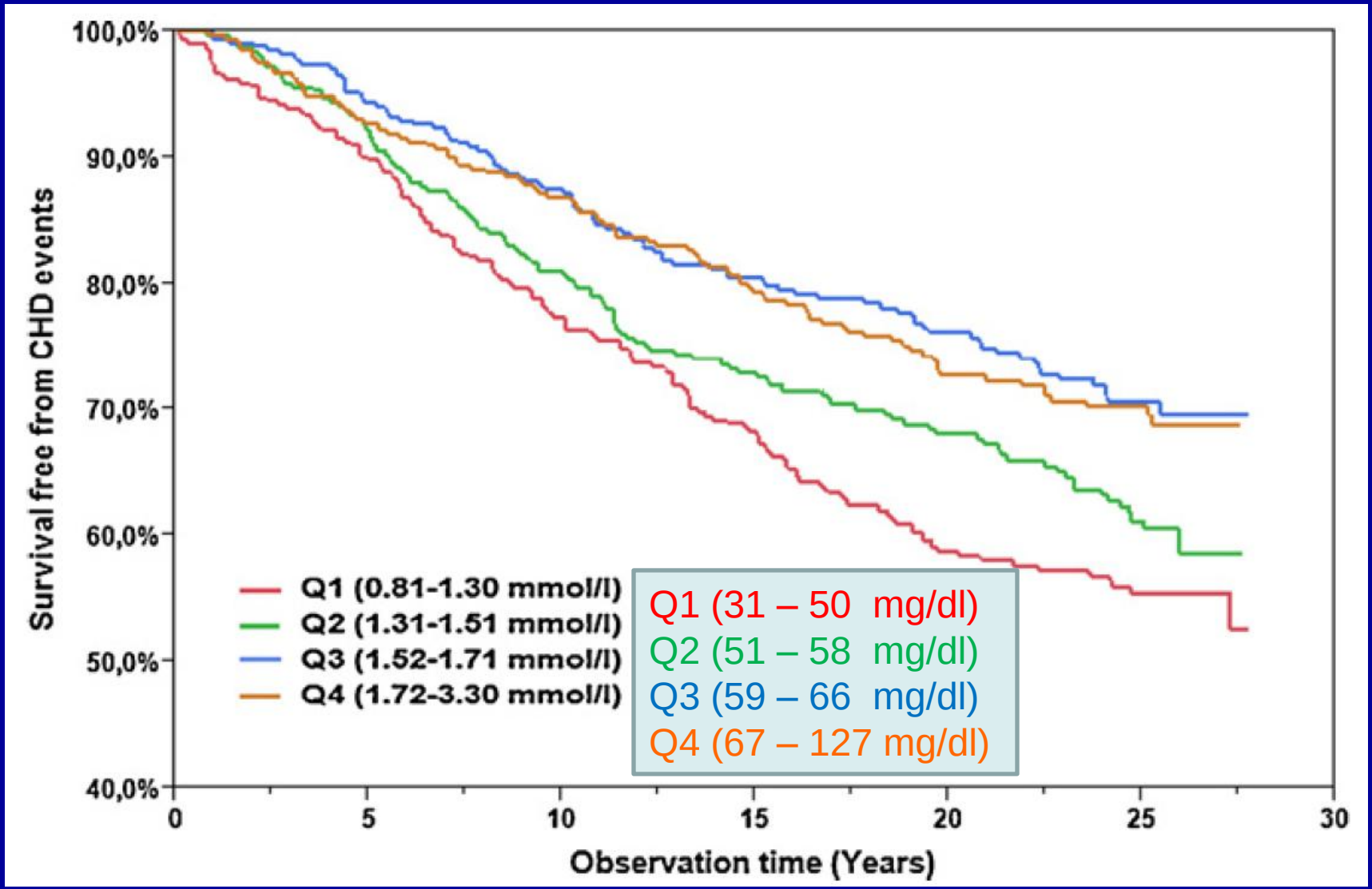
Raising HDL: an update

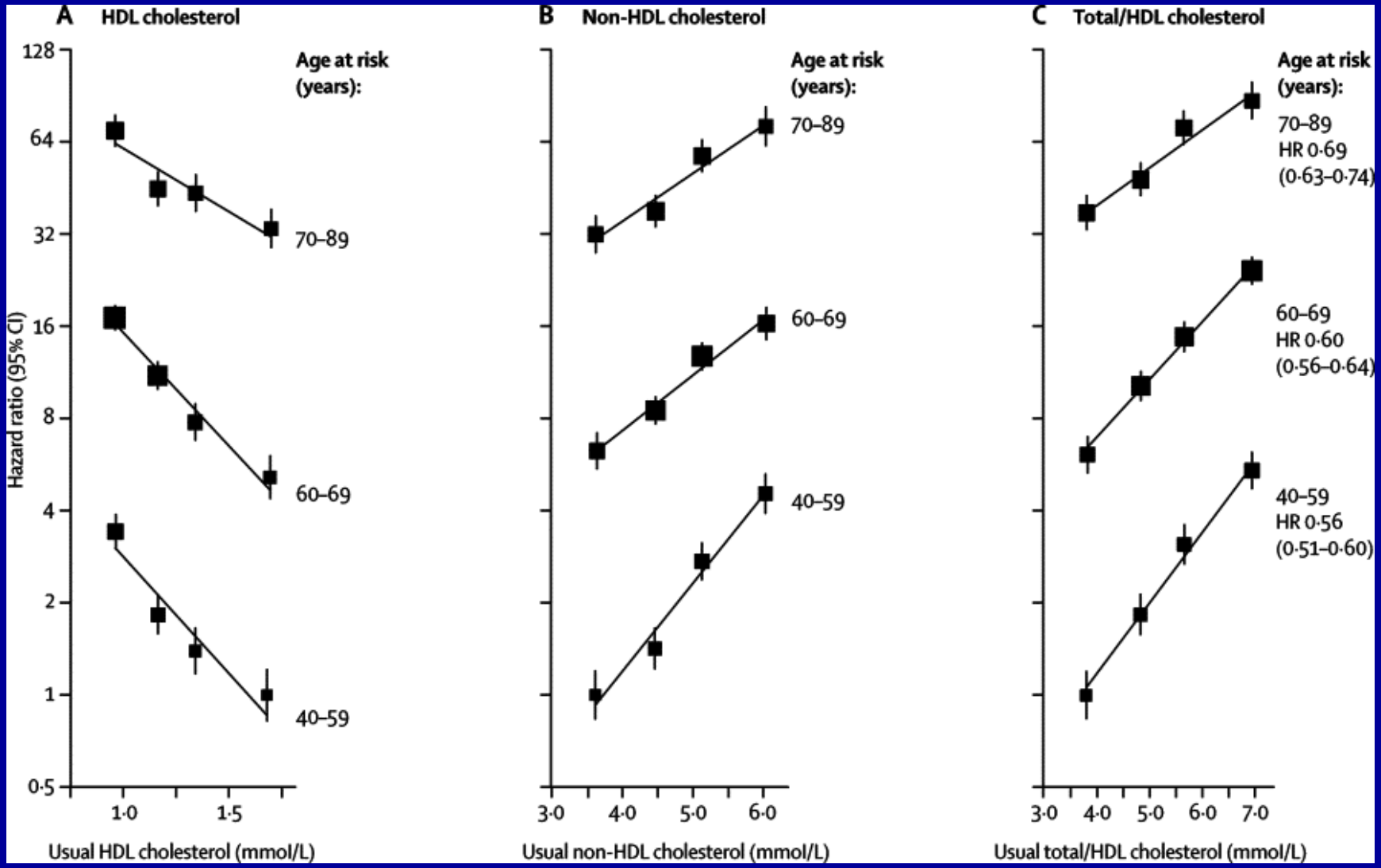
Terje R. Pedersen
Oslo

Survival free of CHD by HDL-C Quartiles
28-year follow-up of 2014 men aged 44-69 years



