Cholesterolverlaging voor iedere hypertensie patient?

Amersfoort, 3 februari 2017

F.L.J. Visseren

Universitair Medisch Centrum
Utrecht

Vascular Medicine Utrecht

Cholesterolverlaging voor iedere hypertensie patient?

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Tuurlijk!!

Cholesterolverlaging voor iedere hypertensie patient?

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De hypertensie patient bestaat niet!

Vaatrisico bij patienten met hoge bloeddruk?

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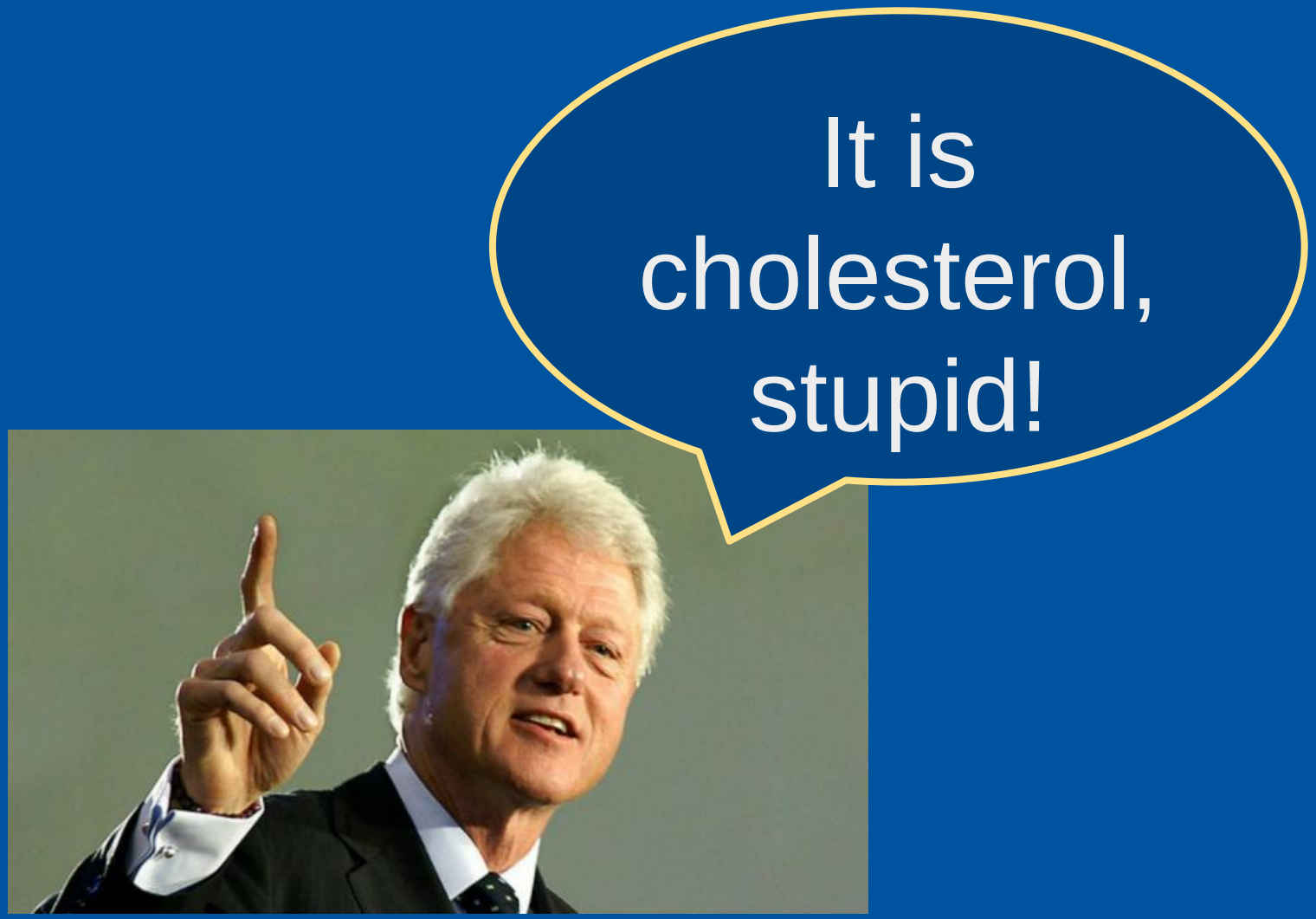

Vraag 1

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Zijn hypertensie en hypercholesterolemie los van elkaar, en eventueel additief, en in elkaars aanwezigheid, risicofactoren voor hart- en vaatziekten?

European Heart Journal (2016) **37**, 2315–2381
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

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2016 European Guidelines on cardiovascular disease prevention in clinical practice

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)

Authors/Task Force Members: Massimo F. Piepoli* (Chairperson) (Italy), Arno W. Hoes* (Co-Chairperson) (The Netherlands), Stefan Agewall (Norway)[1], Christian Albus (Germany)[9], Carlos Brotons (Spain)[10], Alberico L. Catapano (Italy)[3], Marie-Therese Cooney (Ireland)[1], Ugo Corrà (Italy)[1], Bernard Cosyns (Belgium)[1], Christi Deaton (UK)[1], Ian Graham (Ireland)[1], Michael Stephen Hall (UK)[7], F. D. Richard Hobbs (UK)[10], Maja-Lisa Løchen (Norway)[1], Herbert Löllgen (Germany)[8], Pedro Marques-Vidal (Switzerland)[1], Joep Perk (Sweden)[1], Eva Prescott (Denmark)[1], Josep Redon (Spain)[5], Dimitrios J. Richter (Greece)[1], Naveed Sattar (UK)[2], Yvo Smulders (The Netherlands)[1], Monica Tiberi (Italy)[1], H. Bart van der Worp (The Netherlands)[6], Ineke van Dis (The Netherlands)[4], W. M. Monique Verschuren (The Netherlands)[1]

Eur Heart J 2016;37:2315-2381

ESC guidelines on cardiovascular disease prevention: *risk stratification*

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Very high-risk	Subjects with any of the following: • Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE >10%.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10%.
Moderate-risk	SCORE is ≥1% and <5% at 10 years. Many middleaged subjects belong to this category.
Low-risk	SCORE <1%.

Eur Heart J 2016;37:2315-2381

ESC guidelines on cardiovascular disease prevention: *LDL-c treatment goals*

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Recommendations	Class	Level
In patients at VERY HIGH CV risk, an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
In subjects at LOW or MODERATE risk an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C

Eur Heart J 2016;37:2315-2381

ESC guidelines on cardiovascular disease prevention: *lipid-lowering therapy*

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Recommendations	Class	Level
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C

Eur Heart J 2016;37:2315-2381

Risico schatten bij patienten met hart- en vaatziekten ('vaatrisico')

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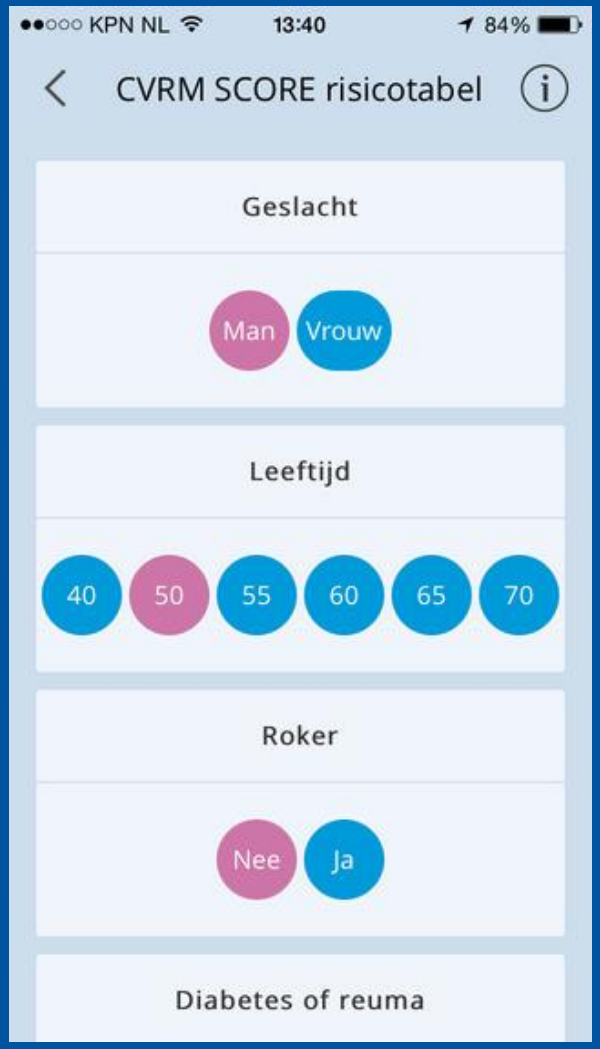

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A Naturally Randomized Trial Comparing the Effect of Long-Term Exposure to Lower LDL-C, Lower SBP, or Both on the Risk of Cardiovascular Disease

Brian A Ference, Thatcher B Ference, Robert D Brook, Alberico L Catapano, Christian T Ruff, David R Neff, George Davey Smith, Kausik K Ray, Marc S Sabatine

From the Division of Cardiovascular Medicine, Wayne State University School of Medicine, Detroit (B.A.F.; T.B.F.); Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor (R.D.B.); Department of Pharmacological and Biomolecular Sciences, University of Milan and Multimedica IRCCS, Milano Italy (A.L.C.); Michigan State University, East Lansing (D.R.N.); MRC Integrative Epidemiology Unit (IEU), University of Bristol, Bristol U.K. (G.D.S.); Department of Primary Care and Public Health, School of Public Health, Imperial College London, London UK (K.K.R.); and the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston (C.T.R, M.S.S.)

