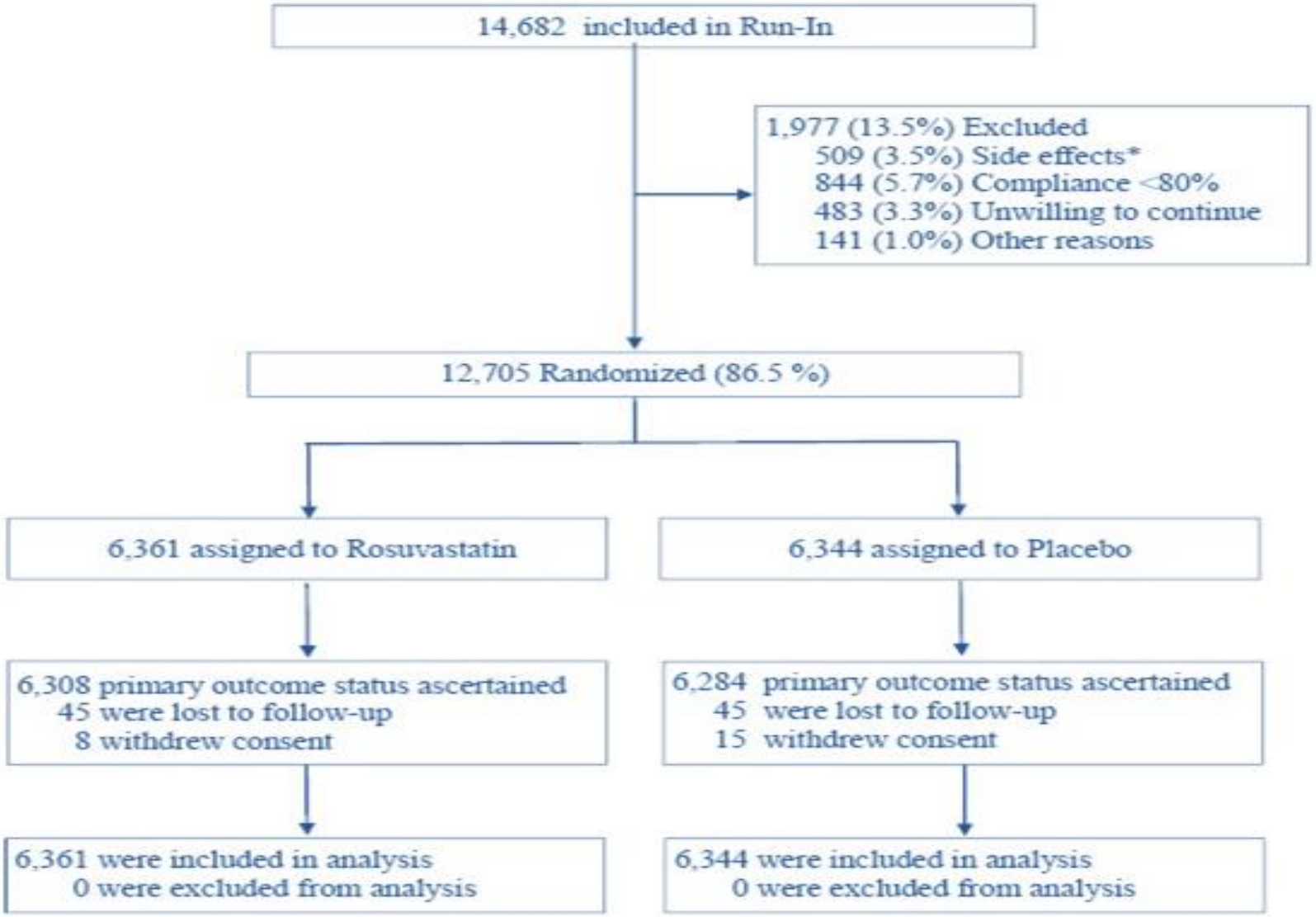

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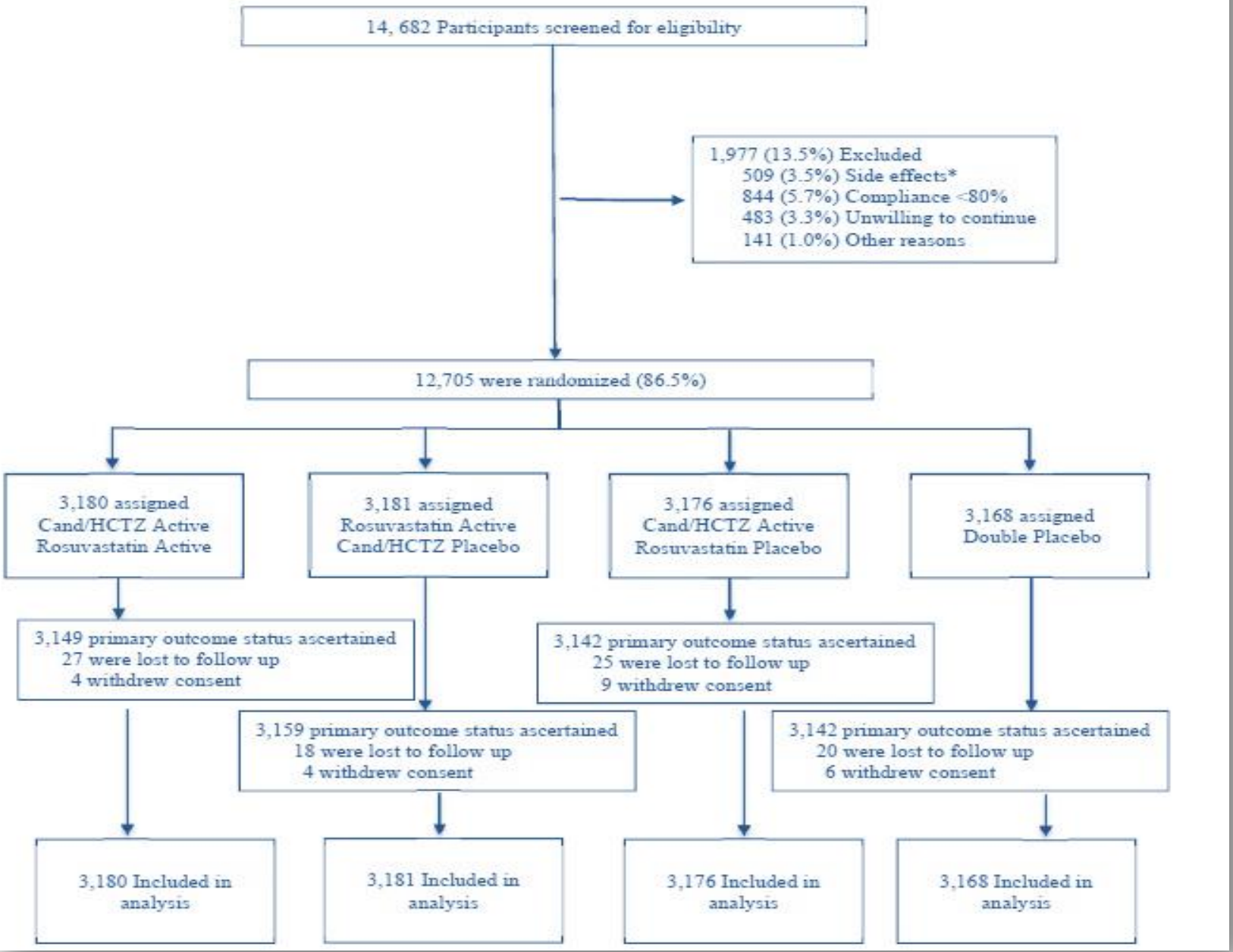
Figure S3: CONSORT Diagram for the Double Active versus Double Placebo Comparison



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The Heart Outcomes Prevention Evaluation (HOPE) - 3 Trial Design
(N=12,705)

Rosuvastatin	Candesartan/HCTZ		Rosuvastatin Margins
	Active	Placebo	
Active	Rosuvastatin Active/ Candesartan/HCTZ Active n=3,180	Rosuvastatin Active/ Candesartan/HCTZ Placebo n=3,181	**Rosuvastatin Active n=6,361**
Placebo	Rosuvastatin Placebo/ Candesartan/HCTZ Active n=3,176	Rosuvastatin Placebo/ Candesartan/HCTZ Placebo n=3,168	**Rosuvastatin Placebo n=6,344**
Candesartan/HCTZ Margins	**Candesartan/HCTZ Active n=6,356**	**Candesartan/HCTZ Placebo n=6,349**	

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TRIAL PROCEDURES

- Eligible persons entered a single-blind run-in phase, during which they received both active treatments for 4 weeks.

- Participants who adhered to the regimen and who did not have an unacceptable level of adverse events were randomly assigned to:

  - Fixed combination of Candesartan (16 mg / day) and Hydrochlorothiazide(12.5 mg / day) or placebo and

  - Rosuvastatin(10 mg /day) or placebo.

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TRIAL PROCEDURES

- Follow-up visits occurred at 6 weeks and 6 months after randomization and every 6 months thereafter.
- Blood pressure was recorded at each visit in the first year and then annually.
- Lipid levels were measured at baseline in all participants and at 1 year, at 3 years, and at the end of the trial.

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OUTCOMES

- Two co-primary outcomes:

  1) Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

  2) Composite of these events plus resuscitated cardiac arrest, heart failure, or revascularization.

- The secondary outcome was the composite of events comprising the second co-primary outcome plus angina with evidence of ischemia.