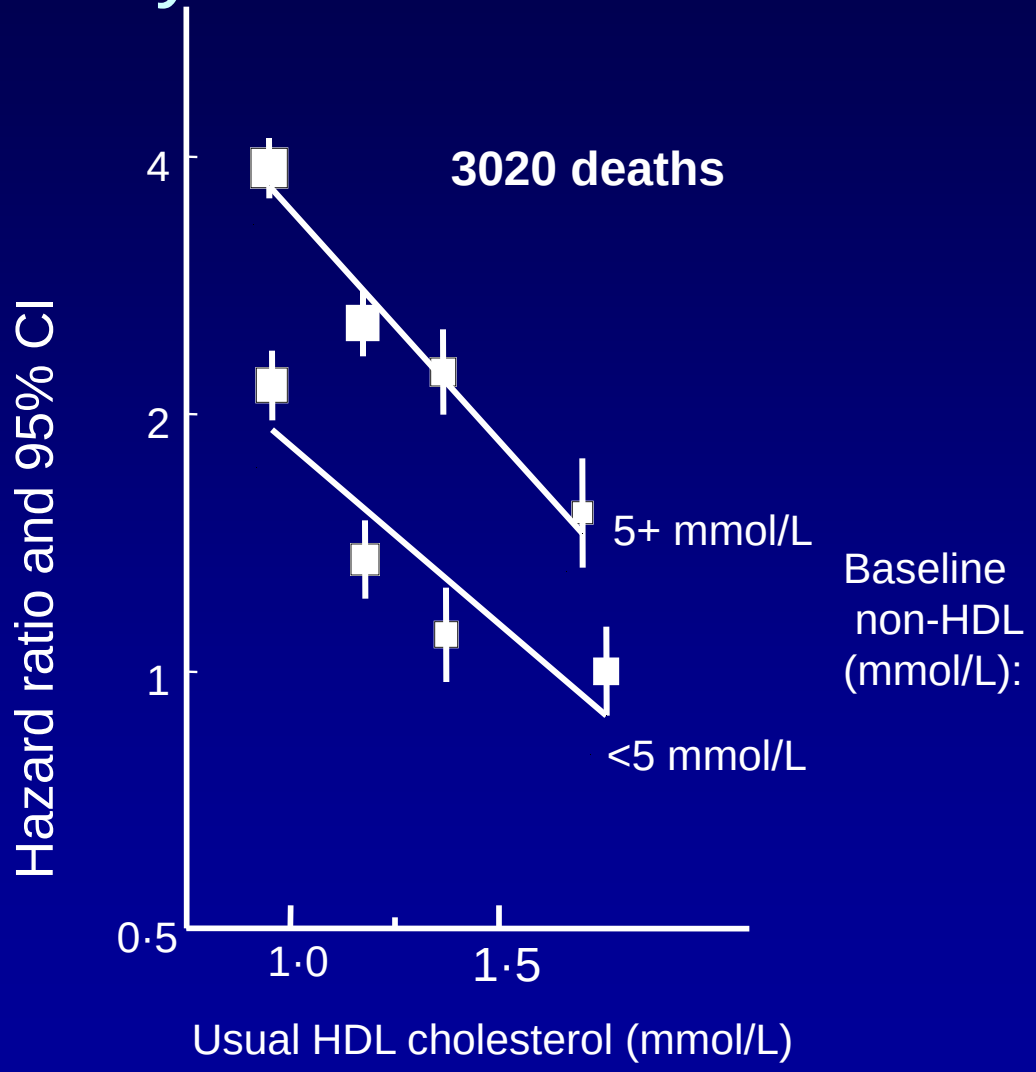
Skretteberg PT, et al. Atherosclerosis 2011 doi:10.1016/j.atherosclerosis.2011.10.009

Mortality from ischemic heart disease and cholesterol
3 020 deaths



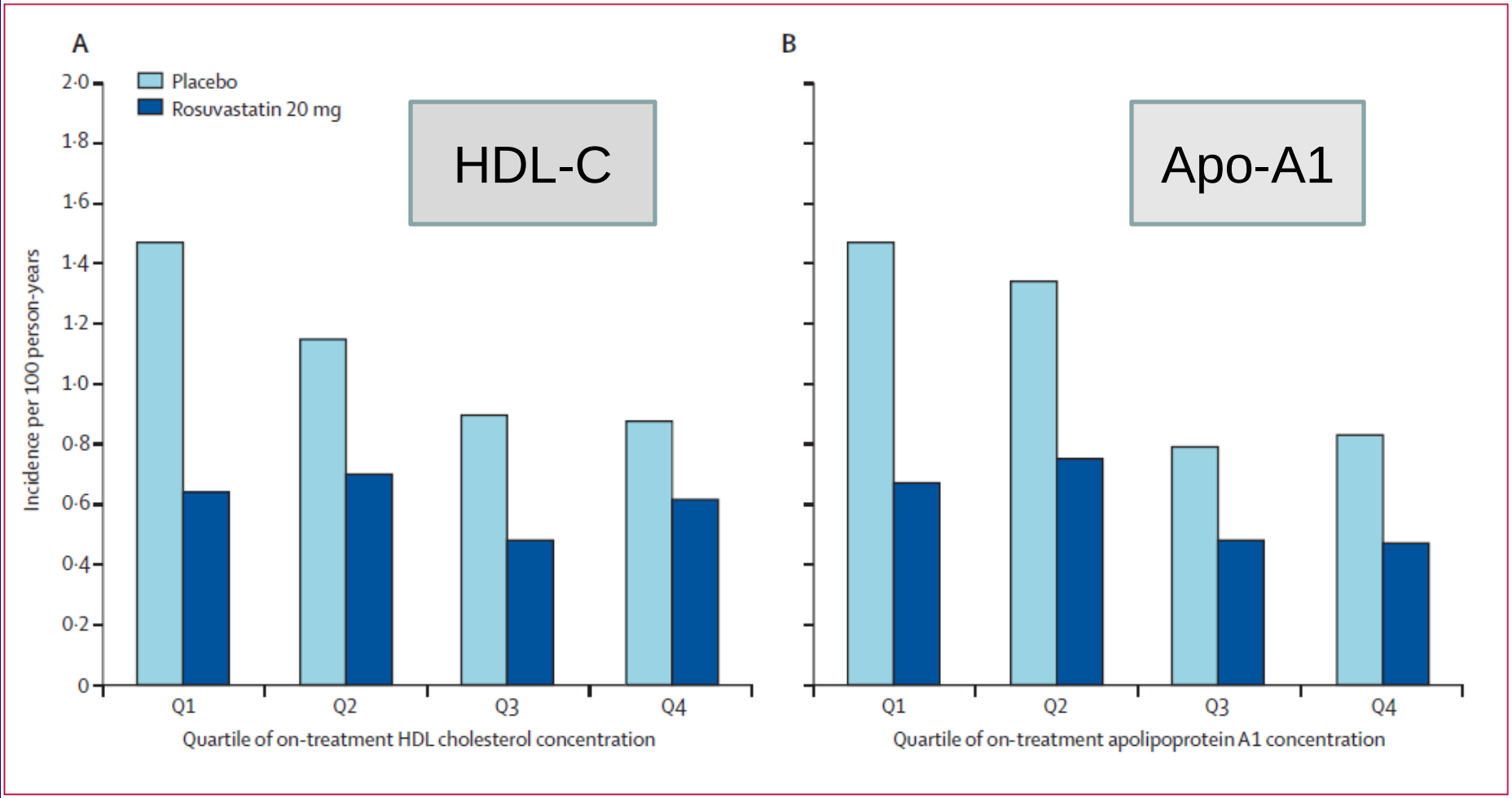
Prospective Studies Collaboration. Lancet 2007;370:1829