Division of Translational Research and Clinical Epidemiology (TRaCE)
Division of Cardiovascular Medicine
Wayne State University School of Medicine

Study Population and Exposures

- Study sample: 102,773 persons (age 27 - 100 years)
  - enrolled in one of 14 prospective cohort or case-control studies
- LDL-C genetic score: 46 polymorphisms associated primarily with lower LDL-C at genome-wide level of significance
- SBP genetic score: 33 polymorphisms associated with lower SBP at genome-wide level of significance
- Genetic scores used as both the instrument of randomization and the instrument of exposure

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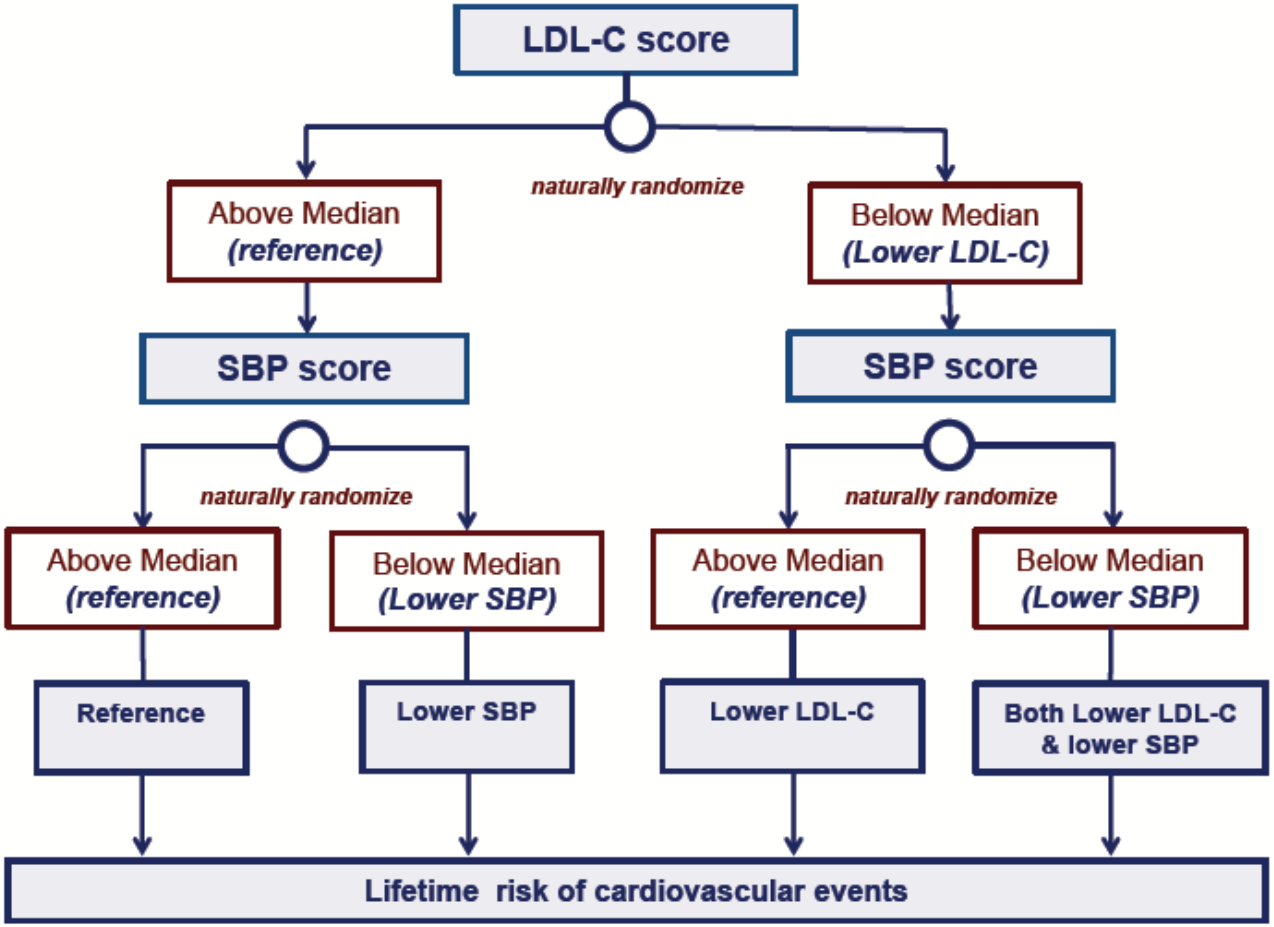
Study Design: 2x2 factorial Mendelian randomization



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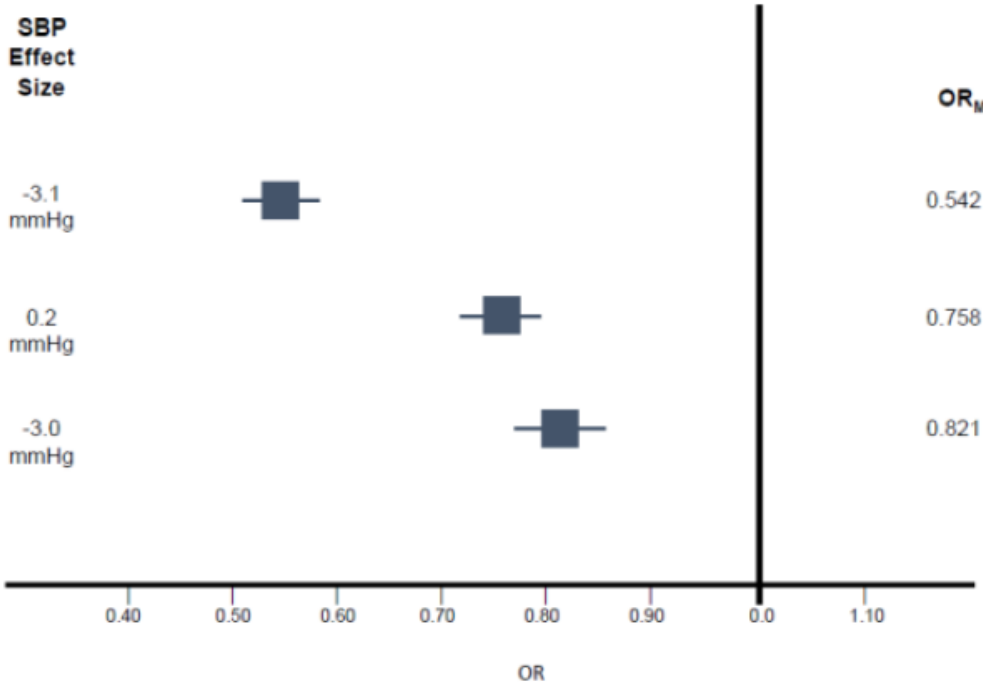
Baseline Characteristics

Characteristic	Reference Group	LDL-C score below median	SBP score below median	Both LDL-C & SBP scores below median	p-value
Sample size (n)	25,795	25,283	26,106	25,589	
Genetic score related lipid and blood pressure baseline characteristics					
LDL-C, mg/dl (SD)	134.4 (31.8)	122.3 (33.1)	134.7 (32.7)	122.2 (32.3)	4.3×10^{-67}
HDL-C, mg/dl (SD)	51.5 (14.7)	53.8 (14.8)	51.2 (14.2)	53.4 (15.1)	7.2×10^{-6}
Non-HDL-C, mg/dl (SD)	162.0 (36.8)	148.5 (35.1)	162.3 (37.7)	148.3 (36.3)	2.1×10^{-74}
SBP, mmHg (SD)	128.1 (15.7)	128.3 (17.1)	125.1 (16.5)	125.0 (16.9)	6.3×10^{-23}
DBP, mmHg (SD)	74.8 (10.2)	74.9 (11.3)	73.3 (10.9)	73.4 (11.3)	4.9×10^{-12}
Non-Lipid and non-blood pressure related baseline characteristics					
Age (SD)	60.1 (6.8)	60.5 (6.3)	61.2 (5.9)	60.9 (6.2)	0.32
Women (%)	57.9	58.1	57.6	57.2	0.53
Weight, lbs (SD)	168.5 (36.5)	169.2 (37.1)	169.5 (36.2)	168.7 (35.4)	0.48
BMI (SD)	27.5 (5.3)	27.9 (5.6)	27.7 (5.7)	27.1 (5.1)	0.18
Ever Smoker (%)	54.1	54.5	53.9	54.6	0.61