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RESULTS

TRIAL PARTICIPANTS AND FOLLOW-UP

Table 1. Characteristics of the 12,705 Participants in the Heart Outcomes Prevention Evaluation–3 Trial at Baseline.*

Characteristic	Candesartan–Hydrochlorothiazide plus Rosuvastatin (N=3180)	Rosuvastatin plus Placebo (N=3181)	Candesartan–Hydrochlorothiazide plus Placebo (N=3176)	Placebo plus Placebo (N=3168)
Age — yr	65.7±6.3	65.8±6.4	65.6±6.4	65.7±6.3
Female sex — no. (%)	1465 (46.1)	1486 (46.7)	1445 (45.5)	1478 (46.7)
Cardiovascular risk factor — no. (%)†				
Elevated waist-to-hip ratio	2771 (87.1)	2769 (87.0)	2740 (86.3)	2754 (86.9)
Recent or current smoking	889 (28.0)	851 (26.8)	893 (28.1)	891 (28.1)
Low concentration of HDL cholesterol	1201 (37.8)	1143 (35.9)	1096 (34.5)	1148 (36.2)
Impaired fasting glucose or impaired glucose tolerance	392 (12.3)	417 (13.1)	407 (12.8)	400 (12.6)
Early diabetes mellitus	196 (6.2)	178 (5.6)	190 (6.0)	167 (5.3)
Family history of premature coronary heart disease	834 (26.2)	841 (26.4)	834 (26.3)	826 (26.1)
Early renal dysfunction	89 (2.8)	80 (2.5)	95 (3.0)	86 (2.7)
Hypertension	1200 (37.7)	1203 (37.8)	1198 (37.7)	1213 (38.3)
2 Risk factors	1486 (46.7)	1516 (47.7)	1486 (46.8)	1438 (45.4)
≥3 Risk factors	795 (25.0)	750 (23.6)	743 (23.4)	780 (24.6)

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Blood pressure — mm Hg				
Systolic	138.2±14.8	137.9±15.0	138.2±14.7	137.9±14.6
Diastolic	81.9±9.4	81.8±9.3	82.0±9.3	81.8±9.2
Heart rate — beats/min	73.0±10.3	72.6±10.2	72.9±10.1	72.5±10.3
Body-mass index‡	27.2±4.8	27.1±4.8	27.1±4.8	27.1±4.7
Waist-to-hip ratio	0.94±0.08	0.94±0.08	0.94±0.08	0.94±0.09
Cholesterol — mg/dl				
Total	201.3±43.5	201.8±41.6	201.5±41.7	201.2±41.7
LDL	127.0±37.0	128.6±35.2	127.9±36.0	127.9±36.0
HDL	44.7±14.1	44.8±13.7	45.1±13.7	44.8±13.8
Triglycerides — mg/dl				
Median	128.3	129.2	126.5	126.5
Interquartile range	92.0–182.3	93.8–176.1	92.9–178.8	92.9–174.9
Fasting plasma glucose — mg/dl				
Median	96.0	95.4	95.4	95.4
Interquartile range	87.0–106.2	86.4–106.0	86.4–106.0	87.0–106.0
Apolipoprotein B — g/liter	1.02±0.27	1.03±0.26	1.02±0.26	1.02±0.26
Apolipoprotein A1 — g/liter	1.46±0.34	1.46±0.34	1.47±0.34	1.46±0.33
Ratio of apolipoprotein B to apolipoprotein A	0.75±0.36	0.75±0.31	0.74±0.31	0.74±0.32
High-sensitivity C-reactive protein — mg/liter				
Median	2.1	2.0	2.0	2.0
Interquartile range	1.0–4.1	1.0–3.9	1.0–4.0	1.0–3.8
Serum creatinine — mg/dl	0.90±0.22	0.89±0.22	0.90±0.22	0.90±0.21
INTERHEART Risk Score§	14.6±5.2	14.5±5.2	14.5±5.1	14.3±5.2

Table 1. (Continued.)

Characteristic	Candesartan–Hydrochlorothiazide plus Rosuvastatin (N=3180)	Rosuvastatin plus Placebo (N=3181)	Candesartan–Hydrochlorothiazide plus Placebo (N=3176)	Placebo plus Placebo (N=3168)
Race or ethnic group — no. (%)¶				
Chinese	922 (29.0)	932 (29.3)	922 (29.0)	915 (28.9)
Hispanic	864 (27.2)	880 (27.7)	875 (27.6)	877 (27.7)
White	651 (20.5)	635 (20.0)	633 (19.9)	627 (19.8)
South Asian	465 (14.6)	462 (14.5)	467 (14.7)	460 (14.5)
Other Asian	169 (5.3)	172 (5.4)	173 (5.4)	182 (5.7)
Black	58 (1.8)	55 (1.7)	58 (1.8)	54 (1.7)
Other	51 (1.6)	45 (1.4)	48 (1.5)	53 (1.7)
Medication use — no. (%)				
Ezetimibe	7 (0.2)	4 (0.1)	3 (0.1)	3 (0.1)
Niacin	4 (0.1)	2 (0.1)	2 (0.1)	3 (0.1)
Aspirin	358 (11.3)	328 (10.3)	381 (12.0)	326 (10.3)
Beta-blocker	259 (8.1)	245 (7.7)	265 (8.3)	251 (7.9)
Calcium-channel blocker	444 (14.0)	497 (15.6)	484 (15.2)	460 (14.5)
Alpha-blocker	38 (1.2)	38 (1.2)	34 (1.1)	31 (1.0)
Nonthiazide diuretic	23 (0.7)	16 (0.5)	13 (0.4)	13 (0.4)
Aldosterone antagonist	3 (0.1)	9 (0.3)	3 (0.1)	2 (0.1)
Oral hypoglycemic agent	92 (2.9)	75 (2.4)	84 (2.6)	86 (2.7)

