The Heart Outcomes Prevention Evaluation (HOPE) – 3 Trial

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For the HOPE-3 Investigators

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Disclosures

- Eva Lonn
  - Institutional Research Grants: Astra Zeneca, CIHR, Amgen, Bayer, GSK, Merck Shering, Eli Lilly
  - Consulting/ Lectures fees: Amgen, Sanofi, Novartis
- Jackie Bosch
  - Institutional Research Grants: Astra Zeneca, CIHR, Bayer, Boehringer-Ingelheim, Novartis, Bristol-Myers Squibb, Cadila Pharma
- Salim Yusuf
  - Institutional Research Grants: Astra Zeneca, Bayer, CIHR, Boehringer-Ingelheim, Novartis, Bristol-Myers Squibb, Cadila Pharma
  - Consulting/Lecture fees and Travel Expenses: Bayer

Study Rationale

- Graded increase in CVD risk for SBP >115 mmHg & for LDL throughout documented ranges in populations
- BP lowering trials indicate reductions in CVD in high risk people and those with SBP>150 -160 mmHg
- Statins lower CVD in secondary prevention and in primary prevention mainly in Whites with increased LDL-C or CRP, diabetes, or hypertension

Study Objectives

To evaluate in an intermediate risk population without CVD the effects on CV events of:

1. BP lowering with combined Candesartan 16 mg + HCTZ 12.5 mg daily
2. Cholesterol lowering with Rosuvastatin 10 mg
3. Combined BP and cholesterol lowering

Intermediate-Risk Population

Inclusion Criteria (Target Risk 1.0%/yr)

Women ≥ 60 yrs, men ≥ 55 yrs with at least one additional Risk Factor

- Increased WHR
- Dysglycemia
- Smoking
- Mild renal dysfunction
- Low HDL
- Family history of CHD

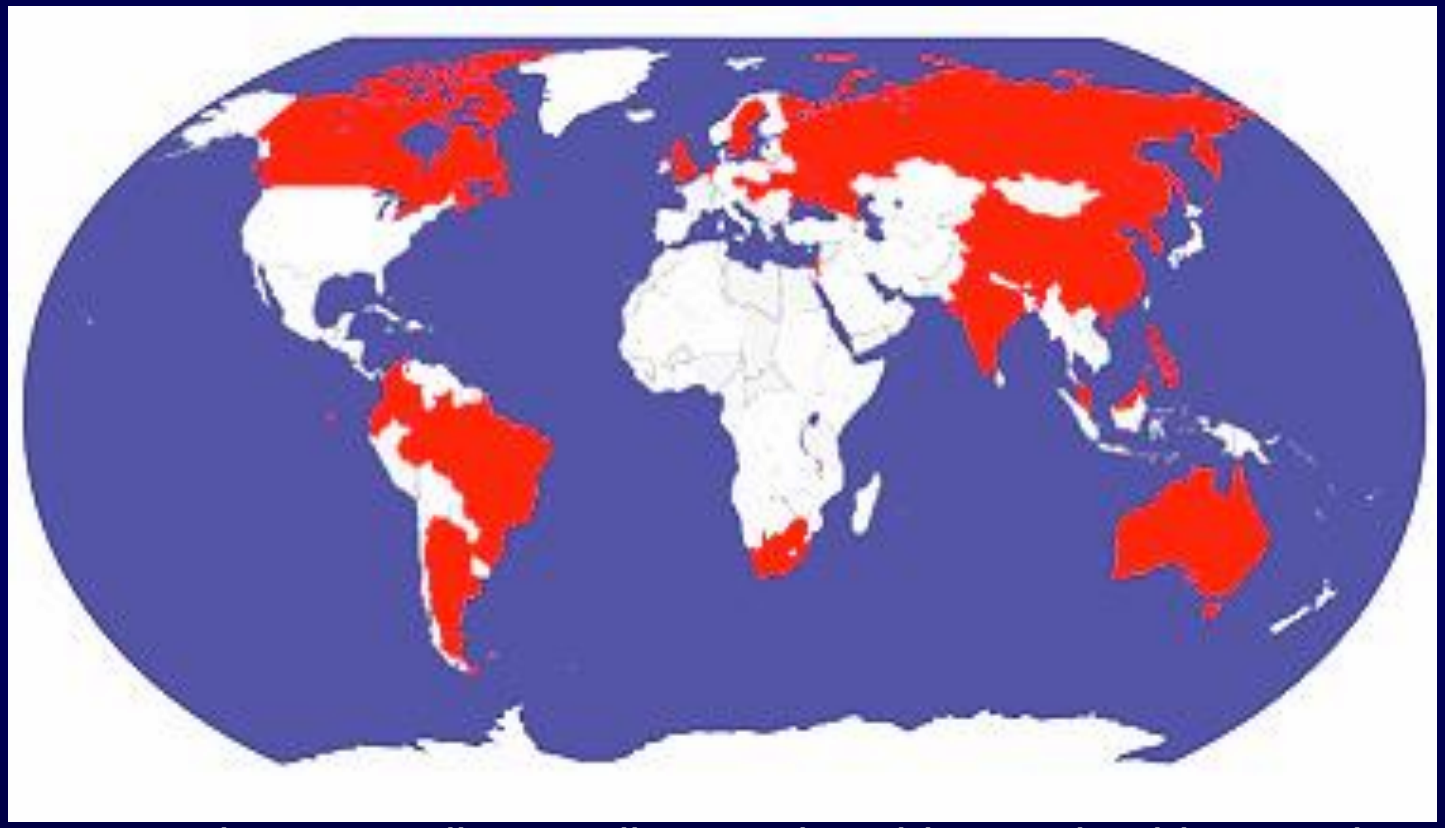
Exclusion Criteria:

CVD or indication(s) or contraindication(s) to study drugs

No strict BP or LDL-C criteria for entry
Uncertainty principle

The HOPE-3 Trial

Global Trial: 228 centers in 21 countries



Argentina, Australia, Brazil, Canada, China, Colombia, Czech Republic, Ecuador, Hungary, India, Israel, Korea, Malaysia, Netherlands, Philippines, Russia, Slovakia, South Africa, Sweden, United Kingdom, Ukraine

HOPE-3: 2 by 2 Factorial Design

14,682 Entered Single-blind 4 week Active Run-in
12,705 (87%) Randomized

	Candesartan 16 mg + HCTZ 12.5 mg n= 6,356	**Placebo n = 6,349**
Rosuvastatin 10 mg n=6,361	**Rosuvastatin Cand+HCTZ n = 3,180**	**Rosuvastatin n = 3,181**
Placebo n = 6,344	**Cand+HCTZ n = 3,176**	**Double Placebo n = 3,168**

Simple follow-up and few blood tests

- Median Follow up: 5.6 years
- Adherence high numbers to be inserted (whole numbers)

- Participant Follow-up: 99.1%

Outcomes

- **Co-Primary 1**
  - Composite of CV death, MI, stroke ($p < 0.04$)
- **Co-Primary 2**
  - Composite 1 + resuscitated cardiac arrest, heart failure, revascularizations ($p < 0.02$)
- **Secondary Outcomes**
  - Composite of Co-Primary 2 + angina with objective ischemia
  - Stroke