Combined Effect of LDL-C & SBP on Cardiovascular Events

N = 14,368 Major Vascular Events

SBP Genetic Score	LDL-C Effect Size	SBP Effect Size	OR_{MVE} (95%CI)	
Both LDL-C and SBP scores below median	-12.2 mg/dL	-3.1 mmHg	0.542 (0.509-0.577)	$P = 9.6 \times 10^{-83}$
LDL-C score below median	-12.1 mg/dl	0.2 mmHg	0.758 (0.715-0.804)	$P_{(diff)} = 1.4 \times 10^{-14}$
SBP score below median	0.3 mg/dL	-3.0 mmHg	0.821 (0.779-0.865)	$P_{(diff)} = 1.8 \times 10^{-23}$



Conclusions

- LDL-C and SBP have independent, multiplicative and cumulative causal effects on the risk of cardiovascular events
- Because their effects are multiplicative and cumulative over time, long-term exposure to combination of modestly lower LDL-C and SBP has the potential to dramatically reduce the lifetime risk of cardiovascular disease
  - *Even among persons with apparently normal cholesterol and blood pressure*
- Cardiovascular events are largely preventable and the prevention of cardiovascular disease can be substantially improved and simplified by designing prevention programs that promote long-term exposure to combination of lower LDL-C and lower SBP beginning in early adulthood

Vraag 2

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Leidt verlaging van de bloeddruk en cholesterol tot meer risicoreductie dan behandeling van 1 van beide?

HOPE-3

University Medical Center Utrecht

ORIGINAL ARTICLE

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

Salim Yusuf, M.B., B.S., D.Phil., Eva Lonn, M.D., Prem Pais, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Denis Xavier, M.D., Alvaro Avezum, M.D., Ph.D., Lawrence A. Leiter, M.D., Leopoldo S. Piegas, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Karen Sliwa, 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., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Jose L. Accini, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Hyejung Jung, M.Sc., Lisheng Liu, M.D., Rafael Diaz, M.D., Antonio Dans, M.D., and Gilles Dagenais, M.D., for the HOPE-3 Investigators†

HOPE-3: Intermediate-risk population

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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-C
- 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

NEJM 2016:374:2032-2043

HOPE-3: 2 x 2 Factorial design

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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

NEJM 2016:374:2032-2043

HOPE-3: baseline characteristics

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N=12,705

Age (yrs)	66
Female	46%
Blood Pressure (mmHg)	138/82
LDL-Cholesterol (mg/dL)	128
LDL-Cholesterol (mmol/L)	3.3
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%

NEJM 2016:374:2032-2043

HOPE-3: cholesterol lowering arm

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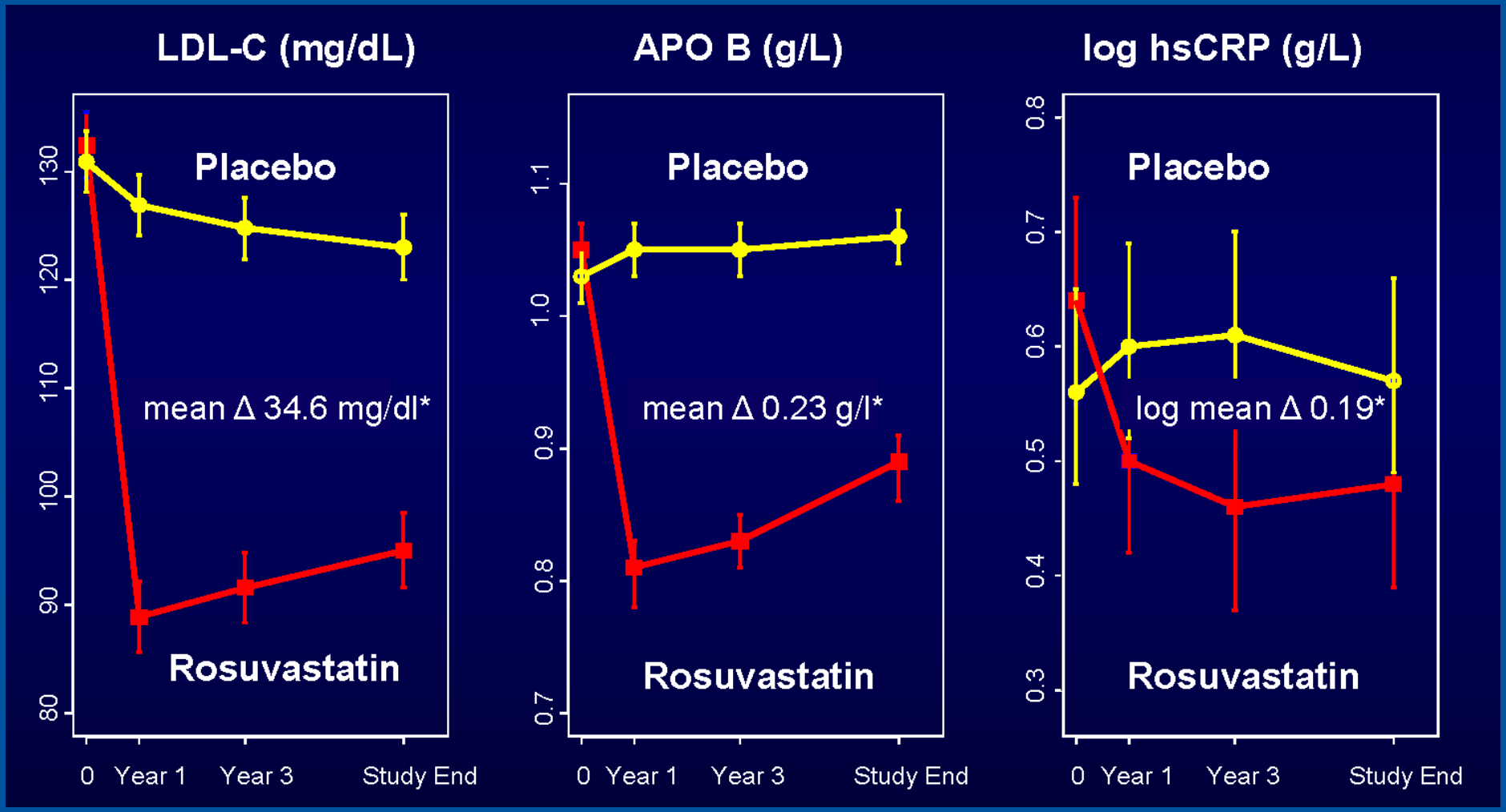

NEJM 2016:374:2021-2031

HOPE-3: cholesterol lowering Outcomes

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Outcome	Rosuvastatin N (%)	Placebo N (%)	HR (95% CI)	p
Co-Primary 1	235 (3.7)	304 (4.8)	0.76 (0.64-0.91)	0.002
Co-Primary 2	277 (4.4)	363 (5.7)	0.75 (0.64-0.88)	0.0004
Secondary 1	306(4.8)	393 (6.2)	0.77 (0.66-0.89)	0.0006
CV Death	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)	0.02
Stroke	70 (1.1)	99 (1.6)	0.70 (0.52-0.95)	0.02
CV Hosp.	281 (4.4)	369 (5.8)	0.75 (0.64-0.88)	0.0003