ADHERENCE TO TRIAL DRUGS

Table S3: Adherence to Study Drug and Open Label Use of ARBs, ACE-Is and Thiazides in the Candesartan/HCTZ and Placebo Groups

A. Candesartan

Visit	Candesartan/HCTZ					
	Eligible	On Study Drug	On Open Label			
		Cand/HCTZ N (%)	ARB N (%)	ACE-I N (%)	Thiazide N (%)	Other BP Lowering Drug(s)* N (%)
1 year	6314	5567(88.2)	14(0.2)	24(0.4)	1(0)	-
2 years	6267	5374(85.8)	28(0.4)	41(0.7)	10(0.2)	1011(16.5)
3 years	6205	5189(83.6)	45(0.7)	48(0.8)	15(0.2)	-
4 years	6101	4967(81.4)	52(0.9)	59(1.0)	30(0.5)	-
5 years	4854	3639(75.0)	60(1.2)	66(1.4)	30(0.6)	-
End	5990	4599(76.8)	93(1.6)	100 (1.7)	47(0.8)	1068(18.2)

B. Placebo

Visit	Placebo					
	Eligible	On Study Drug	On Open Label			
		Cand/HCTZ Placebo N (%)	ARB N (%)	ACE-I N (%)	Thiazide N (%)	Other BP Lowering Drug(s)* N (%)
	6306	5545(87.9)	30(0.5)	48(0.8)	9(0.1)	-
	6262	5359(85.6)	66(1.1)	67(1.1)	27(0.4)	1514(24.7)
	6188	5161(83.4)	76(1.2)	82(1.3)	45(0.7)	-
	6089	4953(81.3)	106(1.7)	102(1.7)	57(0.9)	-
	4818	3588 (74.5)	104(2.2)	110(2.3)	57(1.2)	-
	5985	4530(75.7)	146(2.4)	137(2.3)	79 (1.3)	1688(28.8)

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Table S4: Adherence to Study Drug and Open Label Use of Statins and Other Lipid Lowering Drugs in the Rosuvastatin and Placebo Groups

A. Rosuvastatin

Visit	Rosuvastatin			
	Eligible	On Drug	On Open Label	
		Rosuvastatin N (%)	Statin N (%)	Other Lipid Lowering Drugs N (%)
1 year	6327	5565 (88.0)	35 (0.6)	17 (0.3)
2 years	6286	5384 (85.7)	62 (1.0)	17 (0.3)
3 years	6223	5196 (83.5)	103 (1.7)	20 (0.3)
4 years	6118	4961 (81.1)	124 (2.0)	31 (0.5)
5 years	4870	3678 (75.5)	120 (2.5)	33 (0.7)
End	6014	4649 (77.3)	163 (2.7)	32 (0.5)

B. Placebo

Visit	Placebo			
	Eligible	On Drug	On Open Label	
		Rosuvastatin Placebo N (%)	Statin N (%)	Other Lipid Lowering Drugs N (%)
1 year	6293	5528 (87.8)	76 (1.2)	20 (0.3)
2 years	6243	5312 (85.1)	152 (2.4)	45 (0.7)
3 years	6170	5121 (83.0)	203 (3.3)	64 (1.0)
4 years	6072	4879 (80.4)	265 (4.4)	87 (1.4)
5 years	4802	3515 (73.2)	270 (5.6)	70 (1.5)
End	5961	4457 (74.8)	370 (6.2)	76 (1.3)

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Table S5: Adherence to Study Drug and Open Label Use of ARBs, ACE-Is, Thiazides and Statins in the Candesartan/HCTZ+Rosuvastatin and the Double Placebo Groups

A. Candesartan/HCTZ + Rosuvastatin (Double Active)

Visit	Eligible	On Study Drug N (%)			On Open Label N (%)				
		Both Candesartan/HCTZ and Rosuvastatin	Only Candesartan/HCTZ	Only Rosuvastatin	ARB	ACE-I	Thiazide	Other BP*	Statin
1 year	3164	2728 (86.2)	47 (1.5)	53 (1.7)	8 (0.3)	11 (0.3)	1 (0)	-	16 (0.5)
2 years	3144	2627 (83.6)	44 (1.4)	49 (1.6)	10 (0.3)	21 (0.7)	2 (0.1)	489 (15.9)	31 (1.0)
3 years	3114	2519 (80.9)	50 (1.6)	58 (1.9)	23 (0.7)	22 (0.7)	9 (0.3)	-	50 (1.6)
4 years	3056	2400 (78.5)	51 (1.7)	59 (1.9)	25 (0.8)	31 (1.0)	14 (0.5)	-	61 (2.0)
5 years	2438	1762 (72.3)	39 (1.6)	69 (2.8)	30 (1.2)	38 (1.6)	14 (0.6)	-	62 (2.5)
End	3008	2245 (74.6)	45 (1.5)	87 (2.9)	42 (1.4)	47 (1.6)	23 (0.8)	518 (17.6)	77 (2.6)