PSC: CHD mortality vs usual HDL cholesterol, by non-HDL cholesterol



Prospective Studies Collaboration. Lancet 2007;370:1829

JUPITER: On-treatment HDL and Apo A1 and endpoints/100 person-years

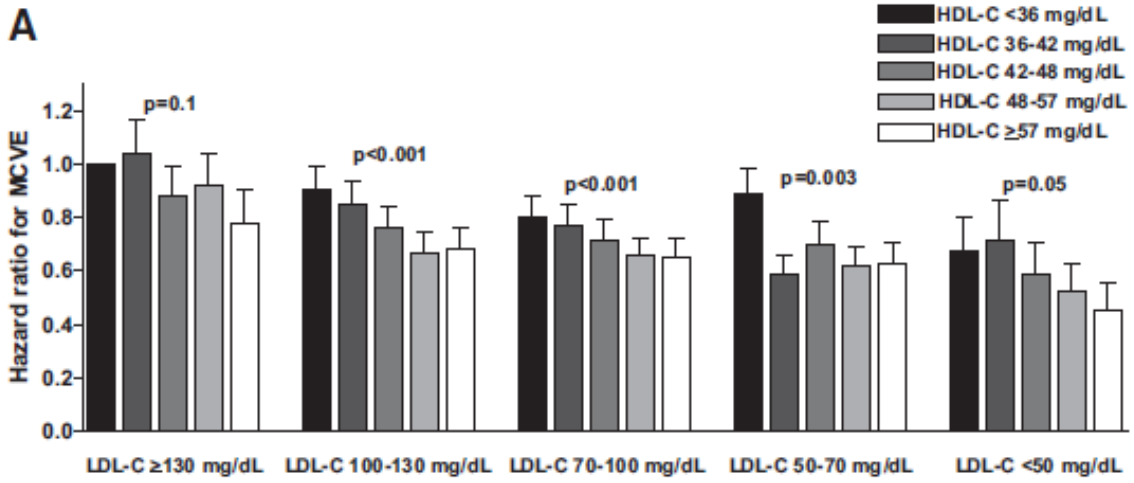


Ridker PM, et al. Lancet 2010;376:333-339

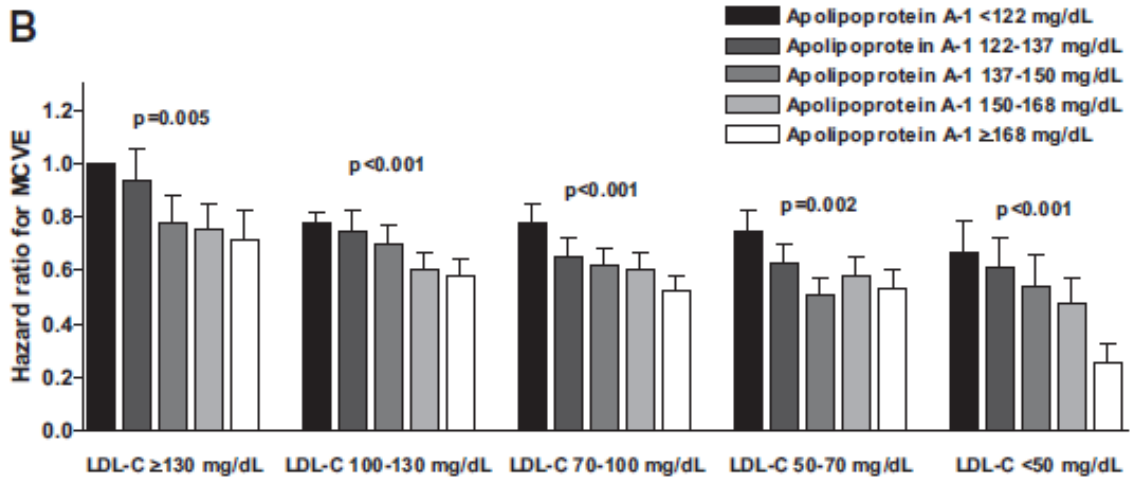
CVD risk by HDL-C quintiles and LDL-C

Meta-analysis of 8 statin trials, n=38 153 statin-treated

HDL-C



Apo A1



Boekholdt SM, et al. Circulation 2013;128:1504-1512

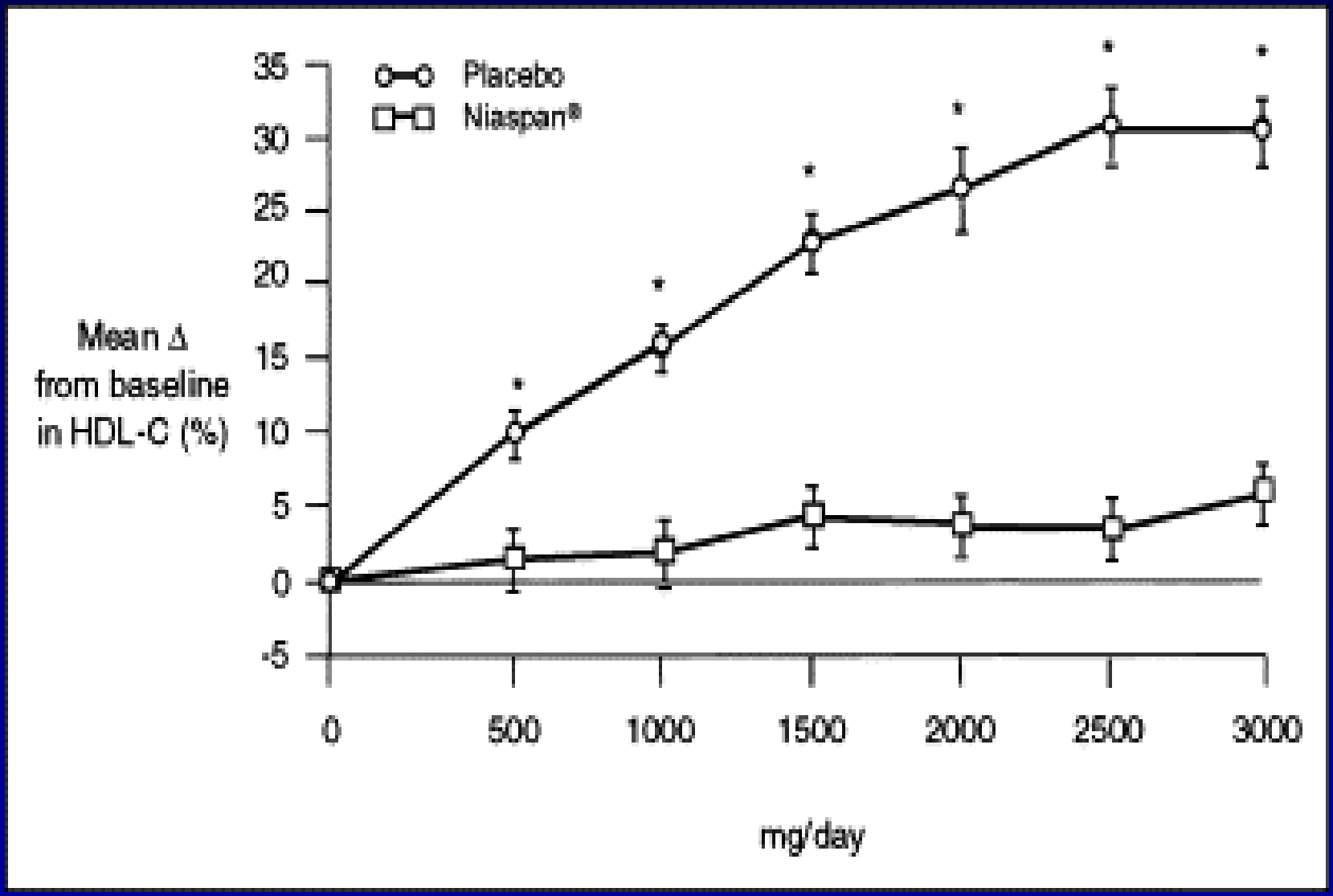
4S Lipoprotein changes explaining the risk reduction

Variable	Regression coefficient	SEM	Risk reduction (%) for each 1 % lipid reduction	95 % CI	p-value
LDL-C	0.0169	0.0035	**1.7**	1.0 - 2.4	**<0.00001**
Triglyc.	0.00187	0.0021	**0.2**	-0.2 - 0.6	**0.37**
Non-HDL-C	0.0166	0.0037	**1.7**	0.9 - 2.4	**0.00001**
Apo B	0.0109	0.0038	**1.1**	0.3 - 1.8	**0.004**
HDL-C	-0.00773	0.0037	**-0.8**	0.1 - 1.5	**0.039**
Apo A-1	-0.00352	0.0051	**-0.4**	-0.6 – 1.3	**0.487**

Mean increase in HDL-C with simvastatin : 8 %

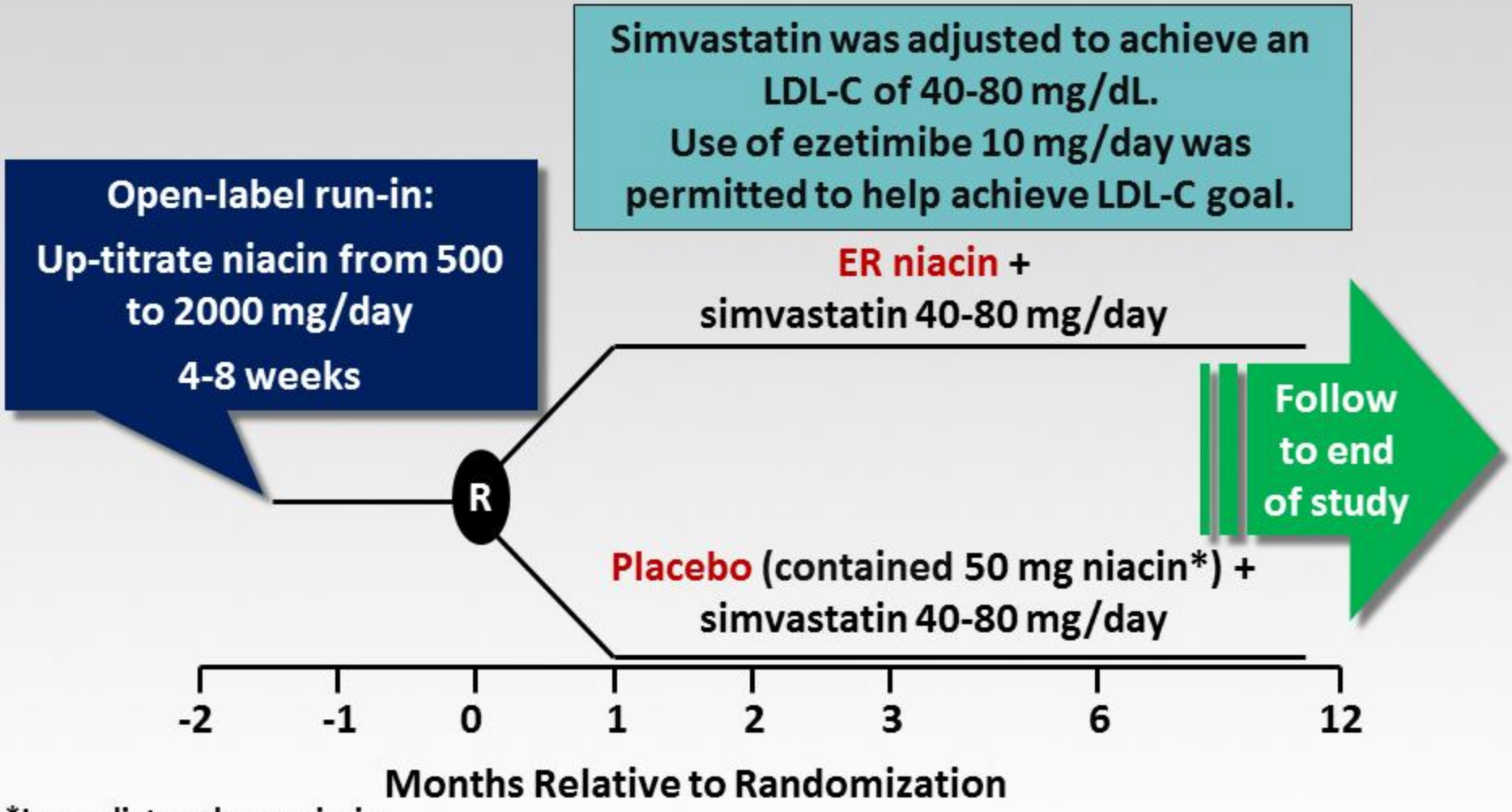
Pedersen TR. Circulation 1998;97:1453-1460