NEJM 2016:374:2021-2031

HOPE-3: CV death, MI, stroke, cardiac arrest, revasc, heart failure

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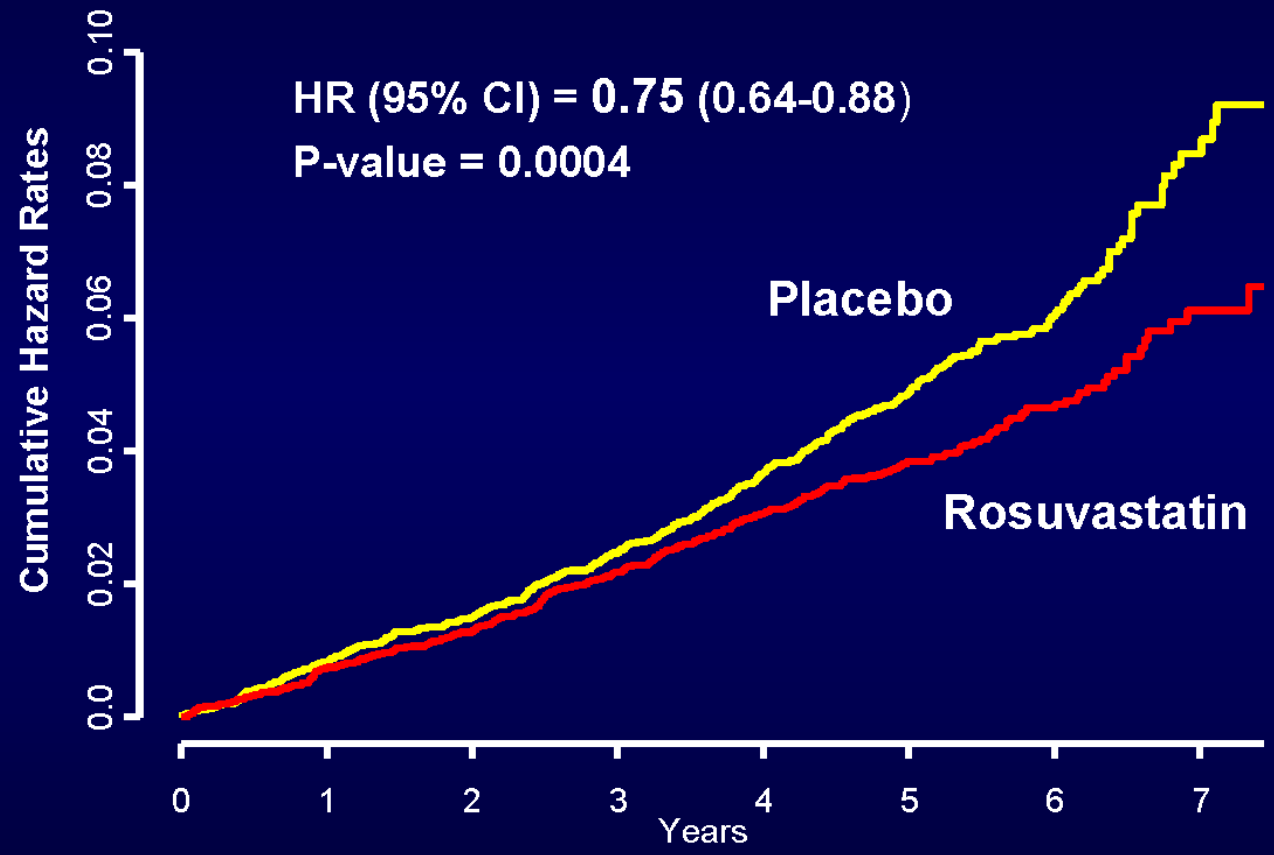

Rosuva	6361	6241	6039	2122
Placebo	6344	6192	5970	2073

NEJM 2016:374:2021-2031

HOPE-3: cholesterol lowering in subgroups

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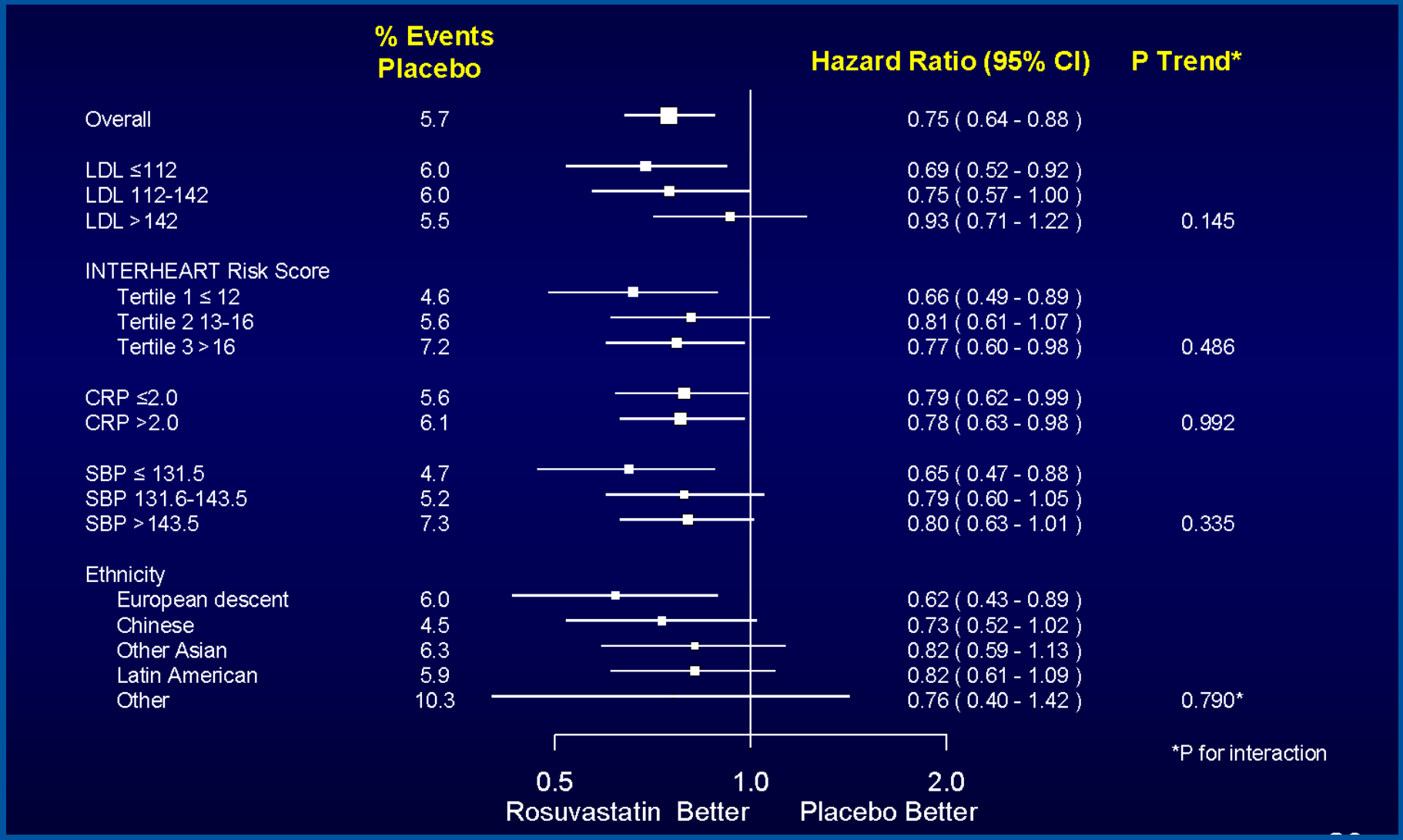

NEJM 2016:374:2021-2031

HOPE-3 & other studies of LDL-c lowering and CVD

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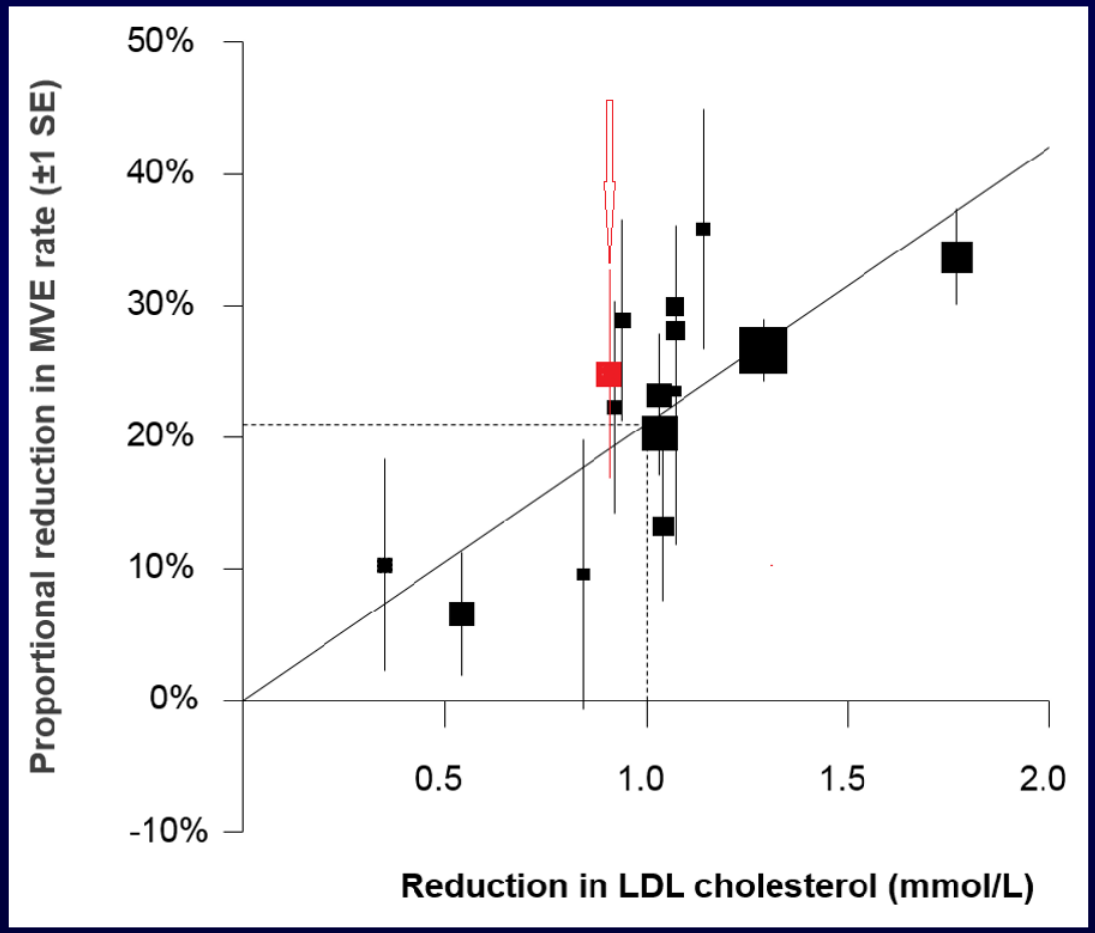