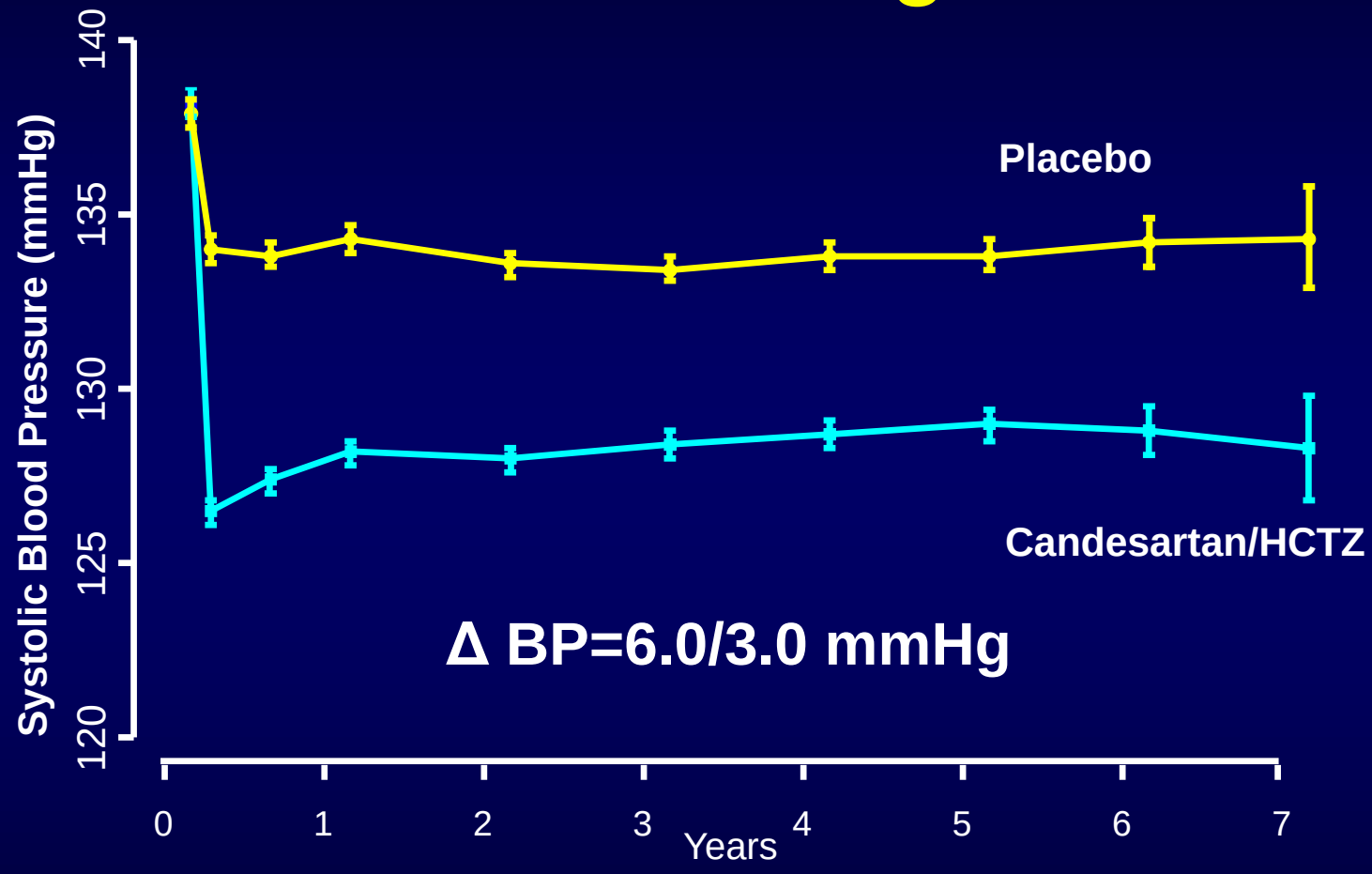
Pre-Specified Hypothesis Based Subgroup Analyses

- According to thirds of baseline:
  - Systolic BP
  - LDL-C
  - INTERHEART Risk Score

Baseline Characteristics

Age	65.6
Female	46%
Blood Pressure (mmHg)	138/82
LDL-Cholesterol (mg/dL)	128
LDL-Cholesterol (mmol/L)	3.4
Elevated waist-to-hip ratio	87%
hsCRP (g/L) median	2.0
Ethnicity	
White Caucasian	20%
Latin American	28%
Chinese	29%
Other Asian	20%
Black African	2%

BP Lowering vs. Placebo: SBP Changes

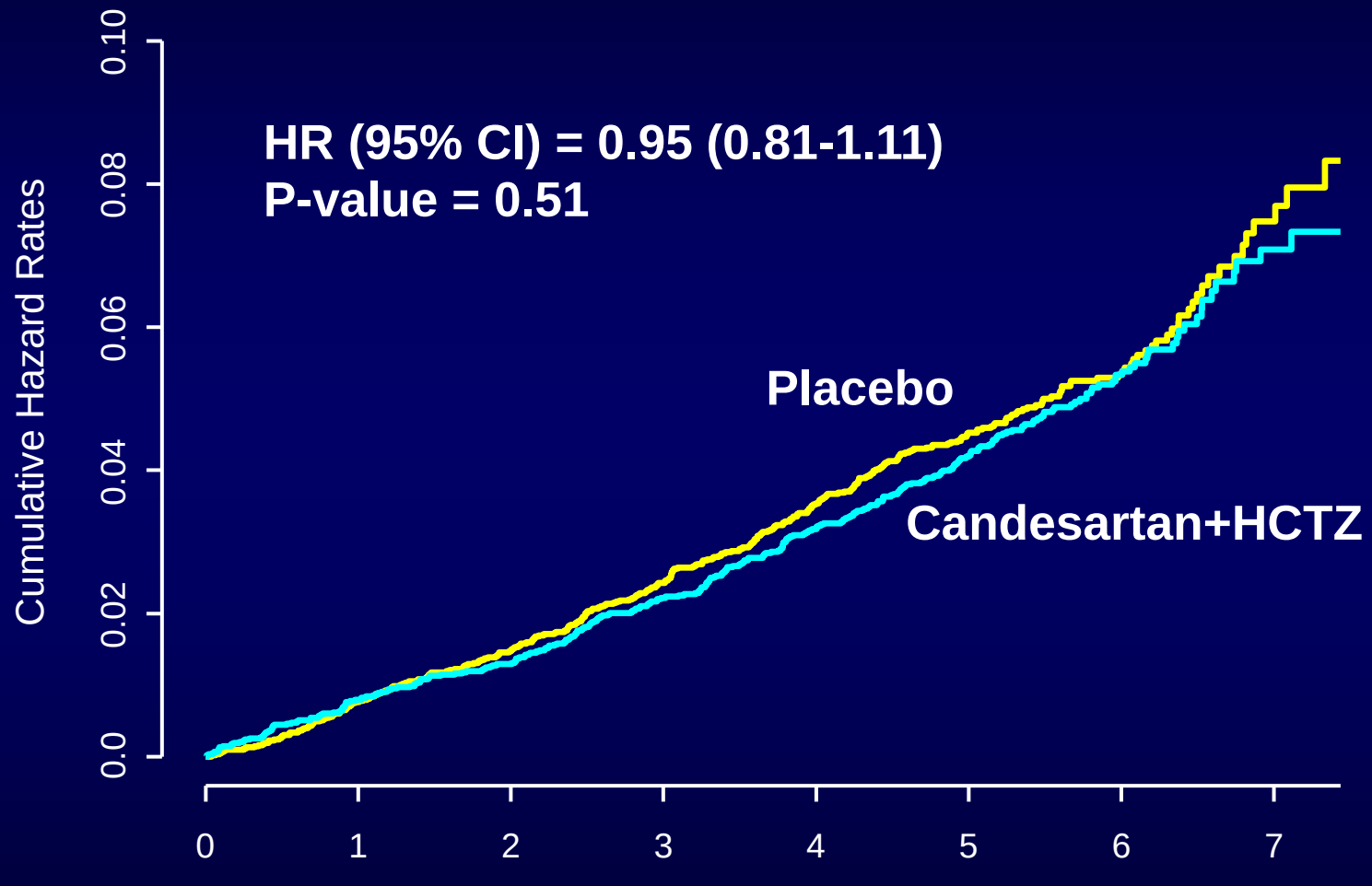


Cand/HCTZ	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

BP Lowering vs. Placebo

Outcome	Cand+HCTZ N=6356	Placebo N=6349	HR (95% CI)	p
Co-Primary 1	260 (4.1%)	279 (4.4%)	0.93 (0.79-1.10)	0.40
Co-Primary 2	312 (4.9%)	328 (5.2%)	0.95 (0.81-1.11)	0.51
Secondary	335 (5.3%)	364 (5.7%)	0.92 (0.79-1.06)	0.26
CV Deaths	155 (2.4%)	170 (2.7%)	0.91 (0.73-1.13)	0.40
MI	52 (0.8%)	62 (1.0%)	0.84 (0.58-1.21)	0.34
Stroke	75 (1.2%)	94 (1.5%)	0.80 (0.59-1.08)	0.14
CV Hosp.	319 (5.0%)	331 (5.2%)	0.96 (0.83-1.12)	0.63