HDL-C : Effect of Niacin



Goldberg A, et al. Am J Cardiol 2000;85:1100

AIM-HIGH: Study Design

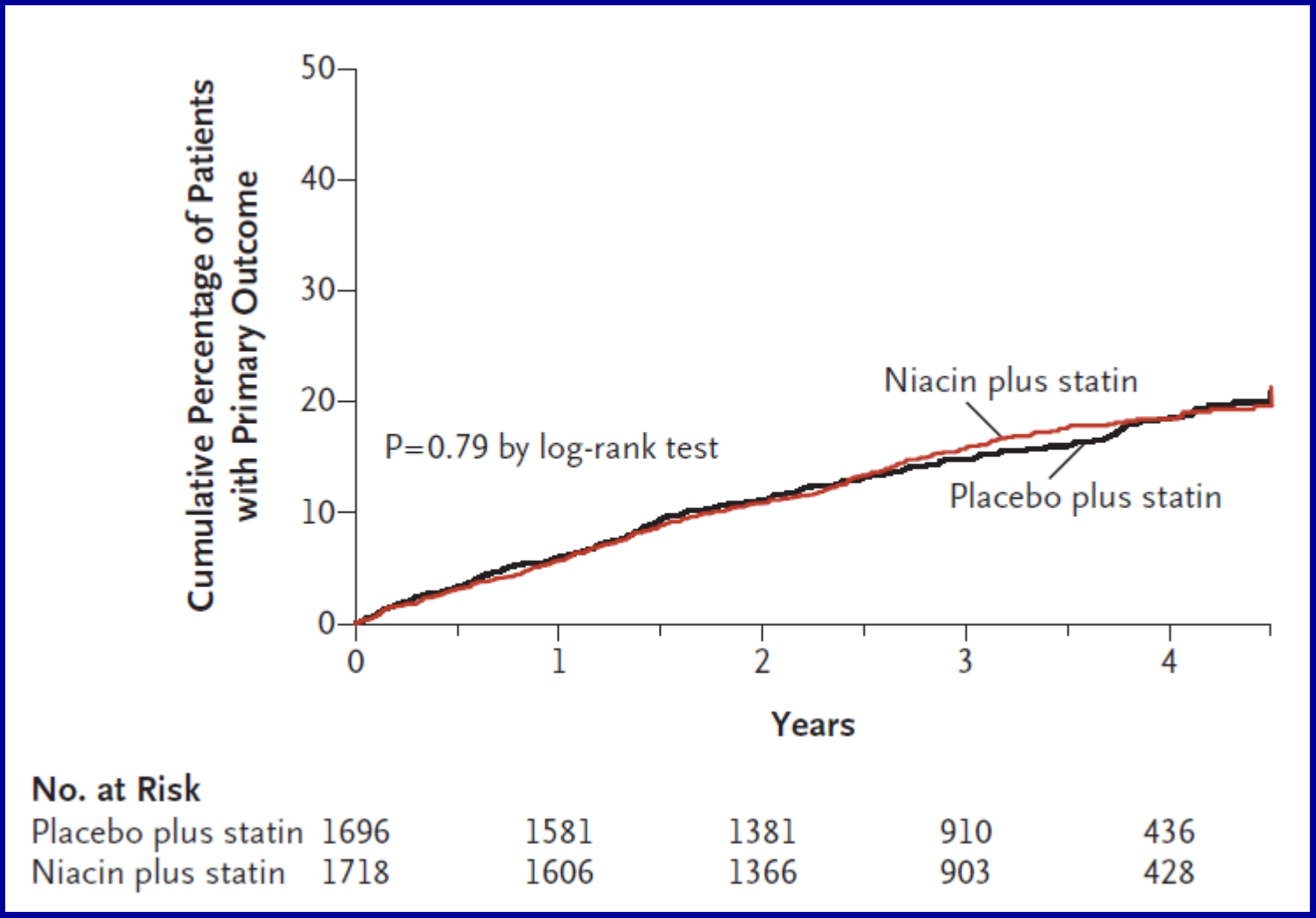


*Immediate-release niacin

LIPID & METABOLIC

Boden WE, et al. AHA 2011.

AIM-HIGH: Primary Endpoint



Boden The AIM-HIGH Investigators. NEJM 2011; Nov. 15 www.NEJM.org

AIM-HIGH: Mean LDL-C

AIM-HIGH Investigators NEJM 2011; Nov. 15 www.NEJM.org

AIM-HIGH Mean HDL-C

AIM-HIGH Investigators NEJM 2011; Nov. 15 www.NEJM.org

www.ctsu.ox.ac.uk/thrive

Characteristics of randomized participants

% or mean (SD)	ERN/LRPT (12,838)	Placebo (12,835)	All
Men	83%	83%	21,229 (83%)
Age (years)	64.9	64.9	64.9 (7.5)
Prior disease			
Coronary	78%	78%	20,137 (78%)
Cerebrovascular	32%	32%	8170 (32%)
Peripheral arterial	13%	12%	3214 (13%)
Diabetes	32%	32%	8299 (32%)

UNIVERSITY OF OXFORD

hps2 THRIVE

Baseline LIPIDS on statin-based therapy

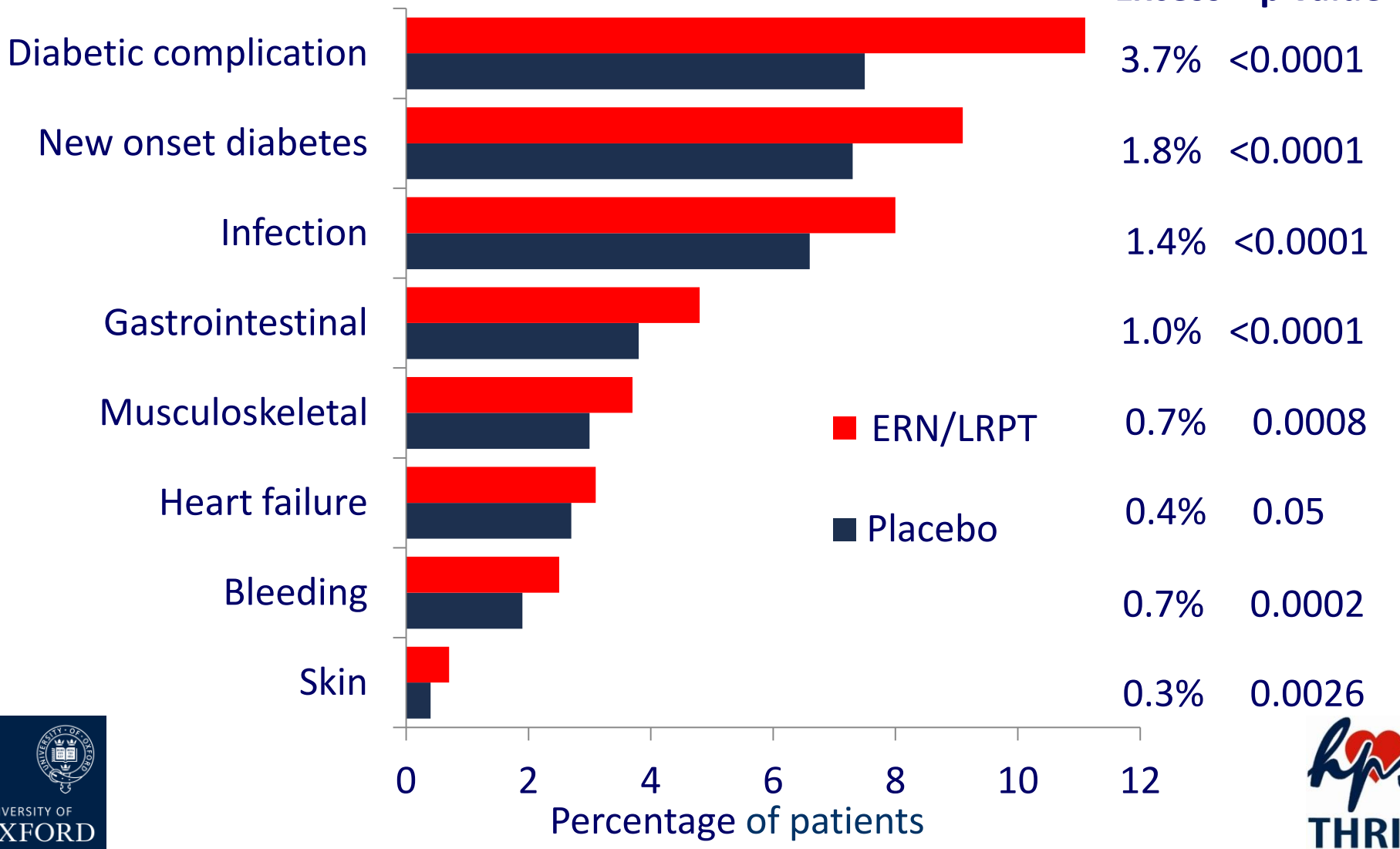
	Mean (SD) baseline	
	mg/dL	mmol/L
Total cholesterol	128 (22)	3.32 (0.57)
Direct-LDL	63 (17)	1.64 (0.44)
HDL	44 (11)	1.14 (0.29)
Triglycerides*	125 (74)	1.43 (0.84)