B. Double Placebo

Visit	Eligible	On Study Drug N (%)			On Open Label N (%)				
		Both Candesartan/HCTZ and Rosuvastatin Placebo	Only Candesartan/HCTZ Placbeo	Only Rosuvastatin Placebo	ARB	ACE-I	Thiazide	Other BP*	Statin
1 year	3143	2700 (85.9)	53 (1.7)	47 (1.5)	20 (0.6)	24 (0.8)	4 (0.1)	-	38 (1.2)
2 years	3120	2598 (83.3)	60 (1.9)	36 (1.2)	38 (1.2)	38 (1.2)	13 (0.4)	744 (24.4)	87 (2.8)
3 years	3079	2489 (80.8)	72 (2.3)	44 (1.4)	42 (1.4)	38 (1.2)	21 (0.7)	-	105 (3.4)
4 years	3027	2367 (78.2)	102 (3.4)	40 (1.3)	62 (2.0)	48 (1.6)	32 (1.1)	-	147 (4.9)
5 years	2386	1666 (69.8)	99 (4.1)	52 (2.2)	58 (2.4)	62 (2.6)	33 (1.4)	-	150 (6.3)
End	2979	2140 (71.8)	103 (3.5)	48 (1.6)	78 (2.6)	79 (2.7)	42 (1.4)	836 (28.7)	196 (6.6)

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BLOOD PRESSURE AND LIPID LEVELS

6.2
- Mean SBP was lower by 6.2 mm Hg

3.2
- Mean DBP was lower by 3.2 mm Hg

33.7
- Mean LDL-C level was lower by 33.7 mg/dL

- The difference in BP was similar for participants assigned to candesartan– hydrochlorothiazide alone versus placebo.
- The difference in LDL cholesterol level was similar for participants assigned to rosuvastatin alone versus placebo.

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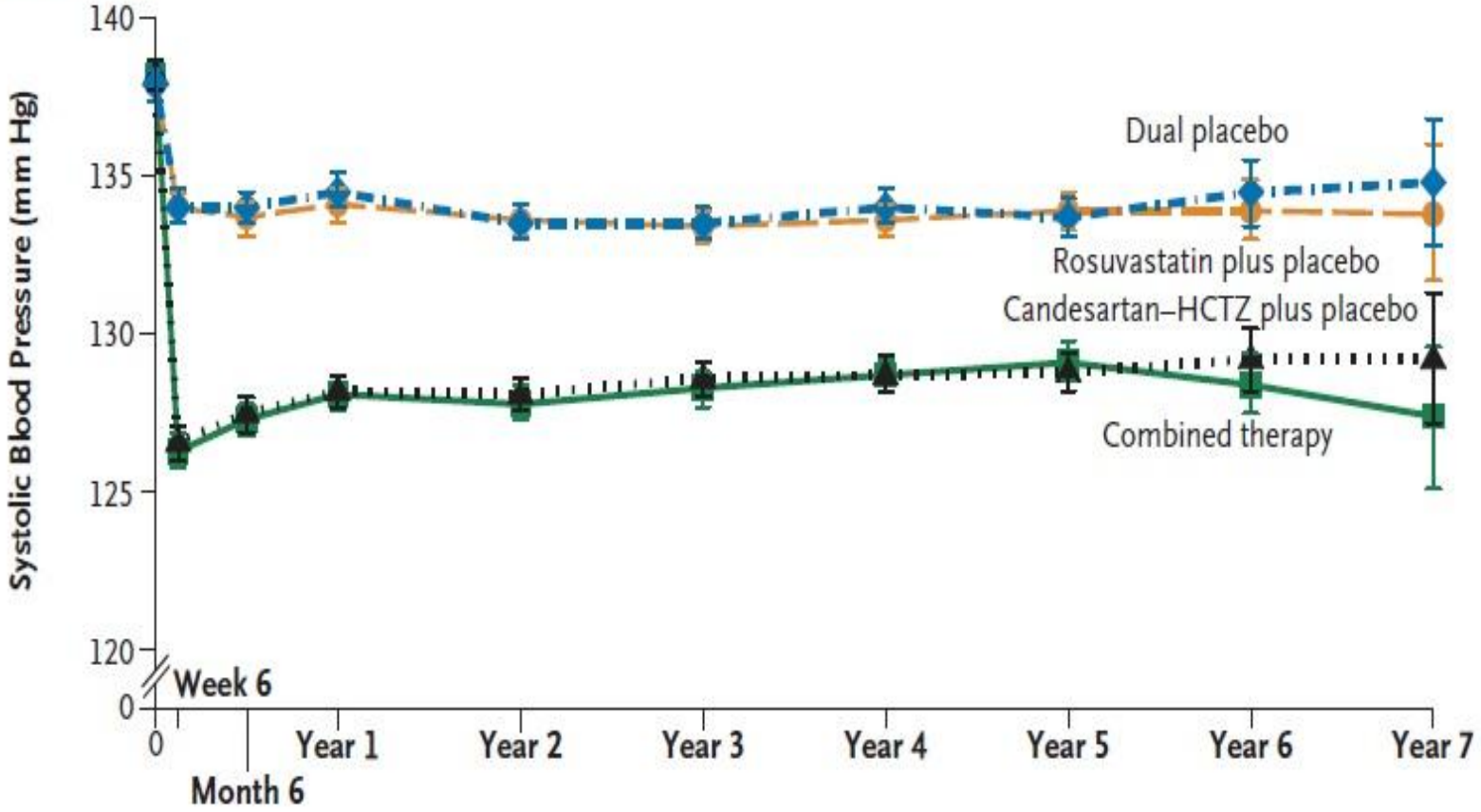
A Systolic Blood Pressure