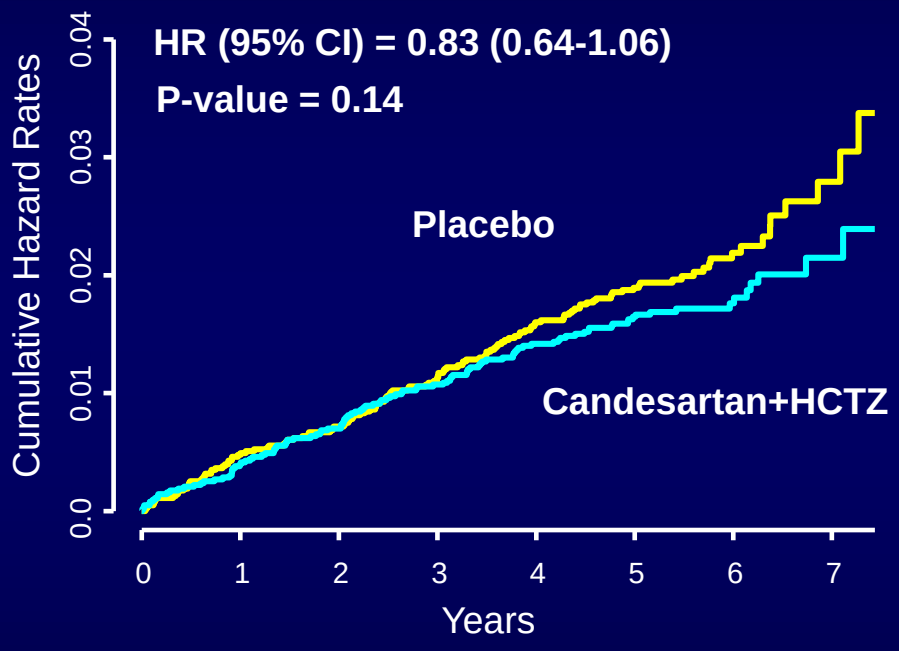
CV Death, MI, Stroke, Cardiac Arrest, Revascularization, Heart Failure



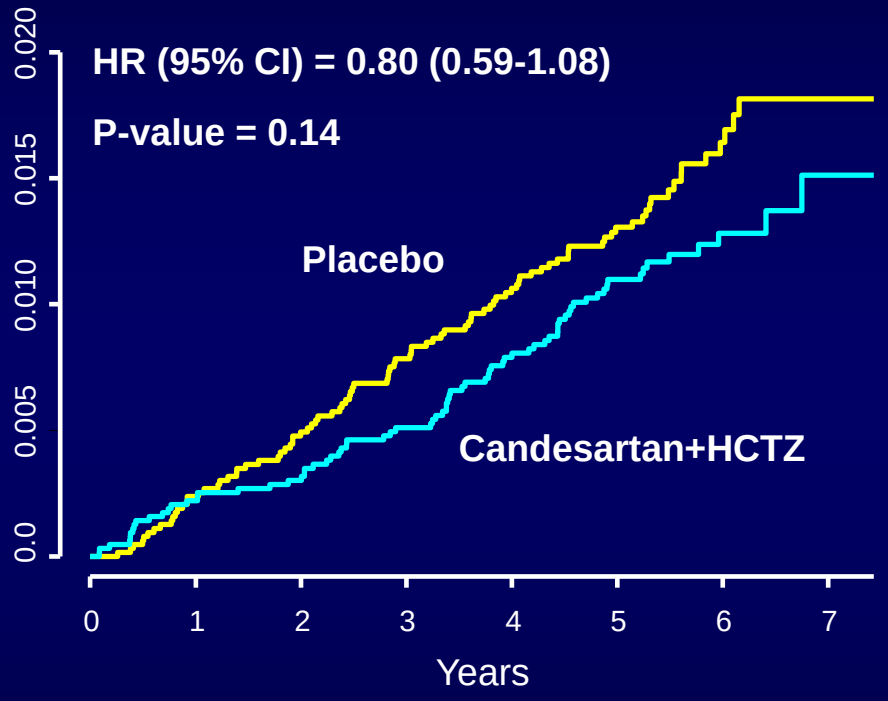
No. at Risk								
Cand + HCTZ	6356	6272	6200	6103	5968	4969	2076	522
Placebo	6349	6270	6198	6096	5967	4970	2075	488

BP Lowering vs. Placebo

Coronary Heart Disease



Stroke

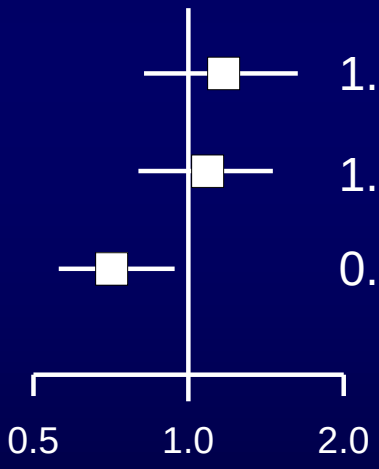


Coronary Heart Disease: Fatal/non-fatal MI, Coronary Revascularization

Prespecified Subgroups: By Thirds of SBP

CV Death, MI, Stroke

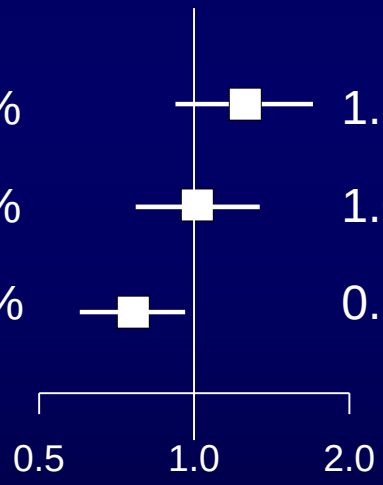
Cutoffs	SBP Mean	Diff	% Events Cand+ HCTZ	% Events Placebo	HR (95% CI)	P Trend
<132	122	6.1	3.4	2.9	1.16 (0.82-1.63)	
132-144	138	5.6	4.1	3.8	1.08 (0.80-1.46)	
>144	154	5.8	4.8	6.5	0.73 (0.56-0.94)	
						0.021



Prespecified Subgroup Analysis by Tertiles of SBP

CV Death, MI, Stroke, Cardiac Arrest, Revasc, HF

	Δ SBP (mmHg)	Cand HCTZ	Placebo	HR (95% CI)	P Trend
SBP-mmHg					0.009
≤131.5	6.1/3.1	4.3%	3.5%	1.25 (0.92-1.70)	
131.6-143.5	5.6/2.7	4.7%	4.6%	1.02 (0.77-1.34)	
>143.5	5.8/3.0	5.7%	7.5%	0.76 (0.60-0.96)	



Candesartan + HCTZ Better Placebo Better

BP Lowering Arm: Safety

	Cand/HCTZ N=6,356	Placebo N=6,349	p
Permanent Discontinuation	1552 (24.4%)	1598 (25.2%)	0.33
Lightheadedness	217 (3.4)%	130 (2.0%)	<0.001
Syncope	7 (0.1%)	4 (0.1%)	0.55
Renal Dysfunction/ Potassium Abn.	32 (0.5%)	20 (0.3%)	0.13