*64% fasted for >8 hours

UNIVERSITY OF OXFORD

HPS2 THRIVE

Effect of ERN/LRPT on SERIOUS adverse events (median follow-up 3.9 years)



UNIVERSITY OF OXFORD

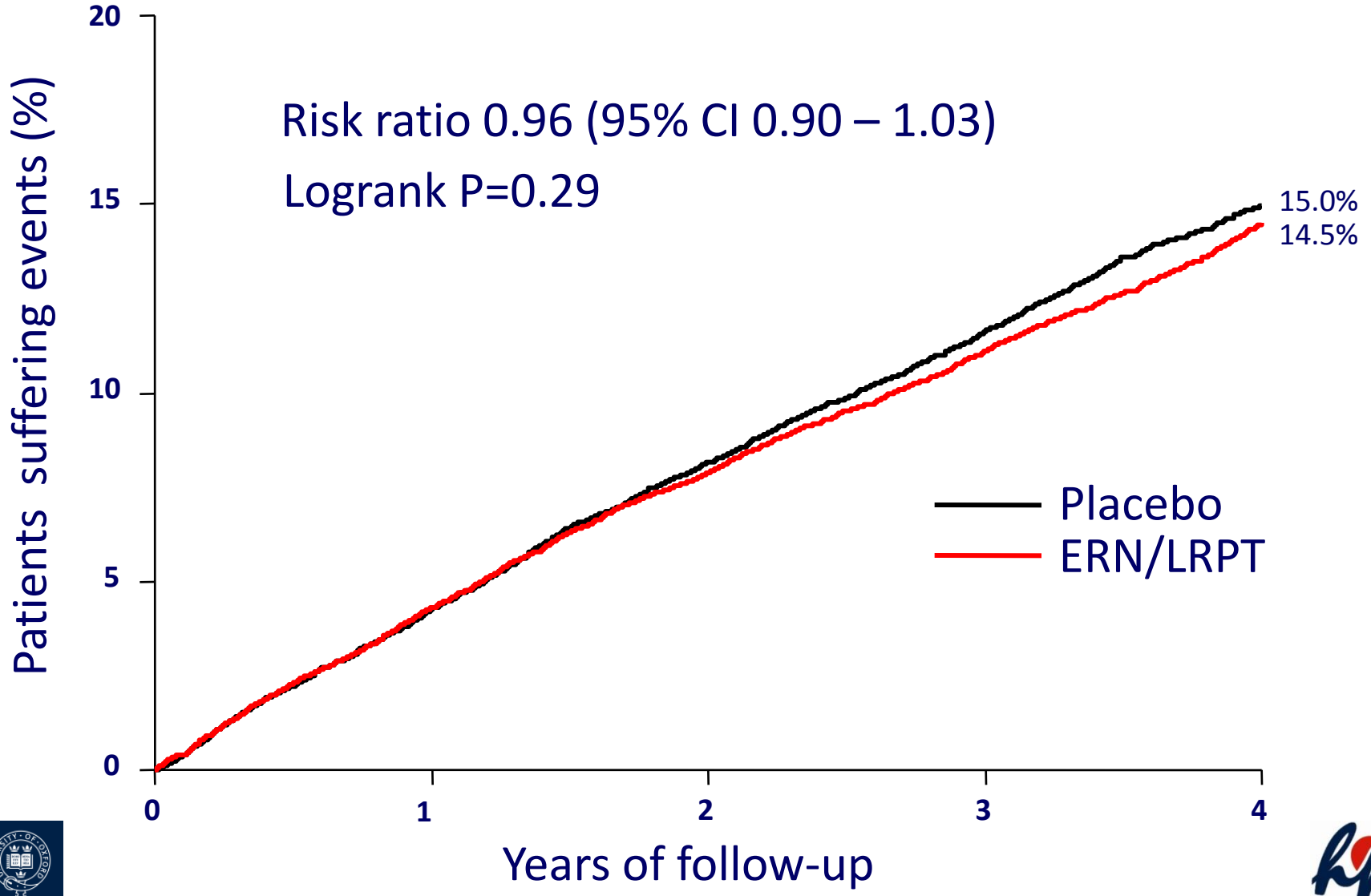
THRIVE

Effects of ER niacin/laropiprant on lipids

Year of FU	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)
1	-12	6	-35
4	-7	6	-31
STUDY AVERAGE	-10	6	-33
(mmol/L)	(-0.25)	(0.16)	(-0.37)

"Based on previous observational studies and randomized trials, it was anticipated such lipid differences might translate into a 10-15% reduction in vascular events"
Eur Heart Journal 2013

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

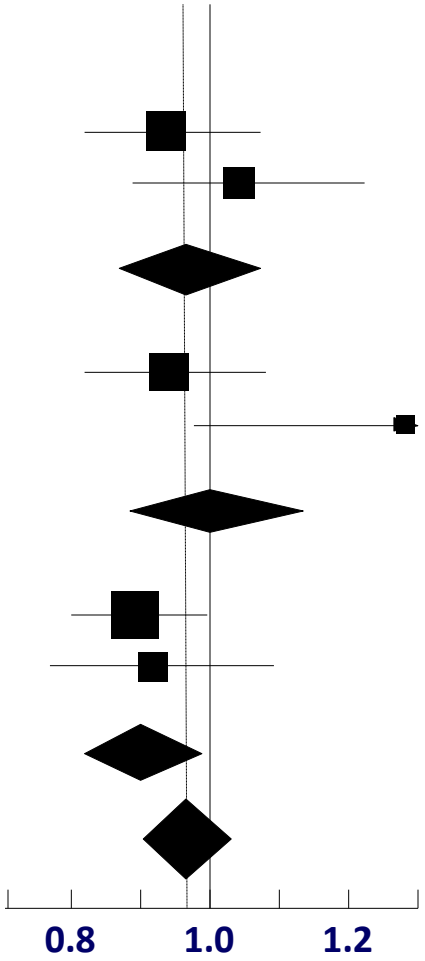


UNIVERSITY OF OXFORD

THRIVE

Effect of ERN/LRPT on MAJOR VASCULAR EVENTS

Event	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	p
Non-fatal MI	402 (3.1%)	431 (3.4%)	0.93 (0.82-1.07)	0.33
Coronary death	302 (2.4%)	291 (2.3%)	1.04 (0.89-1.22)	0.63
Major coronary event	**668 (5.2%)**	**694 (5.4%)**	**0.96 (0.87-1.07)**	**0.51**
Ischaemic stroke	389 (3.0%)	415 (3.2%)	0.94 (0.82-1.08)	0.37
Haemorrhagic stroke	114 (0.9%)	89 (0.7%)	1.28 (0.97-1.69)	0.08
Any stroke	**498 (3.9%)**	**499 (3.9%)**	**1.00 (0.88-1.13)**	**0.56**
Coronary revasc	591 (4.6%)	664 (5.2%)	0.89 (0.80-0.99)	0.04
Non-coronary revasc	236 (1.8%)	258 (2.0%)	0.92 (0.77-1.09)	0.33
Any revascularization	**807 (6.3%)**	**897 (7.0%)**	**0.90 (0.82-0.99)**	**0.03**
Major vascular event	**1696 (13.2%)**	**1758 (13.7%)**	**0.96 (0.90-1.03)**	**0.29**