NEJM 2016:374:2021-2031

HOPE-3: BP Lowering vs. Placebo: SBP changes

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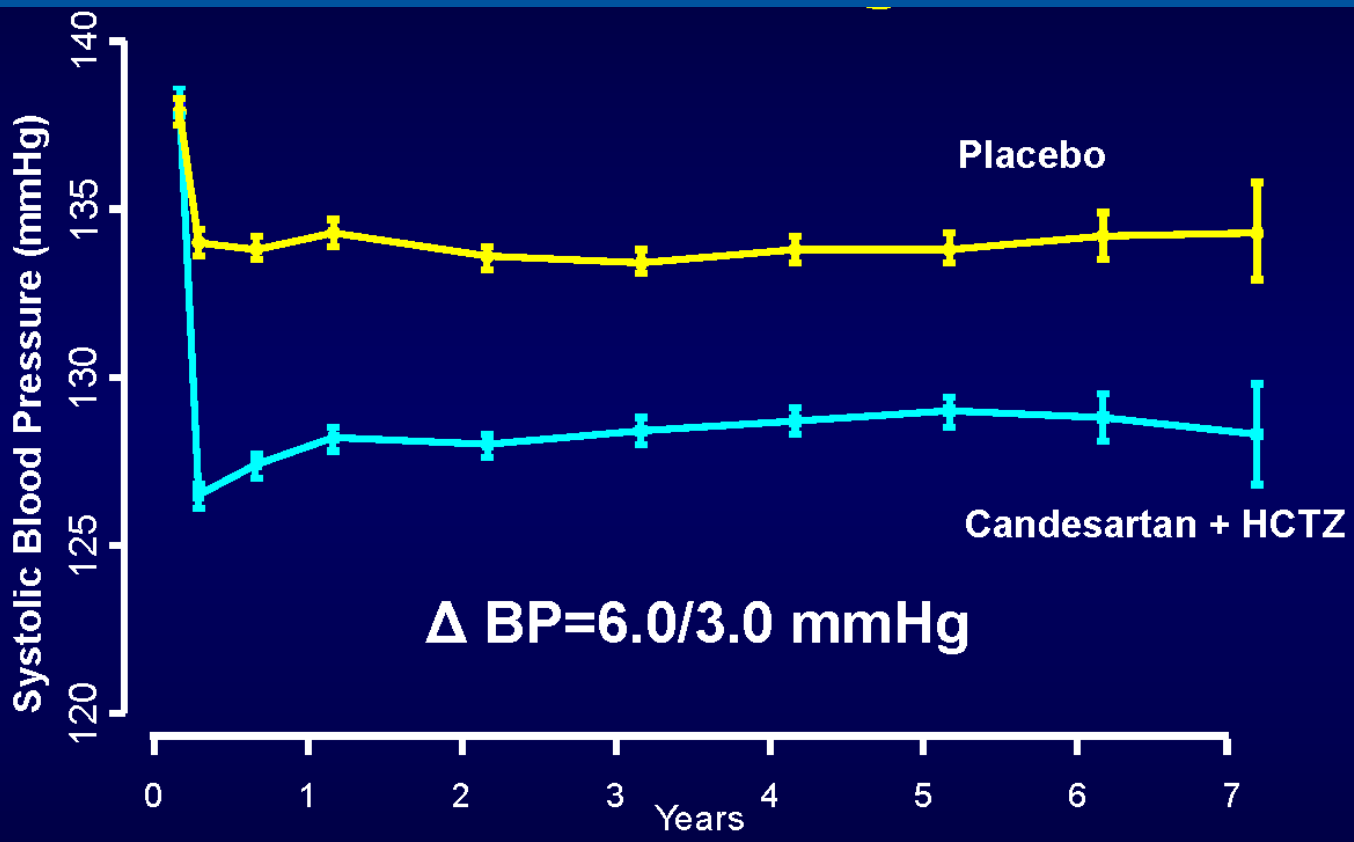

Cand/HCTZ	6356	5907	5667	5446	5213	3862	1437	350
Placebo	6347	5879	5623	5442	5186	3822	1424	334

NEJM 2016:374:2009-2020

HOPE-3: BP Lowering vs. Placebo

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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 Death	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

NEJM 2016:374:2009-2020

HOPE-3: CV Death, MI, Strok, Cardiac Arrest, revascularization, Heart Failure

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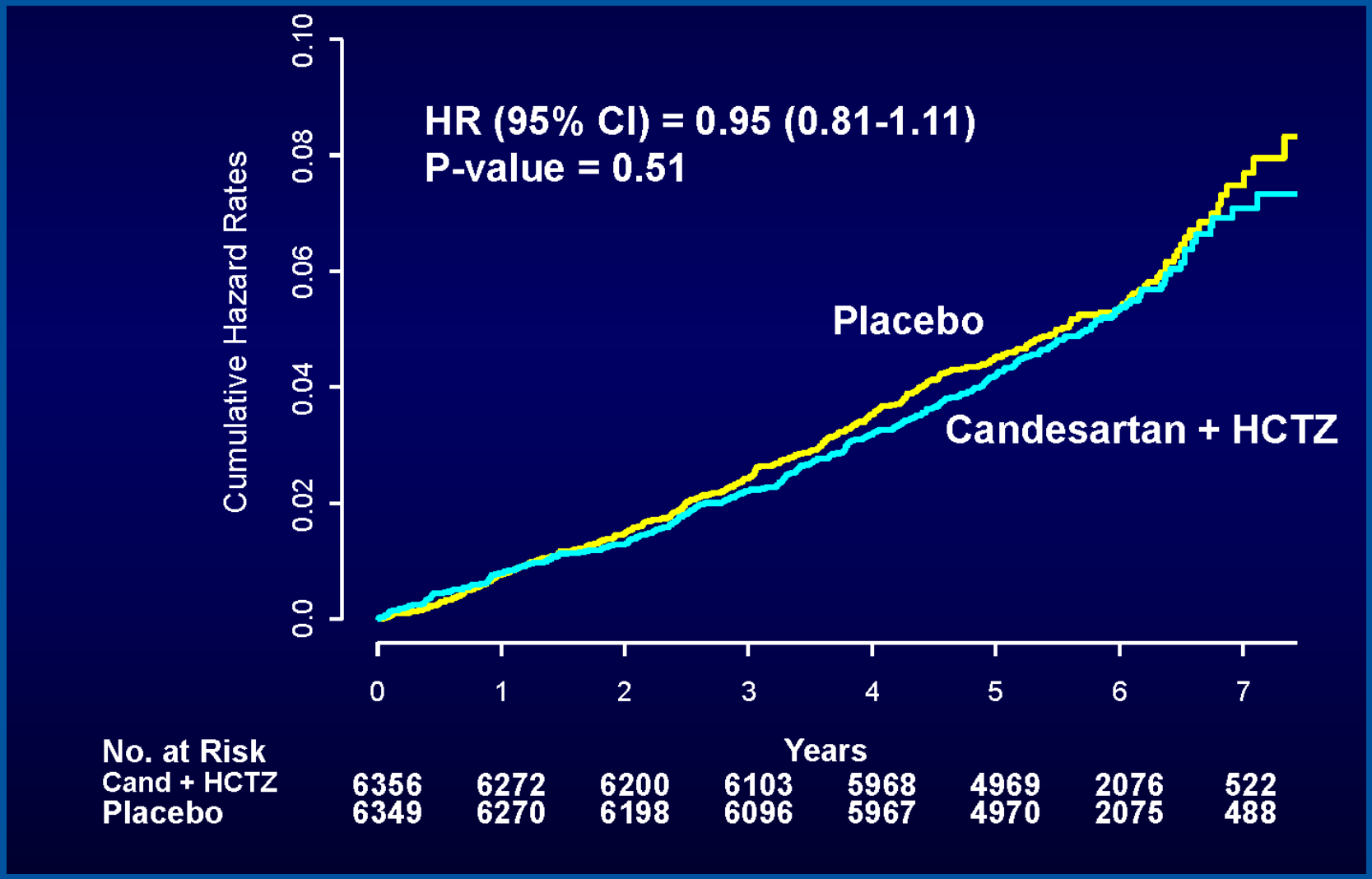