No. at Risk

Combined therapy	3180	3091	3009	2953	2836	2718	2594	1921	731	178
Rosuvastatin plus placebo	3181	3105	3033	2957	2832	2741	2615	1929	728	167
Candesartan–HCTZ plus placebo	3176	3109	3022	2954	2831	2728	2619	1941	706	172
Dual placebo	3166	3093	3000	2922	2791	2701	2571	1893	696	167

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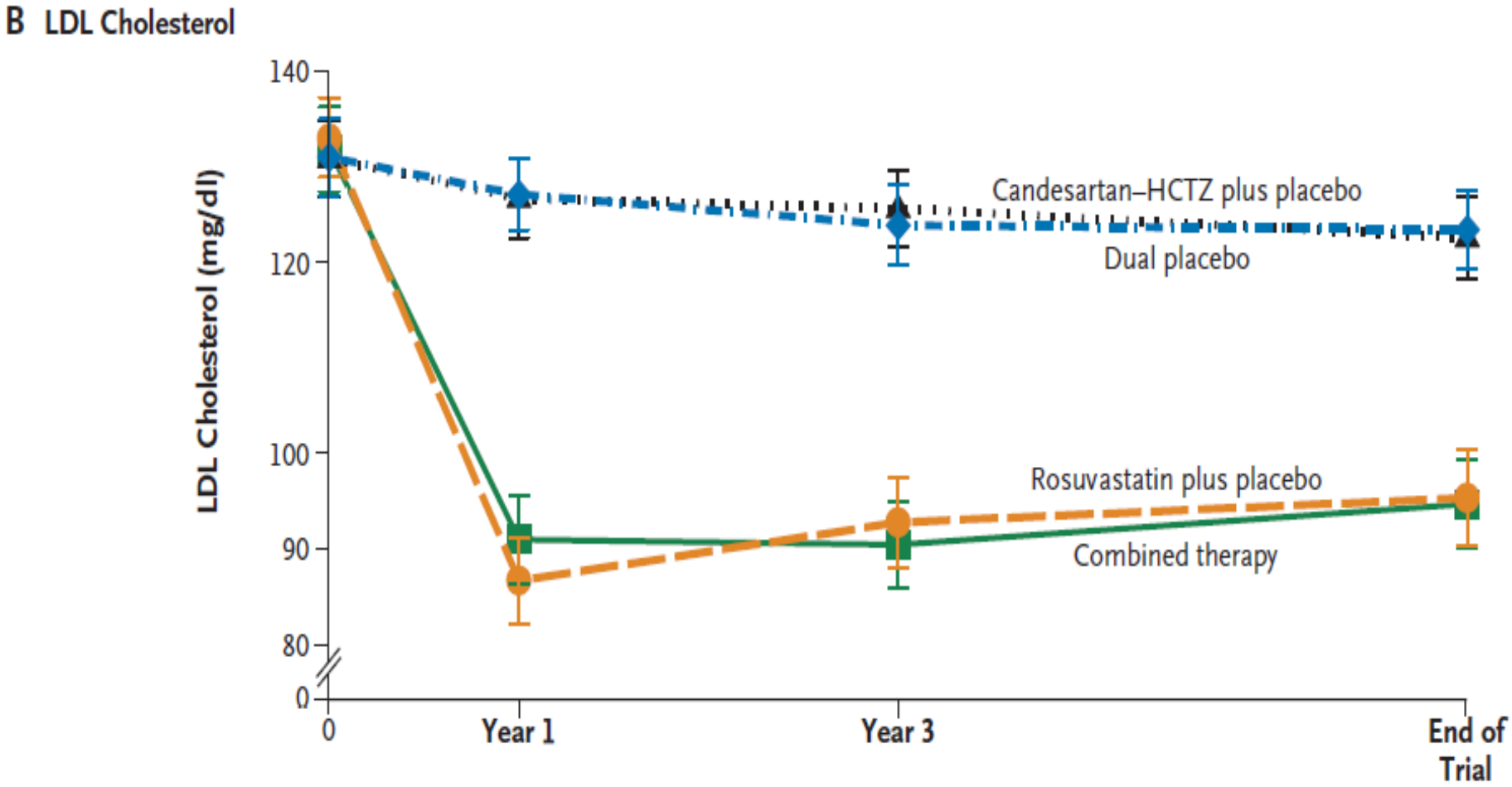

No. at Risk				
Combined therapy	248	248	248	248
Rosuvastatin plus placebo	232	232	232	232
Candesartan–HCTZ plus placebo	247	247	247	247
Dual placebo	248	248	248	248