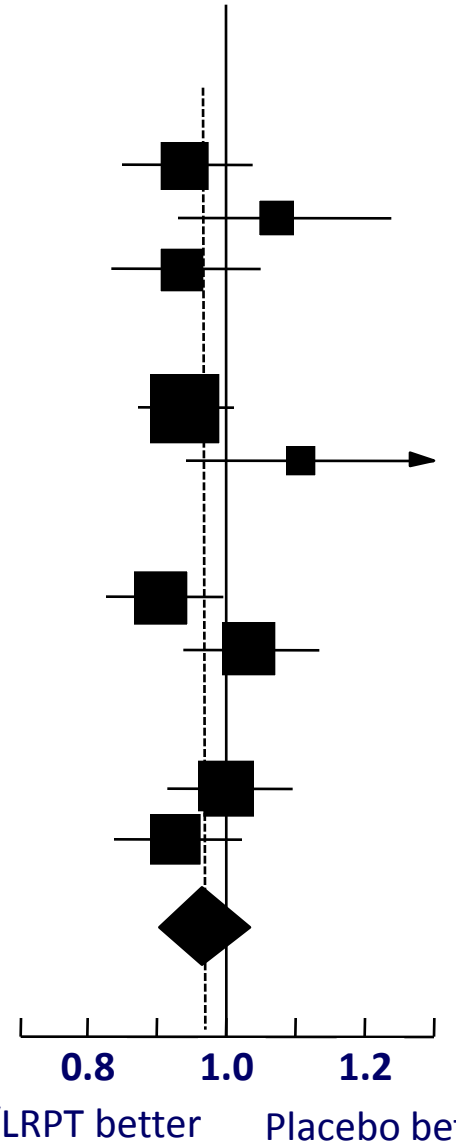


UNIVERSITY OF OXFORD

THRIVE

MVE by age, sex, region and statin-based therapy

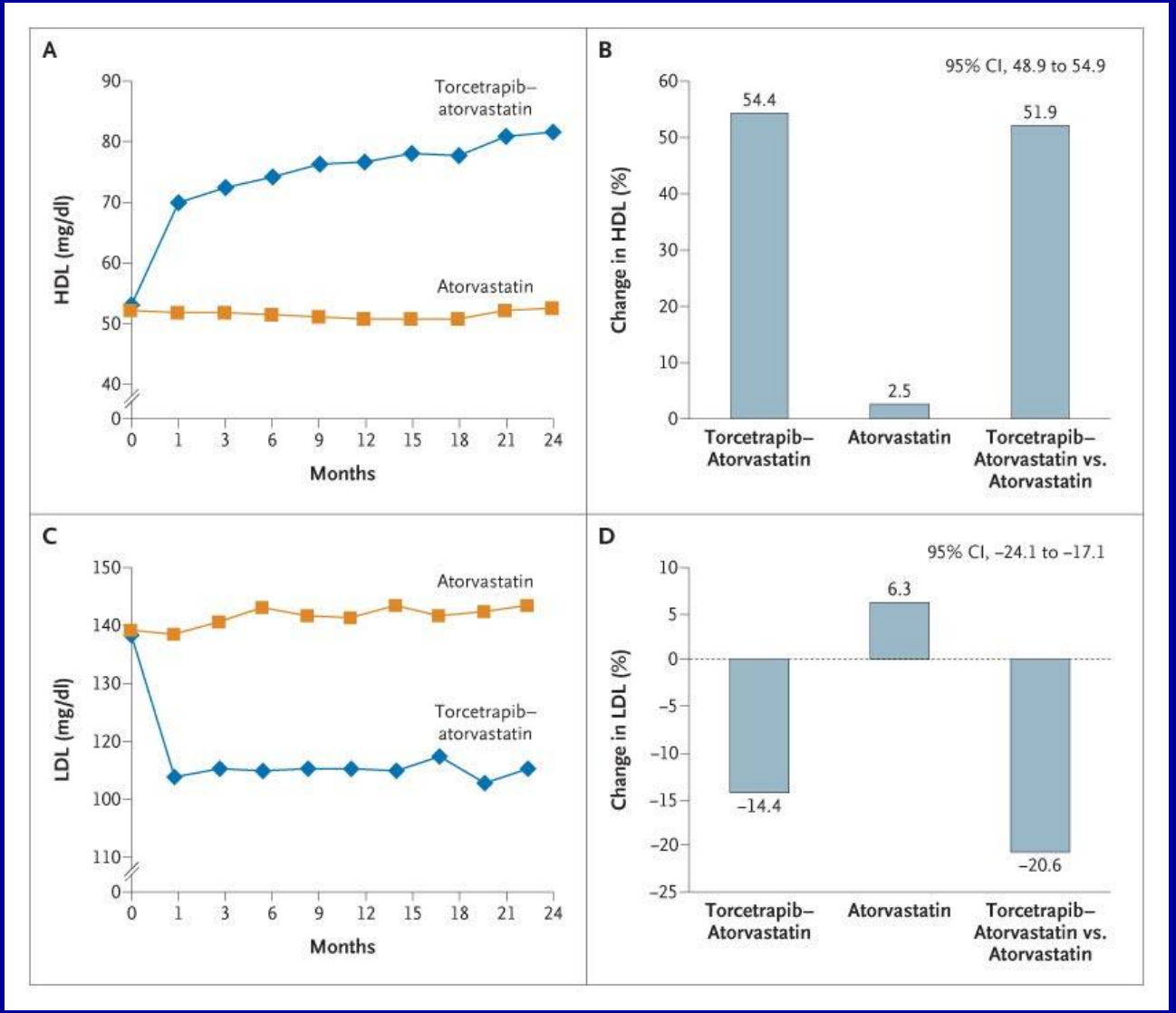
	Randomized allocation ERN/LRPT (12,838)	Placebo (12,835)	Risk ratio & 95% CI	Het or trend χ^2 (uncorrected p value)
Age (years)				
< 65	740 (11.4%)	786 (12.2%)		0.00 (p=0.98)
≥ 65 <70	392 (13.9%)	367 (13.1%)		
≥ 70	564 (15.9%)	605 (17.0%)		
Sex				
Male	1397 (13.2%)	1485 (14.0%)		3.21 (p=0.07)
Female	299 (13.4%)	273 (12.3%)		
Region				
Europe	832 (11.3%)	913 (12.4%)		3.61 (p=0.06)
China	864 (15.8%)	845 (15.5%)		
Statin-based therapy				
Simvastatin 40mg	945 (14.0%)	949 (14.0%)		1.28 (p=0.26)
Ezetimibe/simvastatin	751 (12.4%)	809 (13.3%)		
All	**1696 (13.2%)**	**1758 (13.7%)**		**3.5% SE 3.3 reduction**



UNIVERSITY OF OXFORD

HPS2 THRIVE

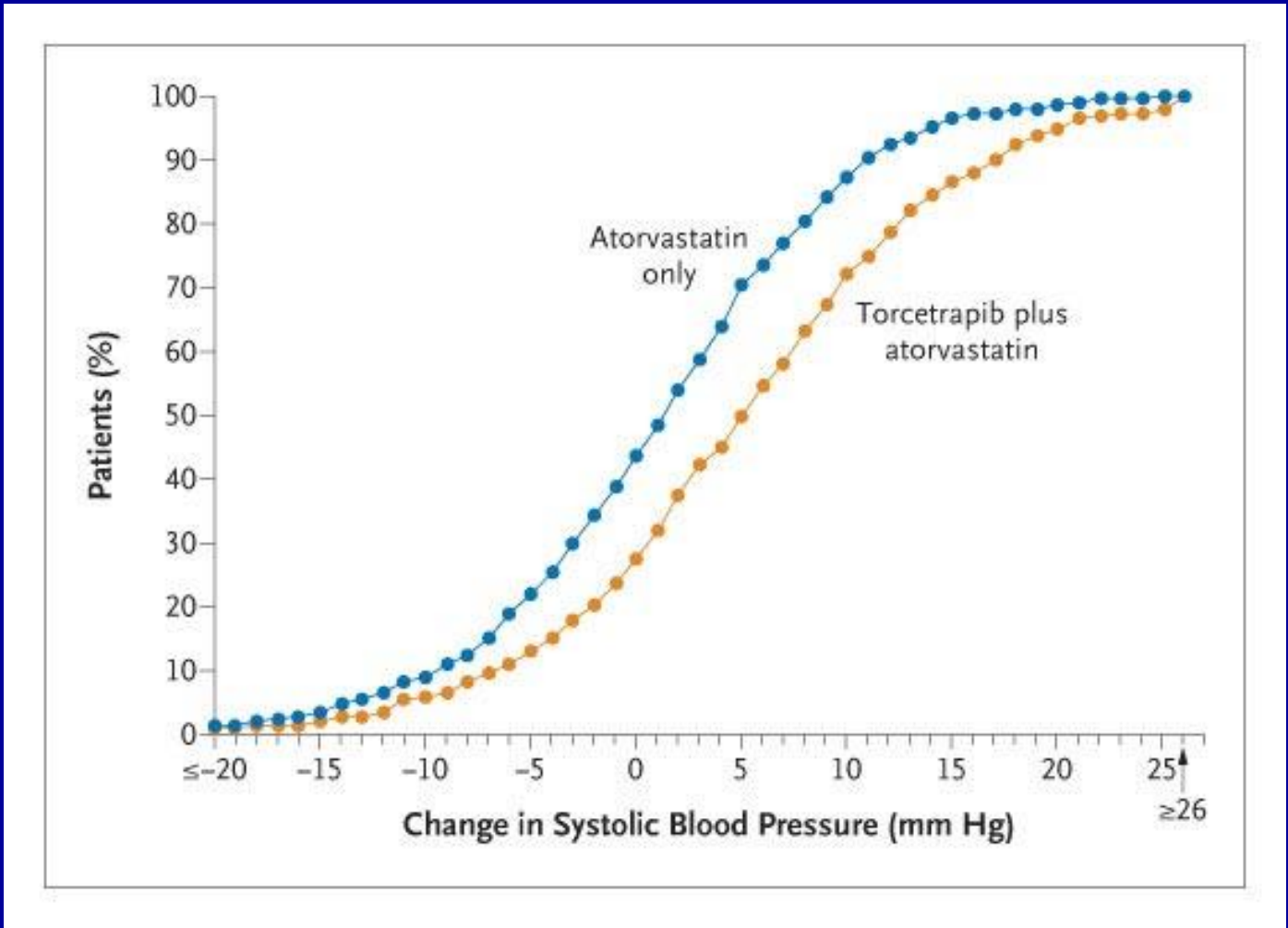
Changes in HDL and LDL Cholesterol Atorvastatin Alone or Atorvastatin plus Torcetrapib