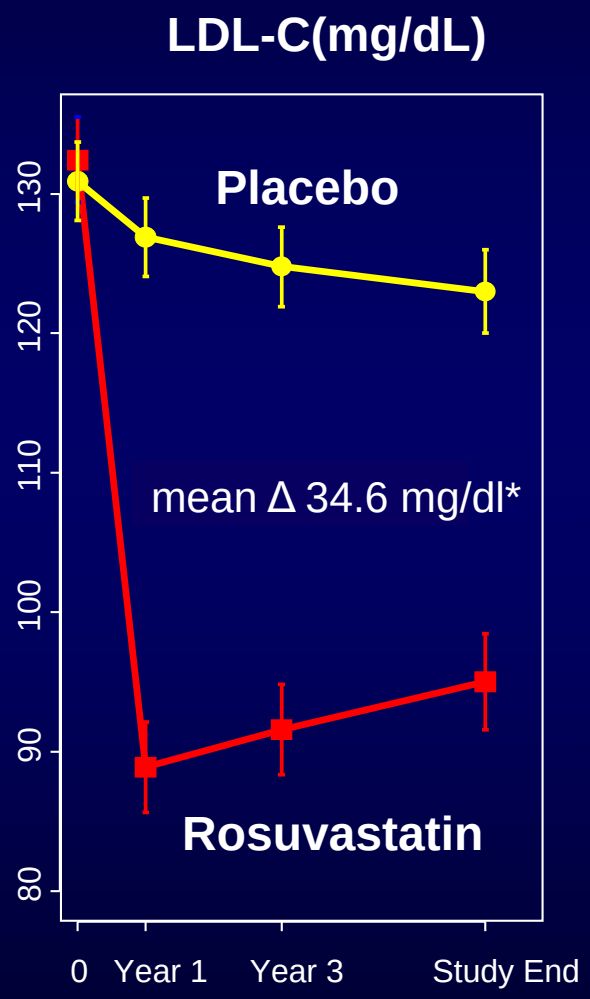
BP Lowering Arm: Conclusions

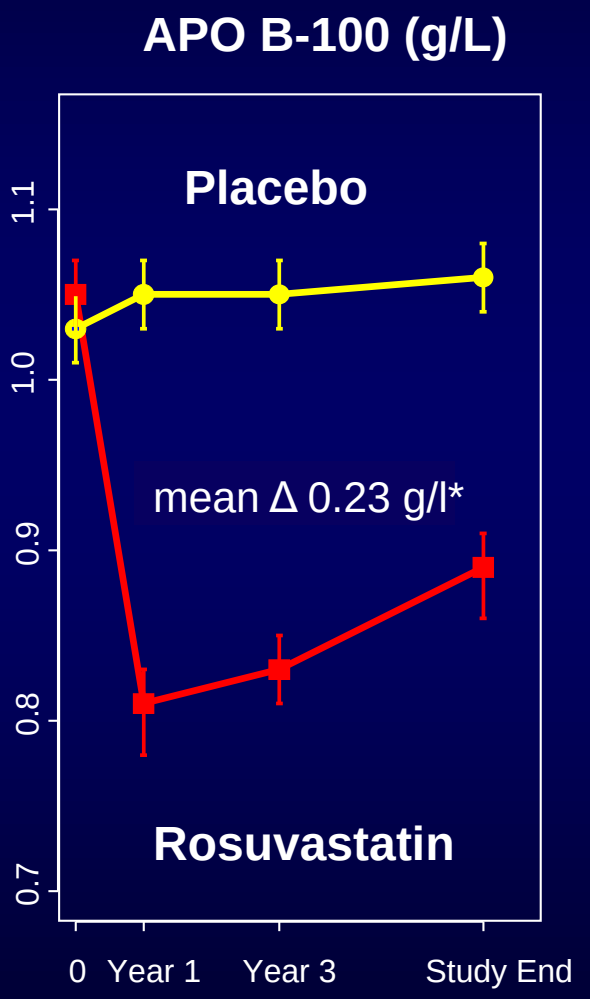
- Fixed dose combination with Candesartan 16 mg + HCTZ 12.5 mg/day reduced BP by 6.0/3.0 mmHg, but did not reduce CV events
- CV events were significantly reduced in the highest third: SBP >143.5 mmHg, mean 154 mmHg
- Results were neutral in the middle third, and tended towards harm in the lowest third of SBP
- Treatment increased lightheadedness, but not syncope or renal dysfunction