NEJM 2016:374:2009-2020

HOPE-3: Prespecified Subgroups: by thirds of SBP

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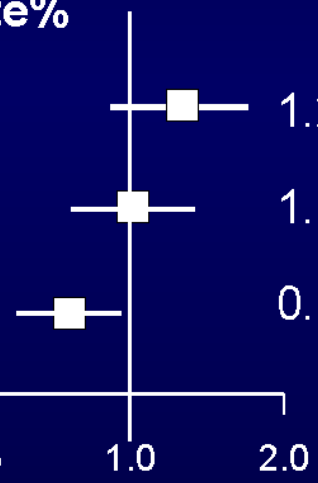
CV Death, MI, Stroke, Cardiac Arrest, Revasc, HF

SBP (mmHg) Cutoffs	Mean	Diff	Placebo Event Rate%	HR (95% CI)	P Trend
≤131.5	122	6.1	3.5	1.25 (0.92-1.70)	0.009
131.6-143.5	138	5.6	4.6	1.02 (0.77-1.34)	
>143.5	154	5.8	7.5	0.76 (0.60-0.96)	



Candesartan + HCTZ Better Placebo Better

NEJM 2016:374:2009-2020

HOPE-3

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N = 6,348

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

NEJM 2016:374:2032-2043

HOPE-3: combination vs double placebo

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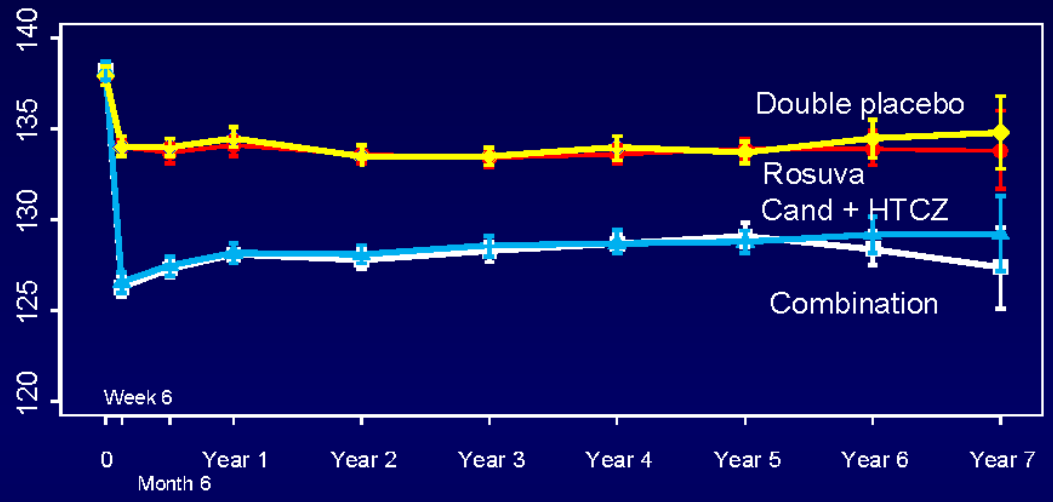
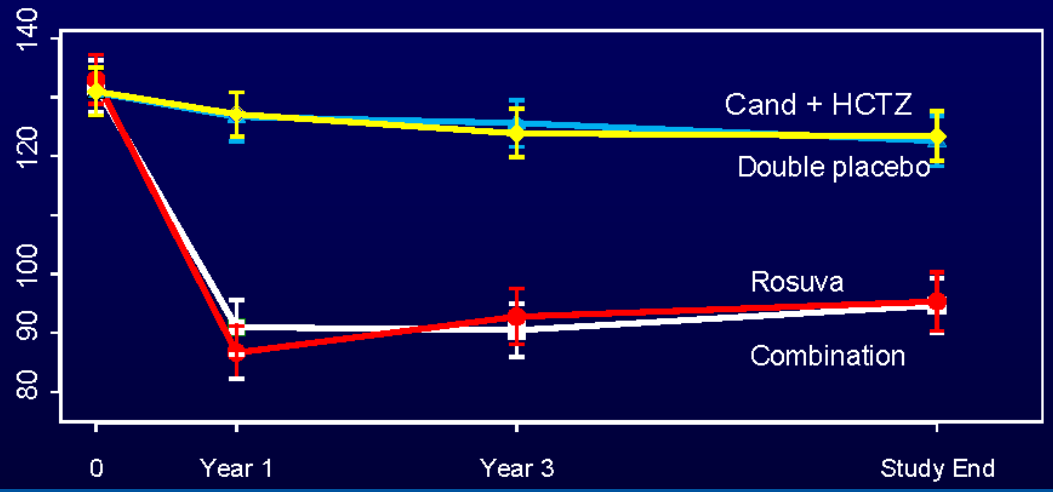
SBP



Mean Δ 6.2 mmHg

LDL-C



Mean Δ 33.7 mg/dl

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

NEJM 2016:374:2032-2043

HOPE-3: combination vs double placebo

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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
CV Death	75 (2.4)	91 (2.9)	0.82 (0.60-1.11)	0.19
MI	21 (0.7)	38 (1.2)	0.55 (0.32-0.93)	0.026
Stroke	31 (1.0)	55 (1.7)	0.56 (0.36-0.87)	0.009
CV Hosp	141(4.4)	191 (6.0)	0.73 (0.59-0.91)	0.0046

NEJM 2016:374:2032-2043

HOPE-3: CV death, MI, stroke, cardiac arrest, revasc, heart failure

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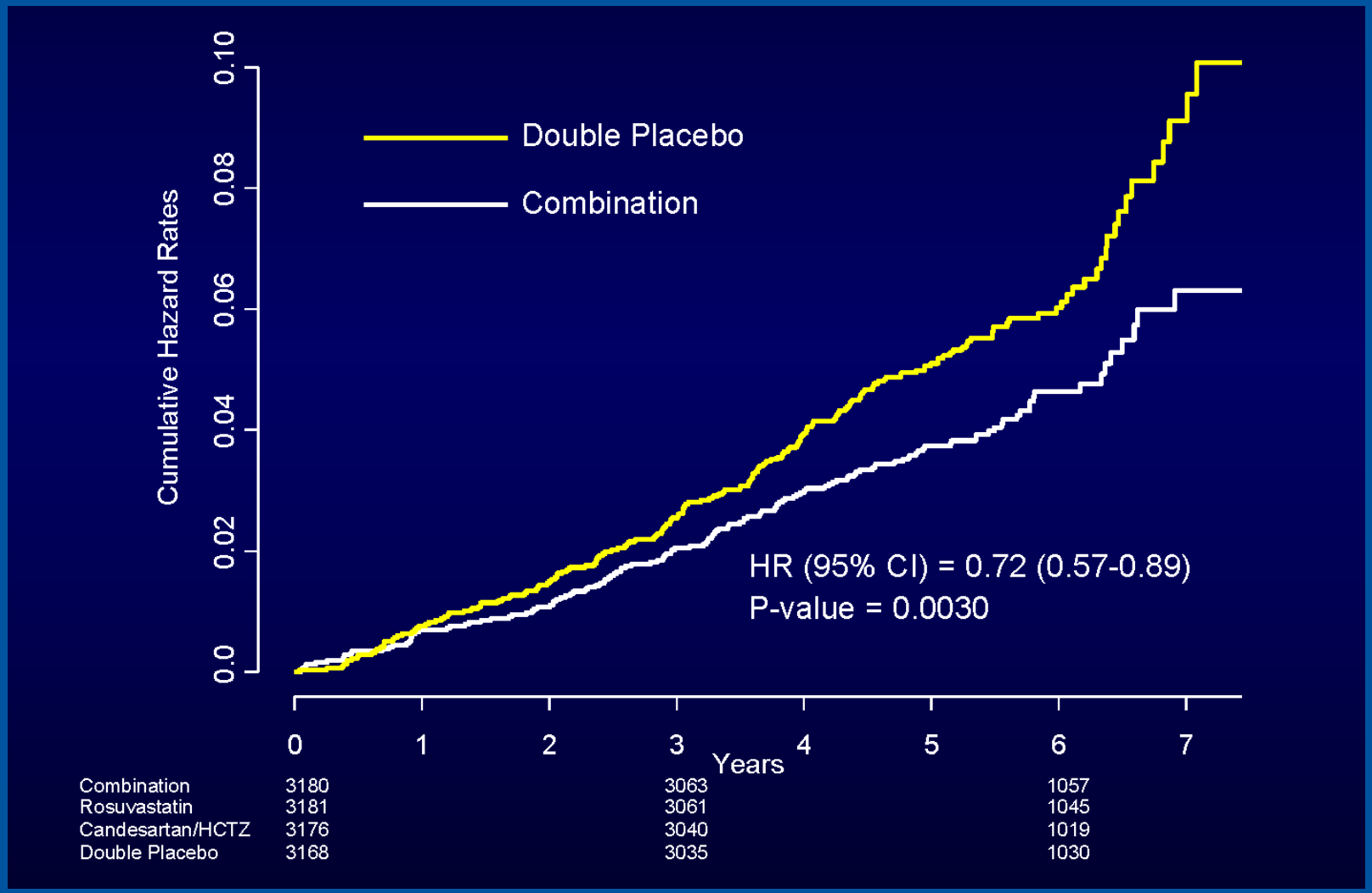