Kastelein J et al. N Engl J Med 2007;356:1620-1630

The NEW ENGLAND JOURNAL of MEDICINE

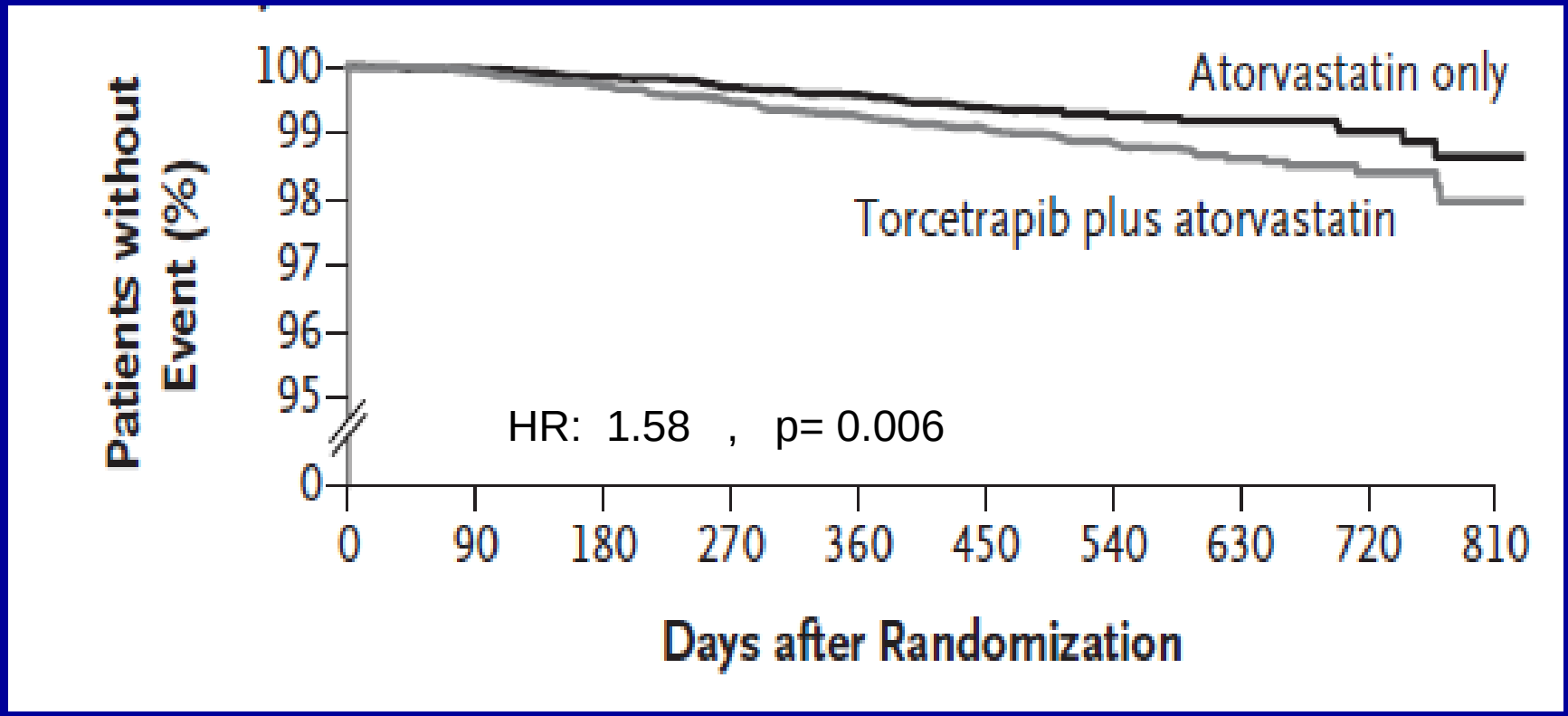
ILLUSTRATE
Changes in Systolic Blood Pressure in the Two Study Groups



Nissen S et al. N Engl J Med 2007;356:1304-1316

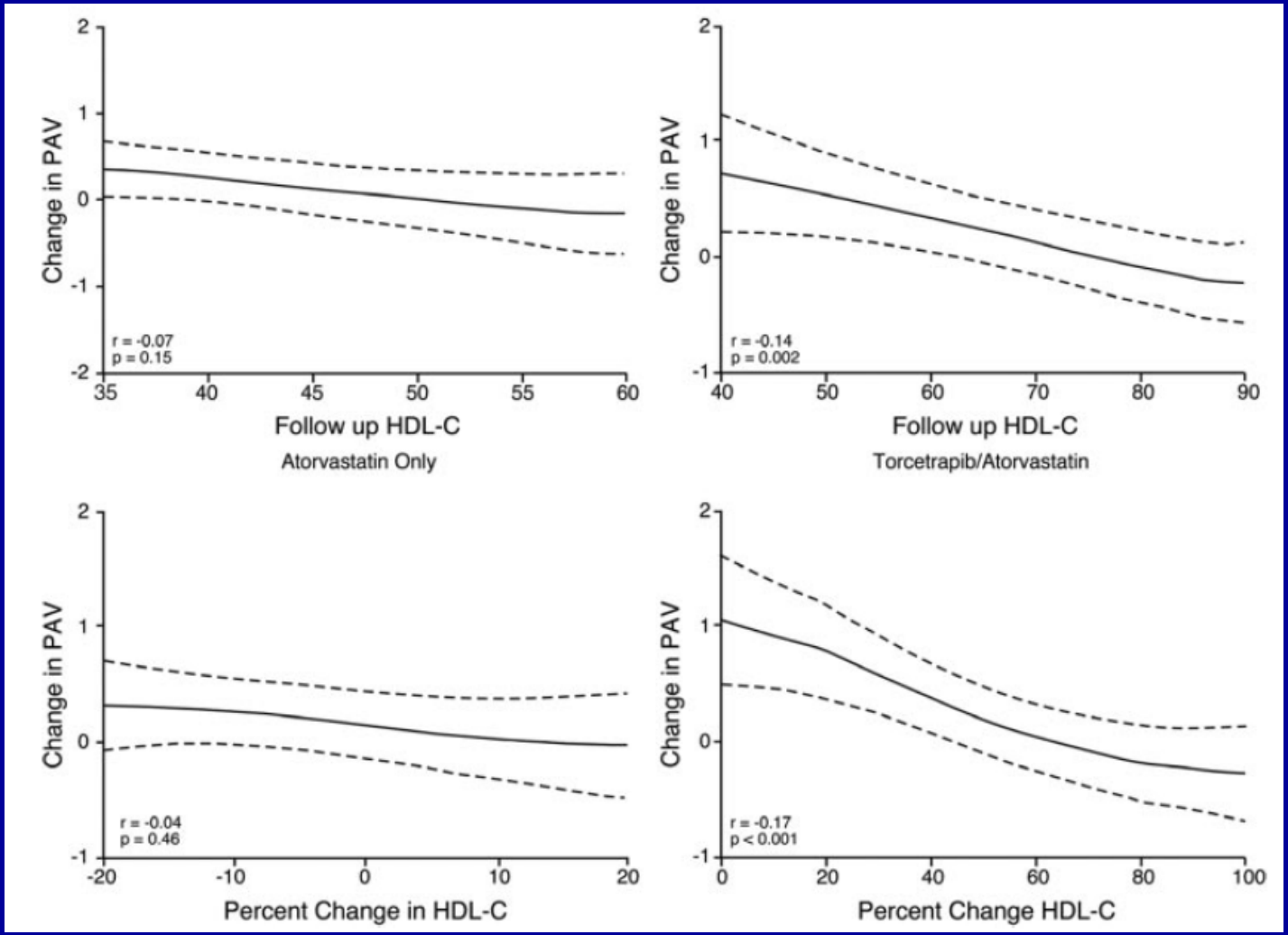
The NEW ENGLAND JOURNAL of MEDICINE

ILLUMINATE
Death from Any Cause



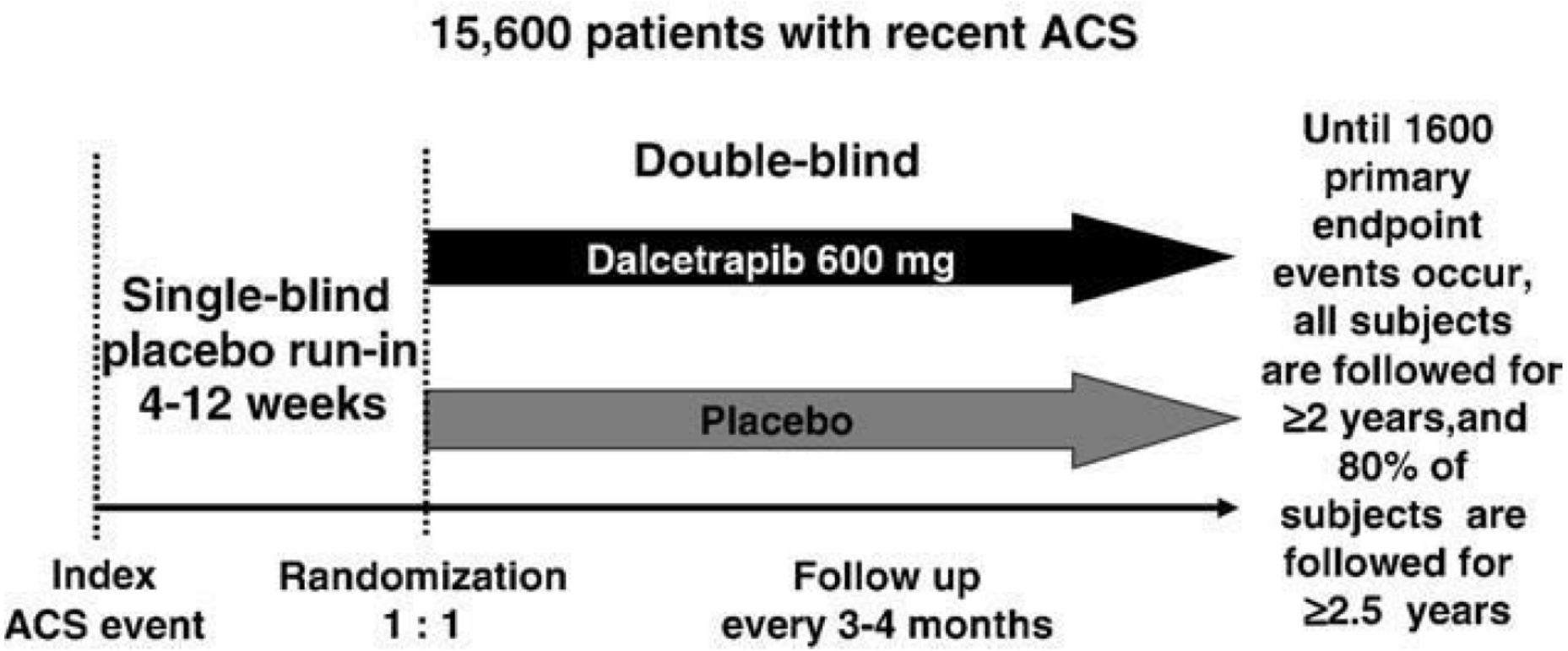
Barter P, et al. N Engl J Med 2007;357: 2109-22