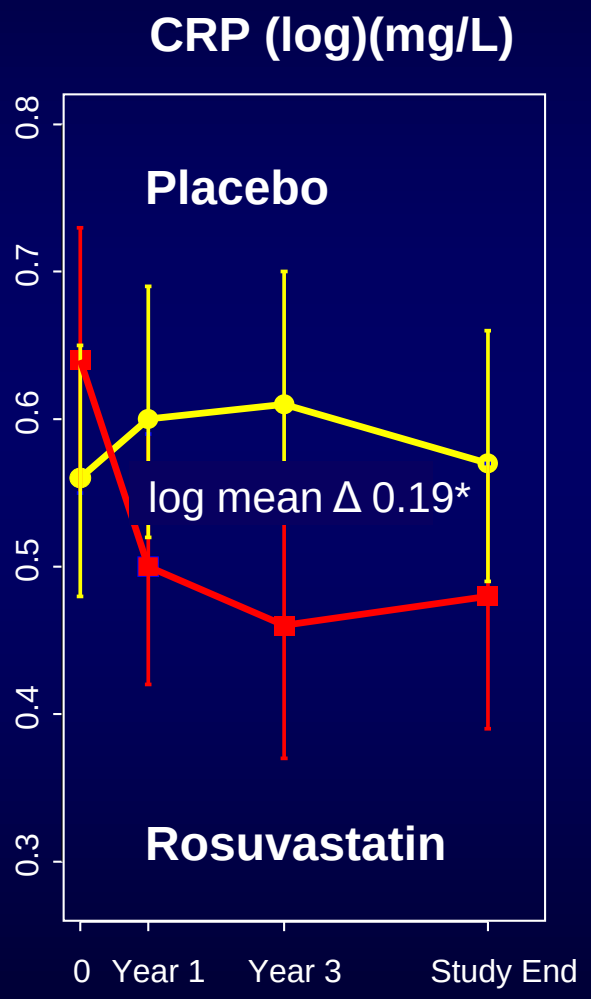
Cholesterol Lowering Arm Results

J. Bosch

Cholesterol Lowering Arm: Change in LDL, Apo-B, and CRP





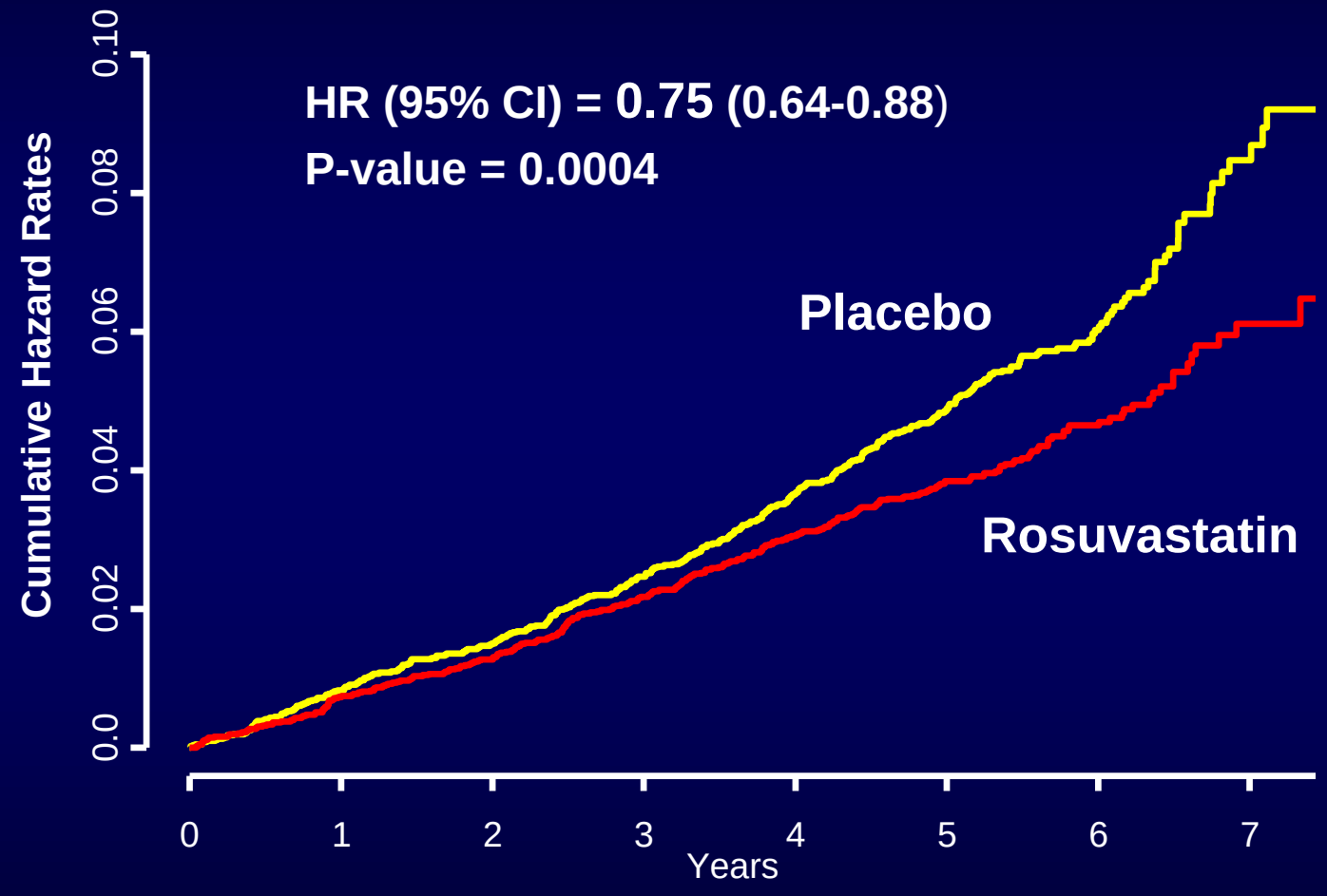


*** P< 0.001 check**

Cholesterol Lowering: Outcomes

Outcome	Rosuvastatin N (%)	Placebo N (%)	HR (95% CI)	p
Co-Primary 1	235 (3.69)	304 (4.79)	0.76 (0.64-0.91)	0.002
Co-Primary 2	277 (4.35)	363 (5.72)	0.75 (0.64-0.88)	0.0004
Secondary 1	306(4.81)	393 (6.19)	0.77 (0.66-0.89)	0.0006
CV Deaths	154 (2.4)	171 (2.7)	0.89 (0.72-1.11)	0.31
MI	45 (0.7%)	69 (1.1)	0.65 (0.44-0.94)	
Stroke	70 (1.1%)	99 (1.6%)	0.70 (0.52-0.95)	
CV Hosp.	281 (4.4)	369 (5.8)	0.75 (0.64-0.88)	0.0003