NEJM 2016:374:2032-2043

HOPE-3

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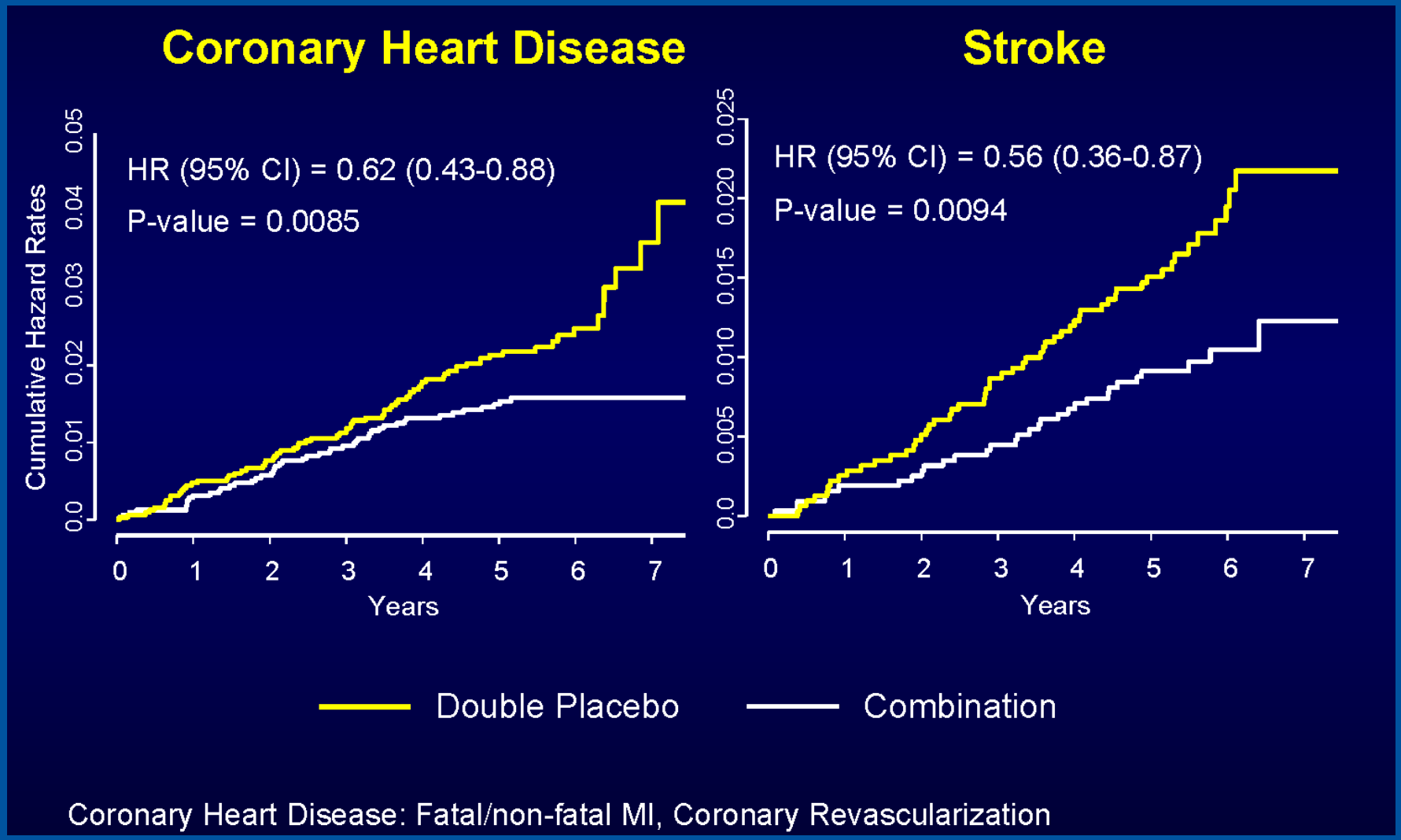

NEJM 2016:374:2032-2043

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ORIGINAL ARTICLE

A Highly Durable RNAi Therapeutic Inhibitor of PCSK9

Kevin Fitzgerald, Ph.D., Suellen White, B.S.N., Anna Borodovsky, Ph.D., Brian R. Bettencourt, Ph.D., Andrew Strahs, Ph.D., Valerie Clausen, Ph.D., Peter Wijngaard, Ph.D., Jay D. Horton, M.D., Jorg Taubel, M.D., Ashley Brooks, M.B., Ch.B., Chamikara Fernando, M.B., B.S., Robert S. Kauffman, M.D., Ph.D., David Kallend, M.D., Akshay Vaishnaw, M.D., and Amy Simon, M.D.

NEJM 2017;376:41-51.

PCSK9 inhibition by RNAi

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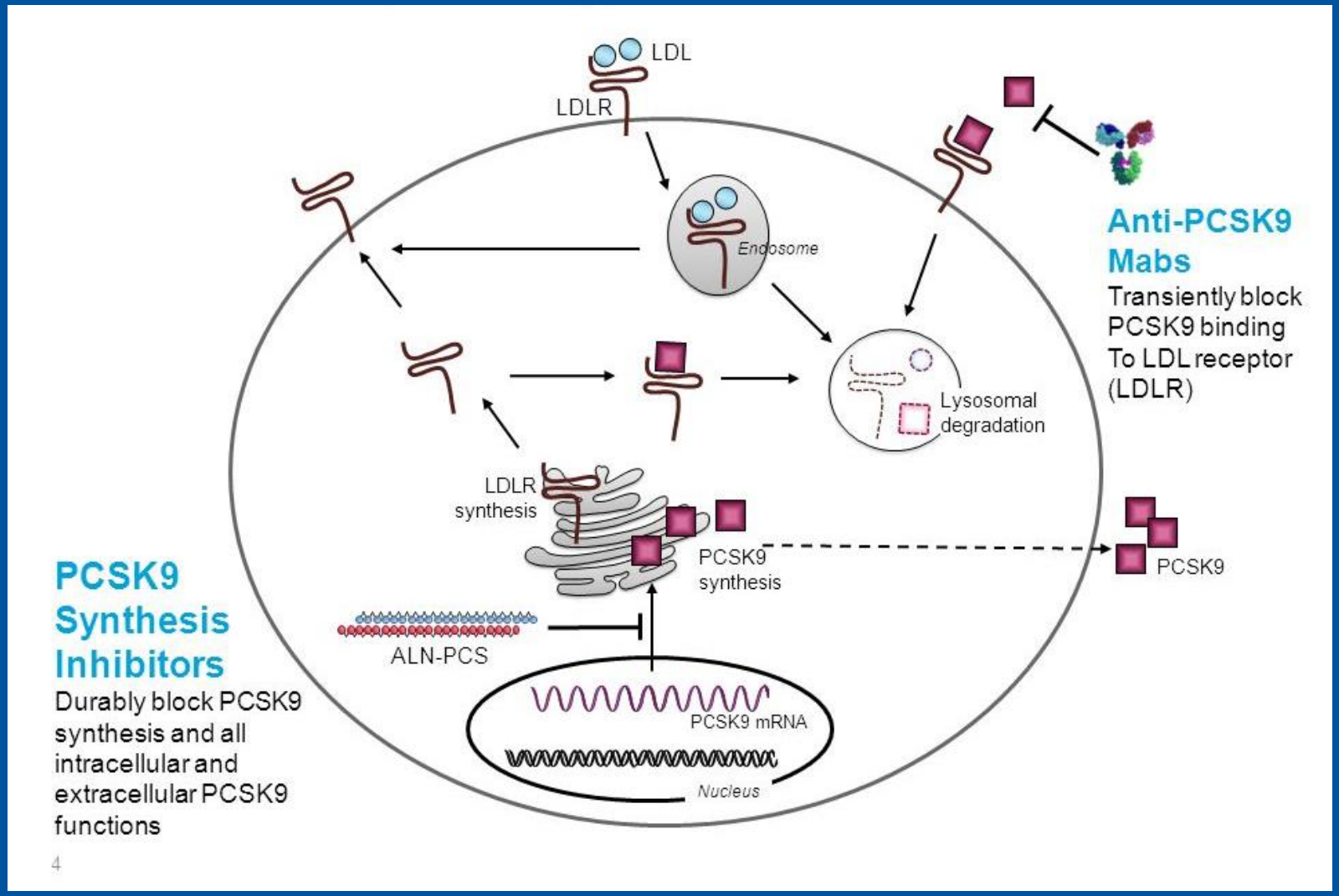