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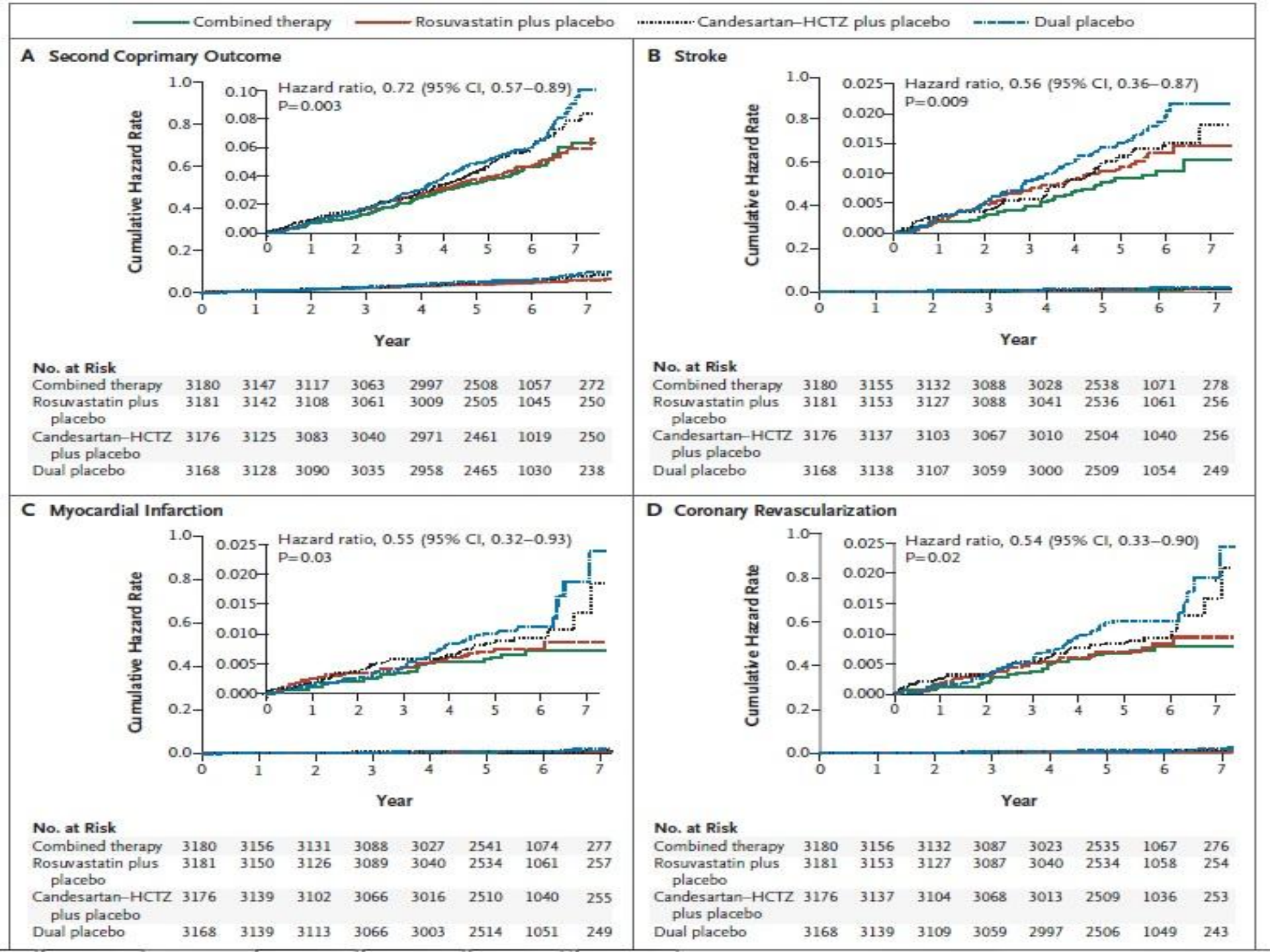
CLINICAL OUTCOMES