CV Death, MI, Stroke, Cardiac Arrest, Revasc, Heart Failure

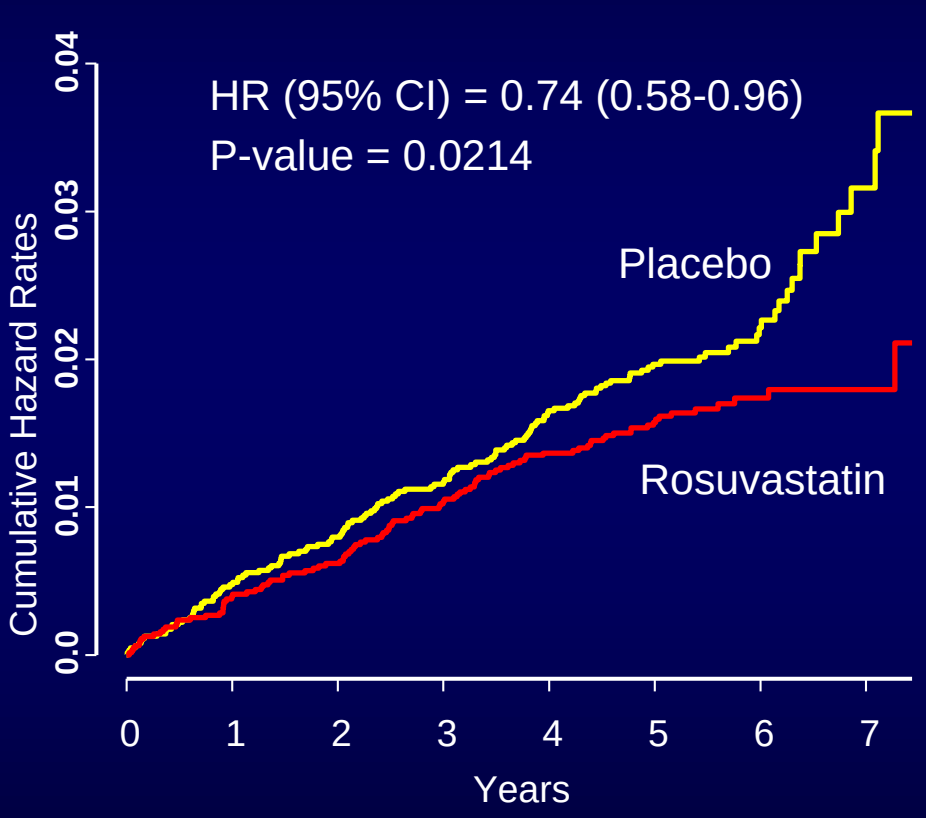


Rosuva	6361	6241	6039	2122
Placebo	6344	6192	5970	2073

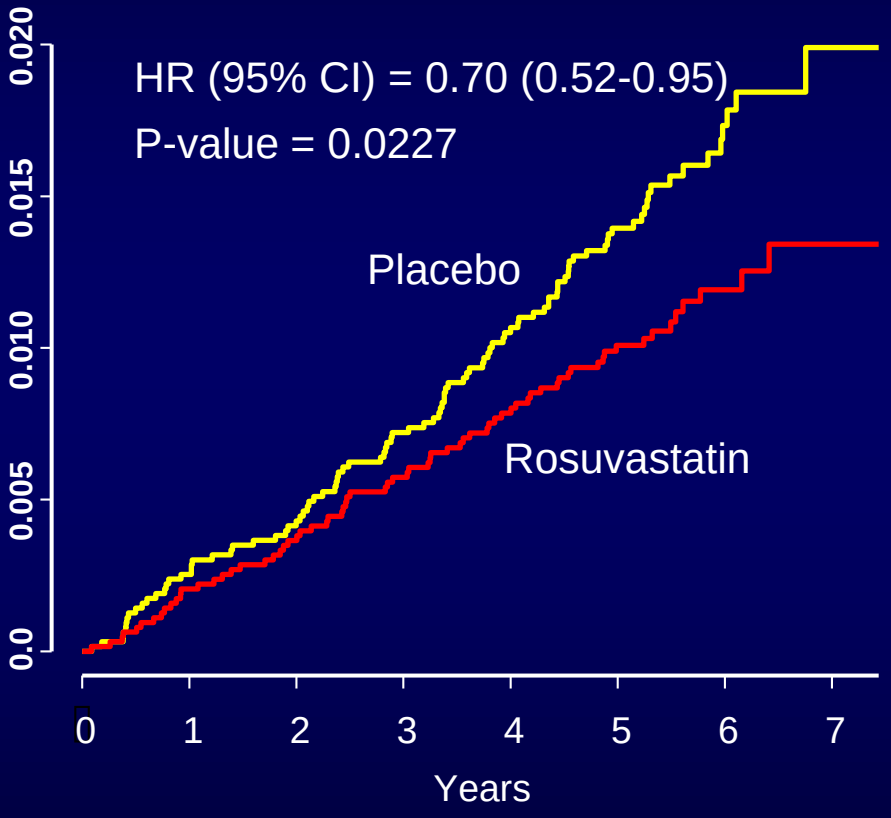
Hope-3

Health Through Knowledge
PHRI

Coronary Heart Disease

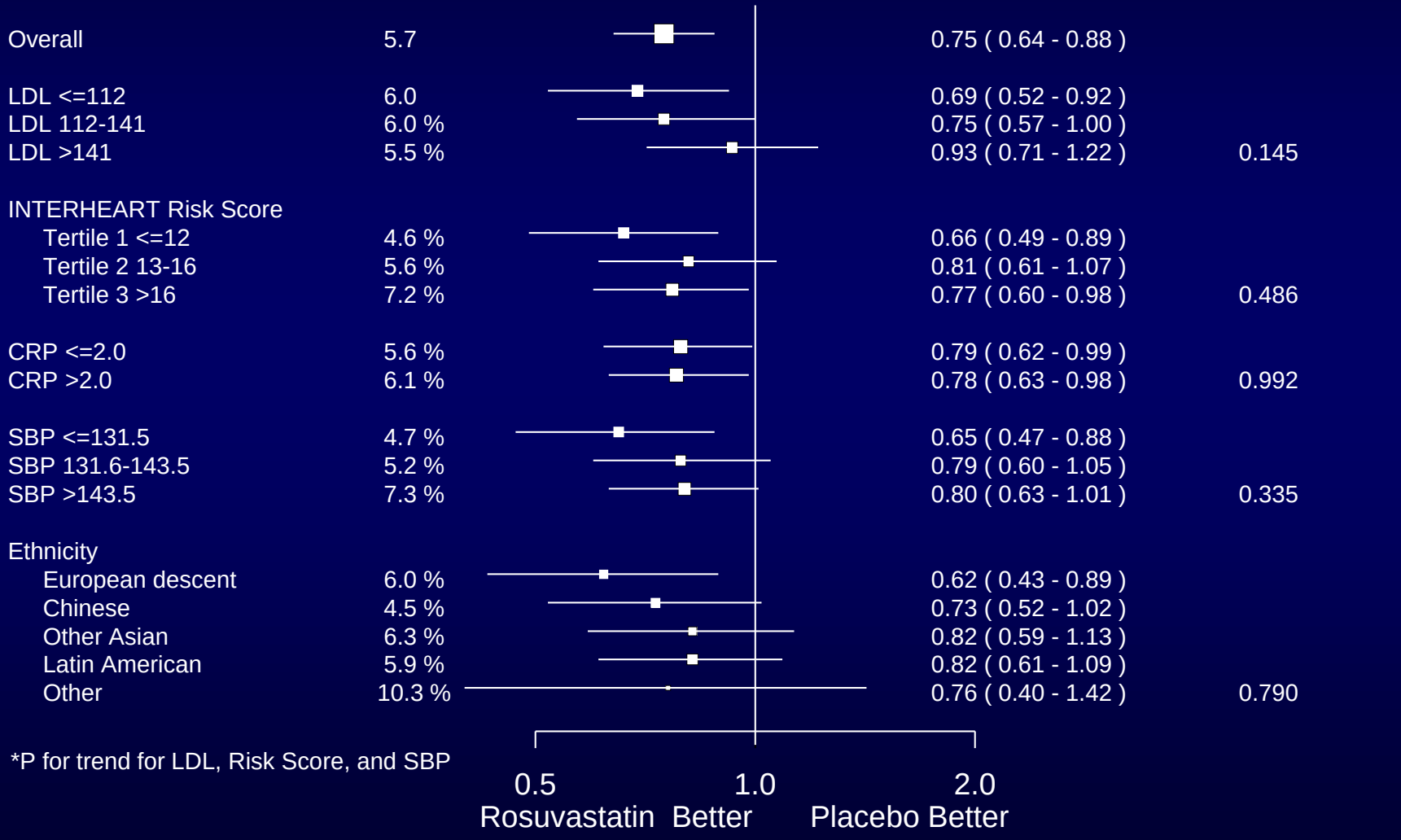


Stroke



Coronary Heart Disease: MI, coronary revascularization

Cholesterol Lowering: Subgroups Co-Primary 2



Cholesterol Lowering: Safety

	Rosuvastatin N (%)	Placebo N (%)	p
Permanent Discontinuation	1510 (23.7)	1664 (26.2)	0.001
Rhabdomyolysis/Myopathy	2 (0.1)	1 (0)	1.0
Muscle pain/ weakness	367 (5.8)	296 (4.7)	0.005
Cataract Surgery	202 (3.3)	159 (2.6)	0.02
New Diabetes	232 (3.9)	226 (3.8)	0.82

Cholesterol Lowering: Conclusions

- Rosuvastatin 10mg/day reduced:
  - LDL-C by 34.6 mg/dl (0.9 mmol/l; i.e. 26% in LDL-C)
  - ***CVD by 25%***
- Consistent benefits regardless of:
  - LDL-C
  - SBP
  - Risk
  - CRP
  - Ethnicity
- No excess in rhabdomyolysis, myopathy or diabetes; excess in muscle pain/weakness (reversible) and cataracts surgery (requires confirmation)

Combined BP & Cholesterol Lowering vs Double Placebo

Salim Yusuf

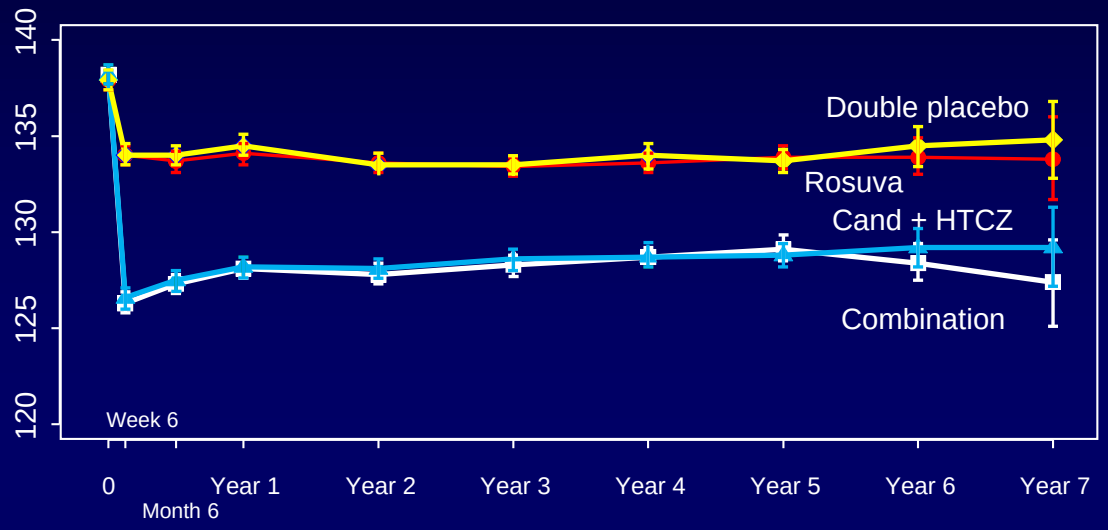
HOPE-3:
2 by 2 Factorial Design

N = 12,705

	Cand 16 mg+ HCTZ 12.5 mg n= 6,356	Placebo n = 6,349
Rosuva 10 mg n=6,361	Rosuva + Cand+HCTZ n = 3,180	Rosuva n = 3,181
Placebo n = 6,344	Cand+HCTZ n = 3,176	Double Placebo n = 3,168

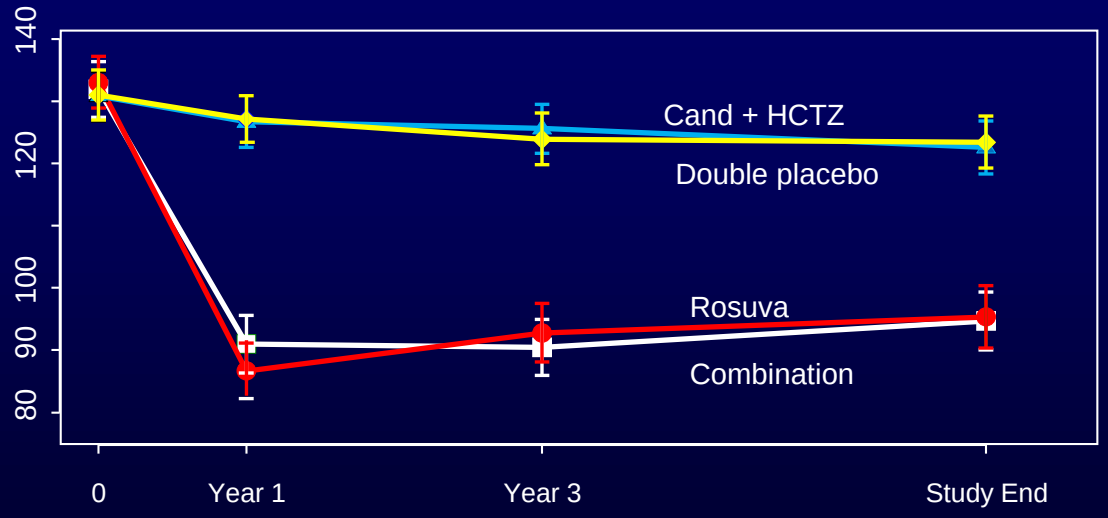
Combination vs Double Placebo: Change in SBP and LDL-C