NEJM 2017;376:41-51.

PCSK9 inhibition by RNAi

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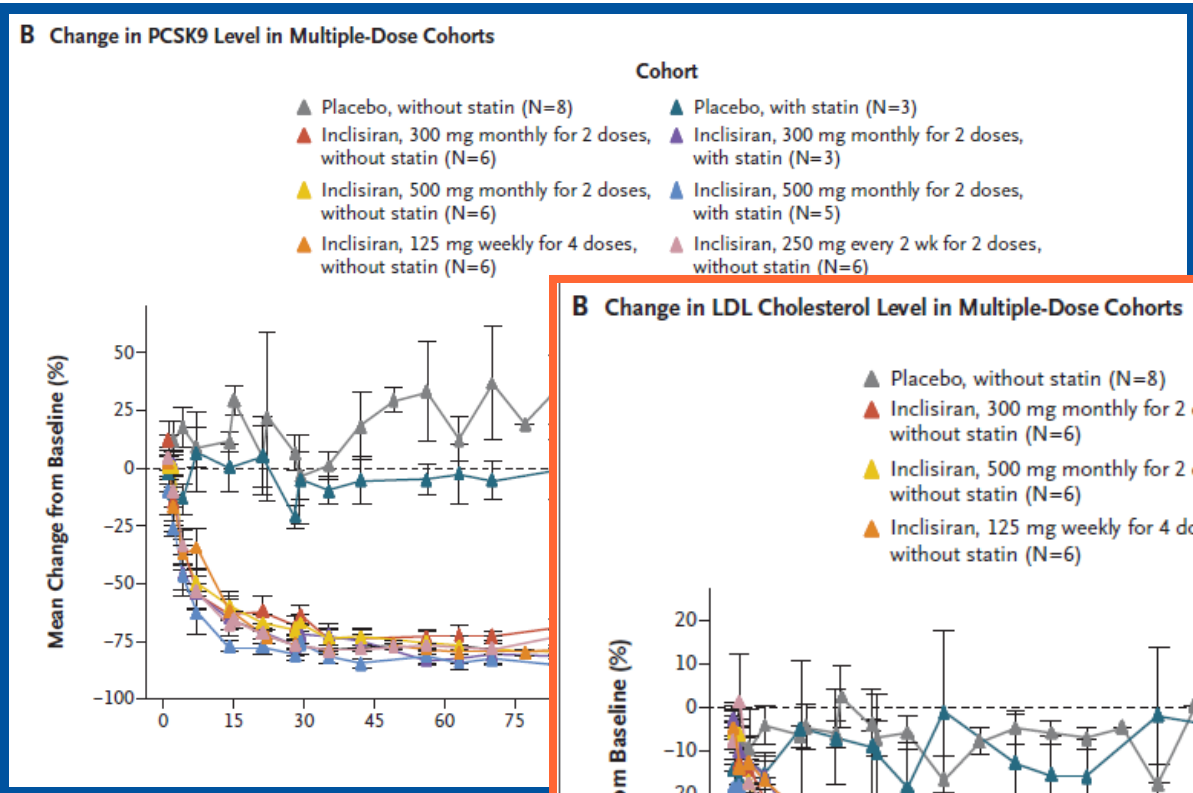

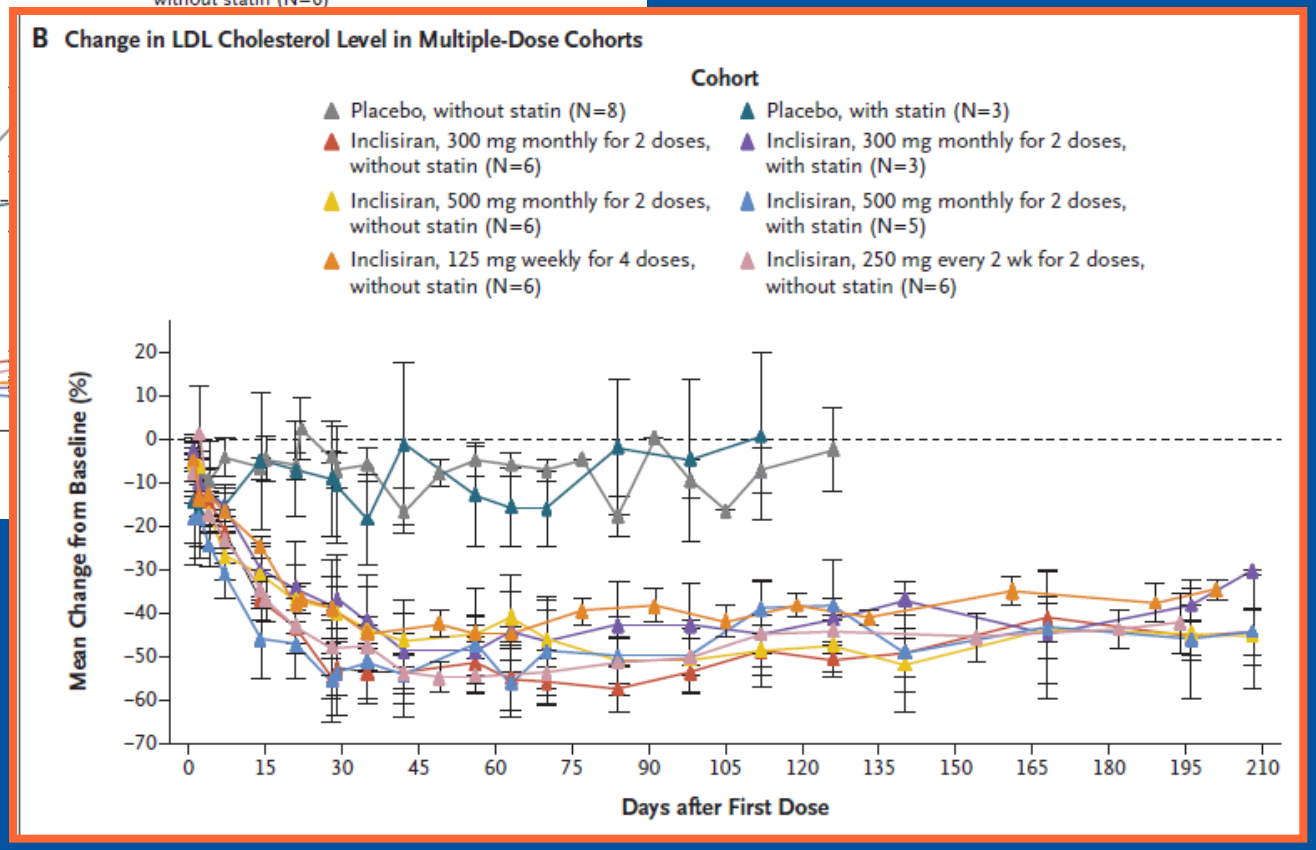

NEJM 2017;376:41-51.

Conclusies

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Bloeddruk en LDL-c zijn onafhankelijke risicofactoren (ook in elkaars aanwezigheid)

LDL-c behandeling bij patienten met hypertensie levert (additionele) risicoreductie op

ESC risicostratificatie tabel voor bepalen van LDL-c streefwaarde, ook bij patienten met hypertensie

2017 wordt een spannend lipiden-jaar (ook voor patienten met hypertensie)!

Vascular Medicine Utrecht

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