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

Outcome	Candesartan–Hydrochlorothiazide plus Rosuvastatin (N=3180)	Rosuvastatin plus Placebo (N=3181)	Candesartan–Hydrochlorothiazide plus Placebo (N=3176)	Placebo plus Placebo (N=3168)	Candesartan–Hydrochlorothiazide plus Rosuvastatin vs. Placebo plus Placebo	
					Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)						
First coprimary outcome	113 (3.6)	122 (3.8)†	147 (4.6)‡	157 (5.0)	0.71 (0.56–0.90)	0.005
Second coprimary outcome	136 (4.3)	141 (4.4)§	176 (5.5)¶	187 (5.9)	0.72 (0.57–0.89)	0.003
Secondary outcome — no. (%)‖	147 (4.6)	159 (5.0)	188 (5.9)	205 (6.5)	0.71 (0.57–0.87)	0.001
Components of the coprimary and secondary outcomes — no. (%)						
Death from cardiovascular causes	75 (2.4)	79 (2.5)	80 (2.5)	91 (2.9)	0.82 (0.60–1.11)	
Fatal or nonfatal myocardial infarction	21 (0.7)	24 (0.8)	31 (1.0)	38 (1.2)	0.55 (0.32–0.93)	
Fatal or nonfatal stroke	31 (1.0)	39 (1.2)	44 (1.4)	55 (1.7)	0.56 (0.36–0.87)	
Resuscitated cardiac arrest	1 (<0.1)	3 (0.1)	1 (<0.1)	3 (0.1)	0.33 (0.03–3.18)	
Revascularization	27 (0.8)	29 (0.9)	37 (1.2)	45 (1.4)	0.59 (0.37–0.95)	
Heart failure	10 (0.3)	11 (0.3)	11 (0.3)	18 (0.6)	0.55 (0.25–1.19)	
Angina with objective evidence of ischemia‖	25 (0.8)	31 (1.0)	26 (0.8)	38 (1.2)	0.65 (0.39–1.08)	
Other outcomes						
Death from any cause — no. (%)	163 (5.1)	171 (5.4)	179 (5.6)	178 (5.6)	0.91 (0.73–1.12)	
New-onset diabetes — no./total no. (%)	123/2982 (4.1)	109/3001 (3.6)	113/2984 (3.8)	113/2999 (3.8)	1.09 (0.85–1.41)	
Hospitalization — no. (%)**						
For cardiovascular causes	141 (4.4)	140 (4.4)	178 (5.6)	191 (6.0)	0.73 (0.59–0.91)	0.005
For noncardiovascular causes	463 (14.6)	418 (13.1)	436 (13.7)	443 (14.0)	1.04 (0.92–1.19)	0.52
First and recurrent events of the second coprimary outcome††						
No. of participants with ≥1 event	136	141	176	187		
No. of participants with ≥2 events	29	39	30	59		
No. of participants with ≥3 events	2	4	3	13		
Total no. of events	169	184	211	262	0.66 (0.52–0.84)	0.001

* 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 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. CI denotes confidence interval.


Combined therapy
Rosuvastatin plus placebo
Candesartan–HCTZ plus placebo
Dual placebo
A Second Coprimary Outcome
Hazard ratio, 0.72 (95% CI, 0.57–0.89)
P=0.003
Cumulative Hazard Rate
Year
No. at Risk
Combined therapy 3180 3147 3117 3063 2997 2508 1057 272
Rosuvastatin plus placebo 3181 3142 3108 3061 3009 2505 1045 250
Candesartan–HCTZ plus placebo 3176 3125 3083 3040 2971 2461 1019 250
Dual placebo 3168 3128 3090 3035 2958 2465 1030 238
B Stroke
Hazard ratio, 0.56 (95% CI, 0.36–0.87)
P=0.009
Cumulative Hazard Rate
Year
No. at Risk
Combined therapy 3180 3155 3132 3088 3028 2538 1071 278
Rosuvastatin plus placebo 3181 3153 3127 3088 3041 2536 1061 256
Candesartan–HCTZ plus placebo 3176 3137 3103 3067 3010 2504 1040 256
Dual placebo 3168 3138 3107 3059 3000 2509 1054 249
C Myocardial Infarction
Hazard ratio, 0.55 (95% CI, 0.32–0.93)
P=0.03
Cumulative Hazard Rate
Year
No. at Risk
Combined therapy 3180 3156 3131 3088 3027 2541 1074 277
Rosuvastatin plus placebo 3181 3150 3126 3089 3040 2534 1061 257
Candesartan–HCTZ plus placebo 3176 3139 3102 3066 3016 2510 1040 255
Dual placebo 3168 3139 3113 3066 3003 2514 1051 249
D Coronary Revascularization
Hazard ratio, 0.54 (95% CI, 0.33–0.90)
P=0.02
Cumulative Hazard Rate
Year
No. at Risk
Combined therapy 3180 3156 3132 3087 3023 2535 1067 276
Rosuvastatin plus placebo 3181 3153 3127 3087 3040 2534 1058 254
Candesartan–HCTZ plus placebo 3176 3137 3104 3068 3013 2509 1036 253
Dual placebo 3168 3139 3109 3059 2997 2506 1049 243

SUMMARY

- Combination therapy with statin, ARB and diuretic for a median of 5.6 years is effective.
- Significantly lower risk of cardiovascular events than dual placebo.
- 29% lower relative risk and 1.4-percentage-point lower absolute risk of the first primary outcome.
- In post hoc recurrent-events analysis, the benefit was slightly larger.

Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

SUMMARY

- The reduction in LDL-C was approx. 33.7 mg per dl over the course of the trial and the reduction in SBP was 6.2 mm Hg.

- Rates of adherence to drugs were high, and so the degree of cholesterol and blood-pressure lowering , in a large population treated over a median of 5.6 years.

Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

SUMMARY

- Post hoc subgroup analysis was performed comparing upper third of baseline SBP *vs.* lower two thirds.
- In the upper third, the risk of the two co-primary outcomes was approx. 40% lower with combined therapy than with dual placebo.
- Relative risk was only about 20% lower among participants with lower SBP.

Lonn EM et al. N Engl J Med. 2016 May 26;374(21):2009-20.

CONCLUSION

The combination of statin , ARB and diuretic was associated with a significantly lower rate of cardiovascular events.

Combination therapy (with a statin and anti-hypertensives) would perform best in patients with hypertension, whereas statins alone would perform best in those without elevated blood pressure.