SBP



Mean Δ 6.2 mmHg

LDL-C



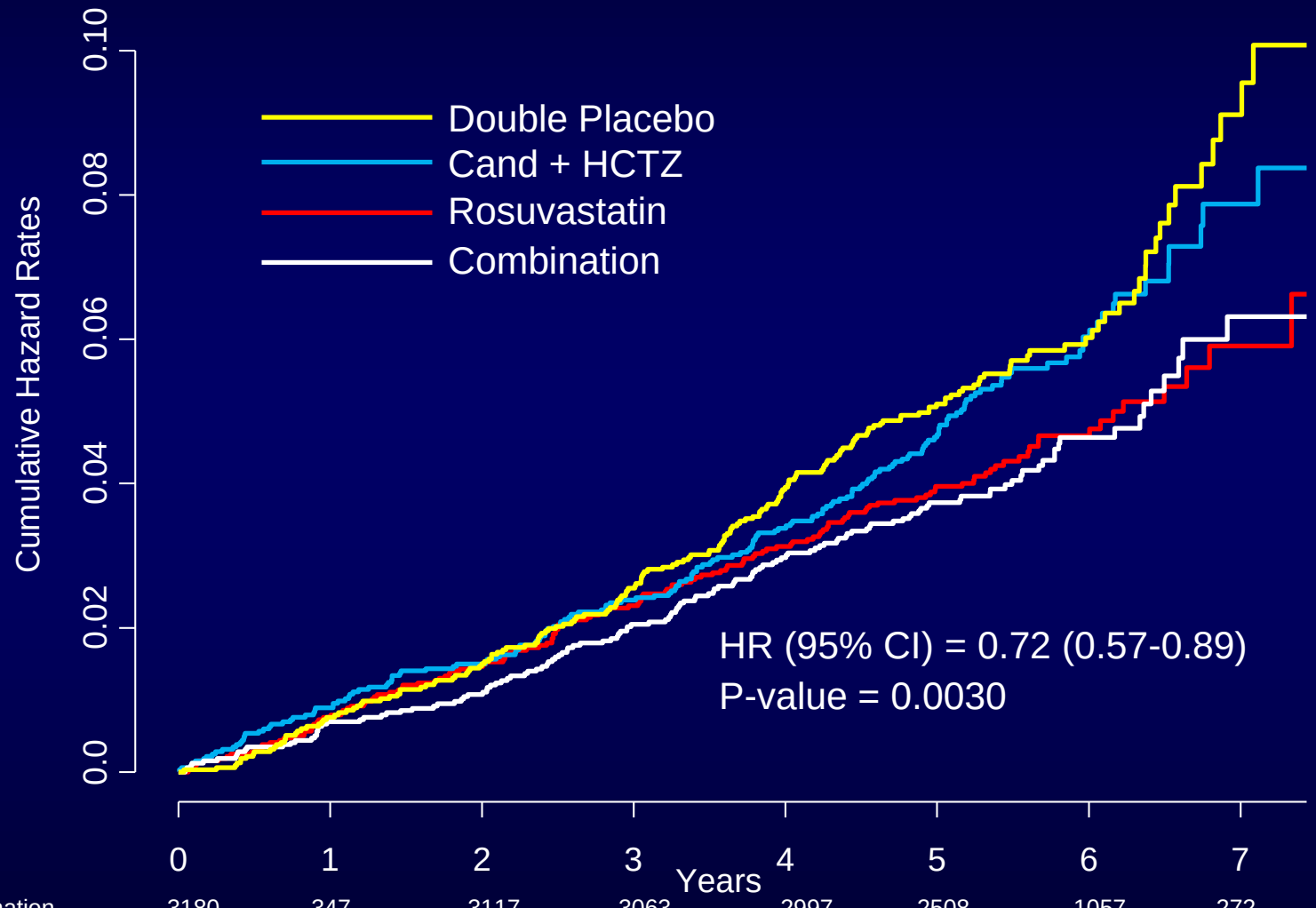
Mean Δ 33.7 mg/dl

- Double Placebo
- Rosuva.
- Cand+HCTZ
- Combination

Combination vs Double Placebo

Outcome	Double Active N=3,180 N (%)	Double Placebo N=3,168 N (%)	HR (95% CI)	p
Co-Primary 1	113 (3.6)	157 (5.0)	0.71 (0.56, 0.90)	0.0054
Co-Primary 2	136 (4.3)	187 (5.9)	0.72 (0.57, 0.89)	0.0030
Secondary 1	147 (4.6)	205 (6.5)	0.71 (0.57, 0.87)	0.0012
MI				
Stroke				
CV Deaths	75 (2.4)	91 (2.9)	0.82 (0.60-1.11)	0.19
CV Hosp	141(4.4)	191 (6.0)	0.73(0.59-0.91)	0.0046

CV Death, MI, Stroke, Cardiac Arrest, Revasc, Heart Failure



Combination	3180	347	3117	3063	2997	2508	1057	272
Rosuvastatin	3181		3108	3061	3009	2505	1045	250
Candesartan/HCTZ	3176		3083	3040	2971	2461	1019	250
Double Placebo	3168		3090	3035	2958	2465	1030	238

Hope-3

Health Through Knowledge
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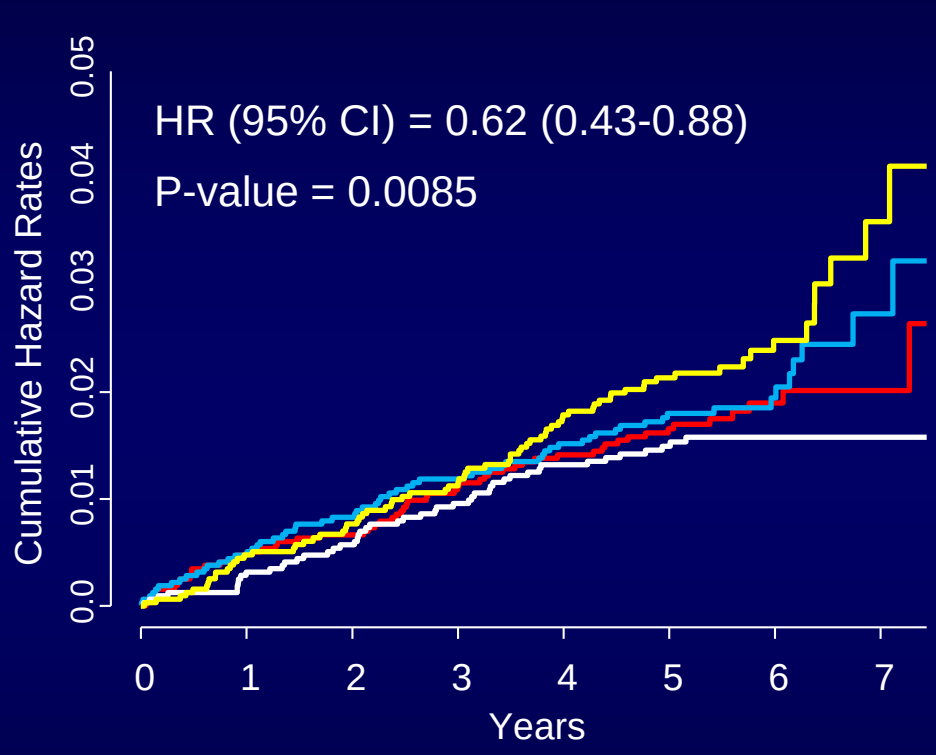
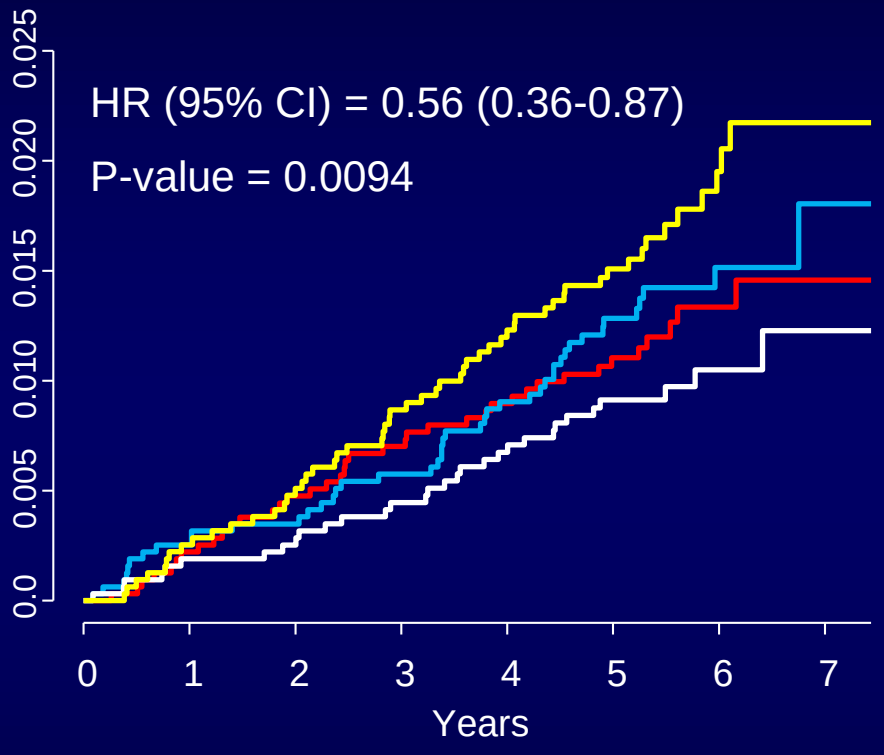
Coronary Heart Disease



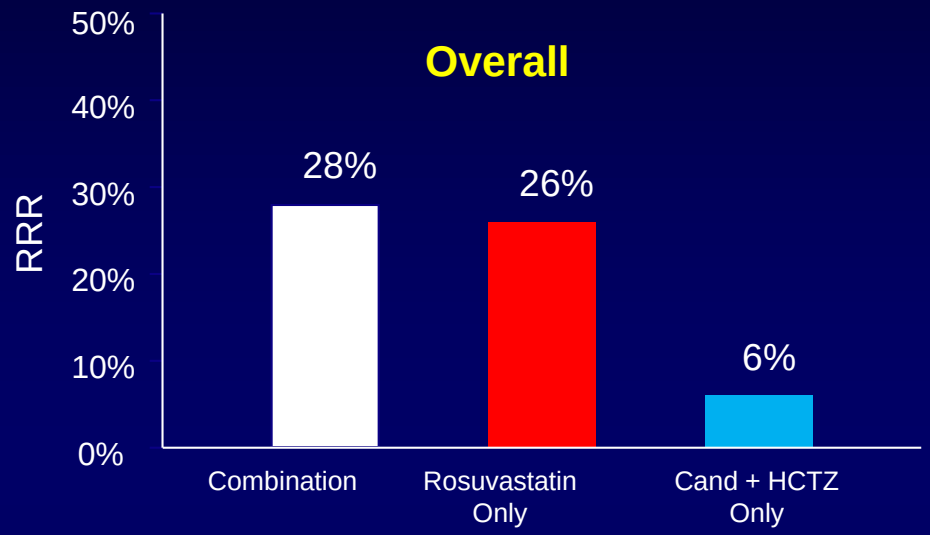
Stroke

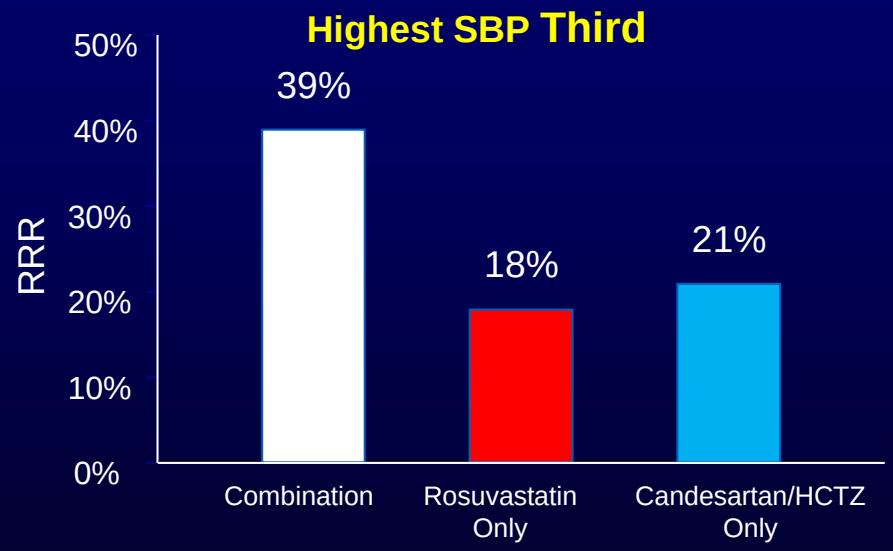


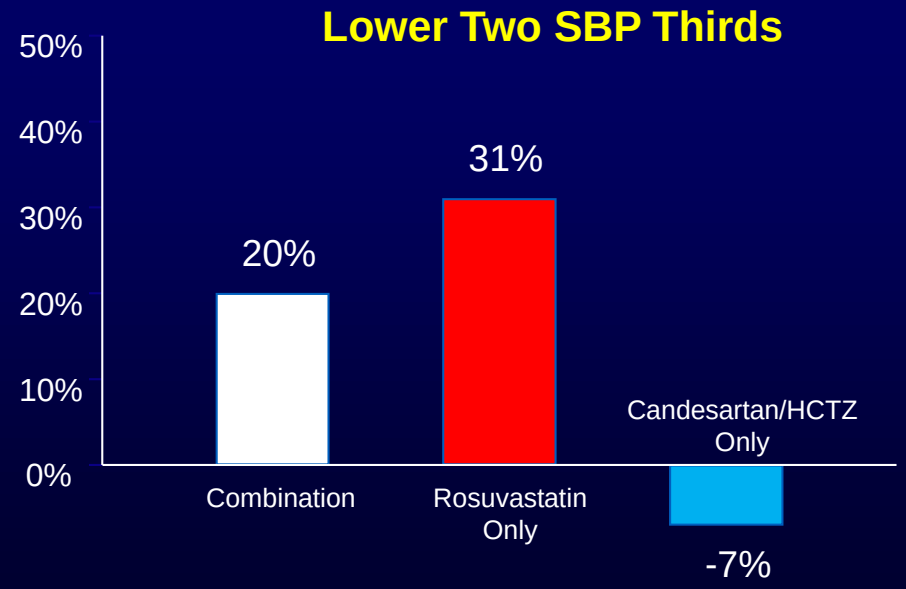
Double Placebo
Rosuvastatin only
Candesartan/HCTZ only
Combination

Coronary Heart Disease: Fatal/non-fatal MI, Coronary Revascularization

Benefits of Combination and Each Intervention vs. Double Placebo







Combination vs Double Placebo: Safety

	Combination N=3,180 N (%)	Double Placebo N=3,168 N (%)
Permanent Discontinuation of Both	697 (21.9)	757 (23.9)
Rhabdomyolysis/Myopathy of Rosuva	1 (0)	1 (0)
Muscle pain/ weakness	196 (6.2)	131 (4.1)
Lightheadedness (BP Only)	48 (1.5)	40 (1.3)
Renal Dysfunction/Potassium Abn.	6 (0.2)	6 (0.2)
New Diabetes	123 (4.1)	113 (3.8)
Cataract Surgery	84 (2.8)	88 (2.9)

Combination vs Double Placebo: Conclusions

- About a 30% reduction in major vascular events
- Benefits of combination therapy:
  - Largely seen in those in the upper third of SBP (40% RRR in CVD)
  - In lower two thirds the benefit is from rosuvastatin only (30% RRR in CVD)

Clinical Implications

- Statins beneficial in all participants
- BP lowering benefits only those with elevated BP
- Combination therapy:
  - In hypertensives, leads to a 40% risk reduction (benefits from both BP lowering and statin)
  - In others, 30% RRR from statin alone
- Pragmatic strategy without:
  - Lipid or BP criteria
  - Dose titration
  - Frequent monitoring

HOPE-3 strategy is simple, effective, safe and low cost, and is globally applicable

HOPE-3 Results

Published today in the NEJM:

- Lonn E, Bosch J, Lopez-Jaramillo P, et al., for the HOPE-3 Investigators**. Blood pressure lowering in intermediate risk people without vascular disease**. NEJM 2016.
- Yusuf, S., Bosch, J., Dagenais, G., et al. for the HOPE-3 Investigators. **Rosuvastatin in intermediate-risk people without cardiovascular disease.** NEJM 2016.
- Yusuf, S., Lonn, E., Pais, P. et al. for the HOPE-3 Investigators. **Blood pressure and cholesterol lowering in people without cardiovascular disease**. NEJM 2016.

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