ILLUSTRATE
Change in Percent Atheroma Volume and HDL-C



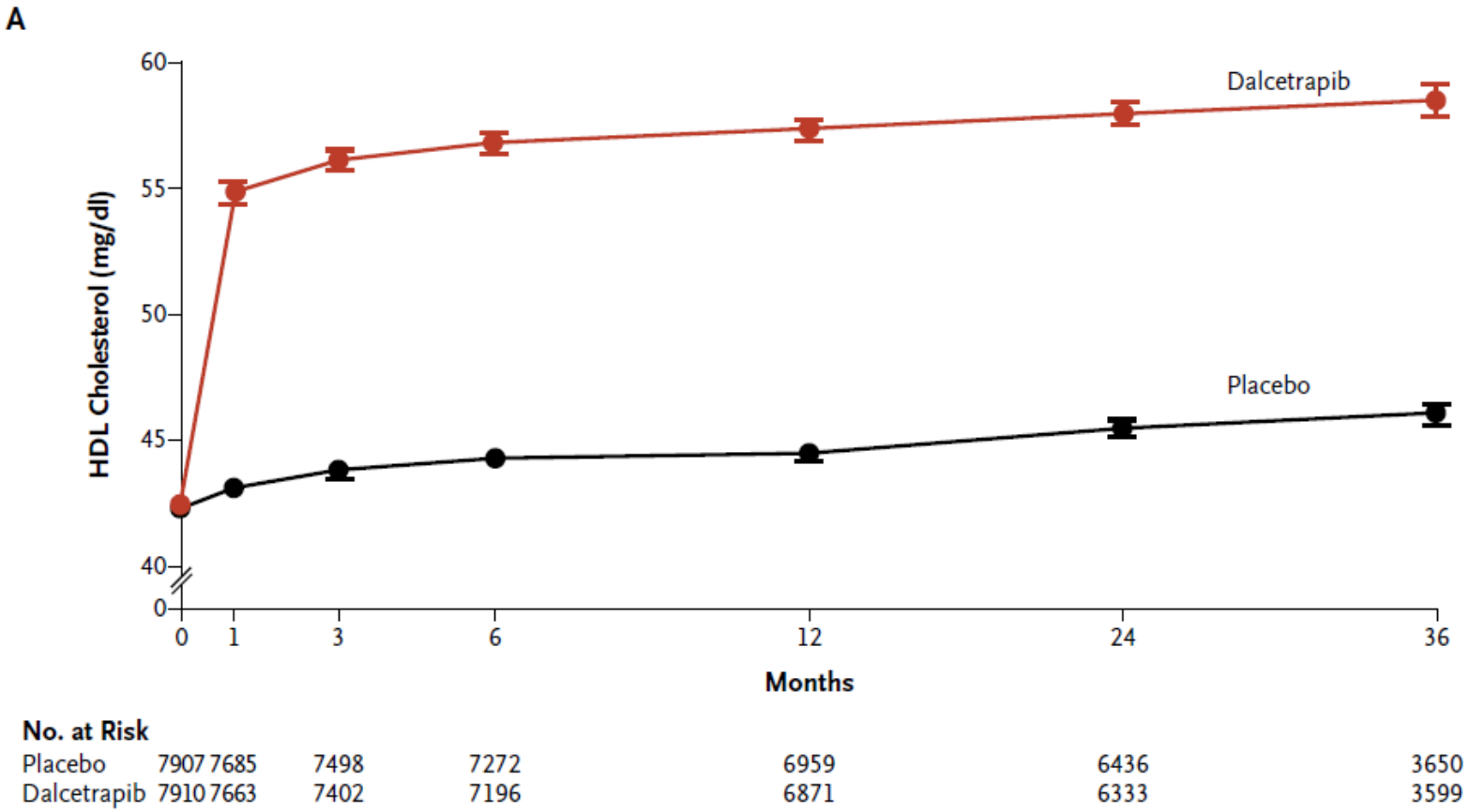
Nicholls SJ, et al. Circulation 2008;118:2506-2514

Dal-OUTCOMES Design



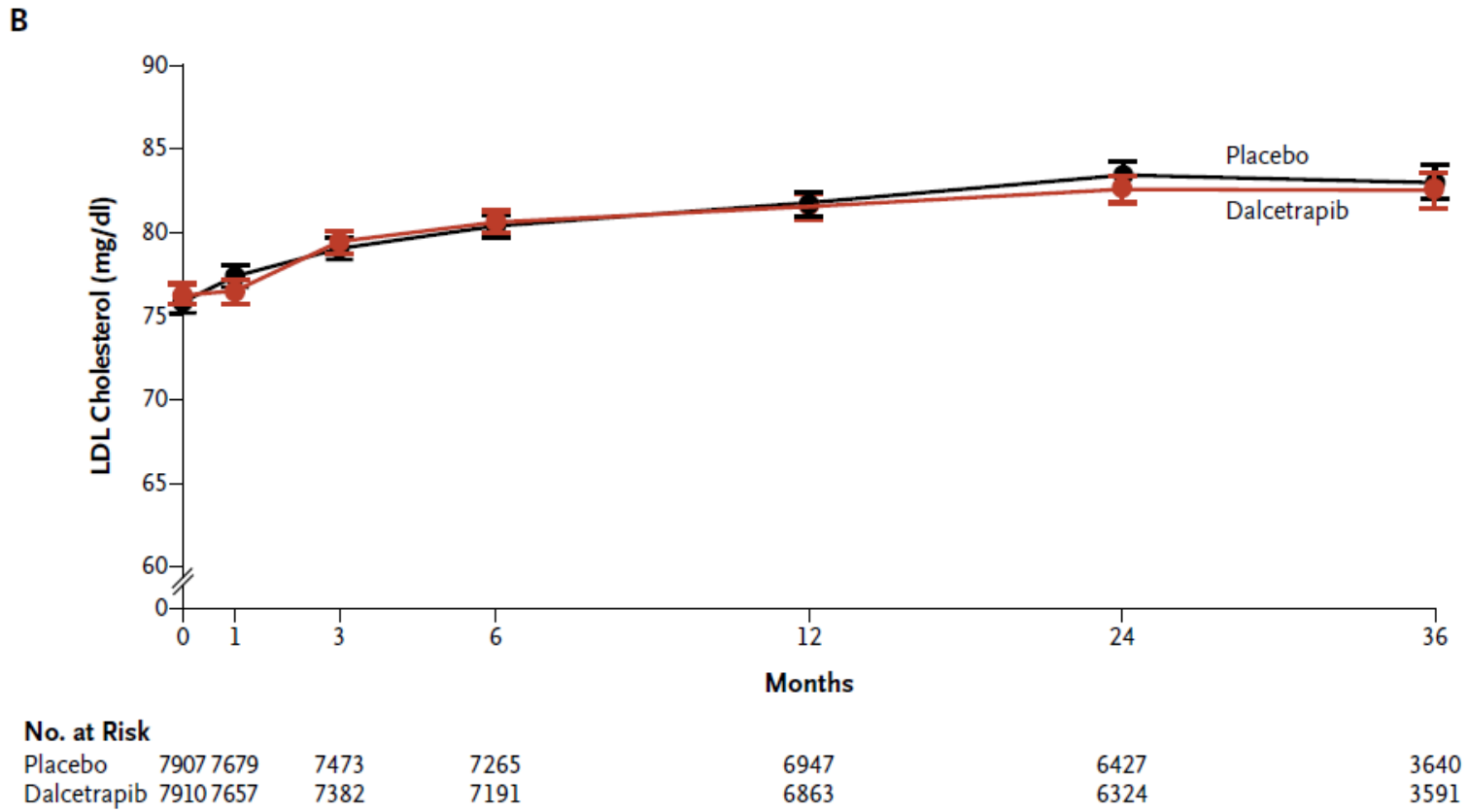
Schwartz GG, et al. Am J Cardiol 2009;156:896-901

Dal-OUTCOMES: Effect on HDL-C



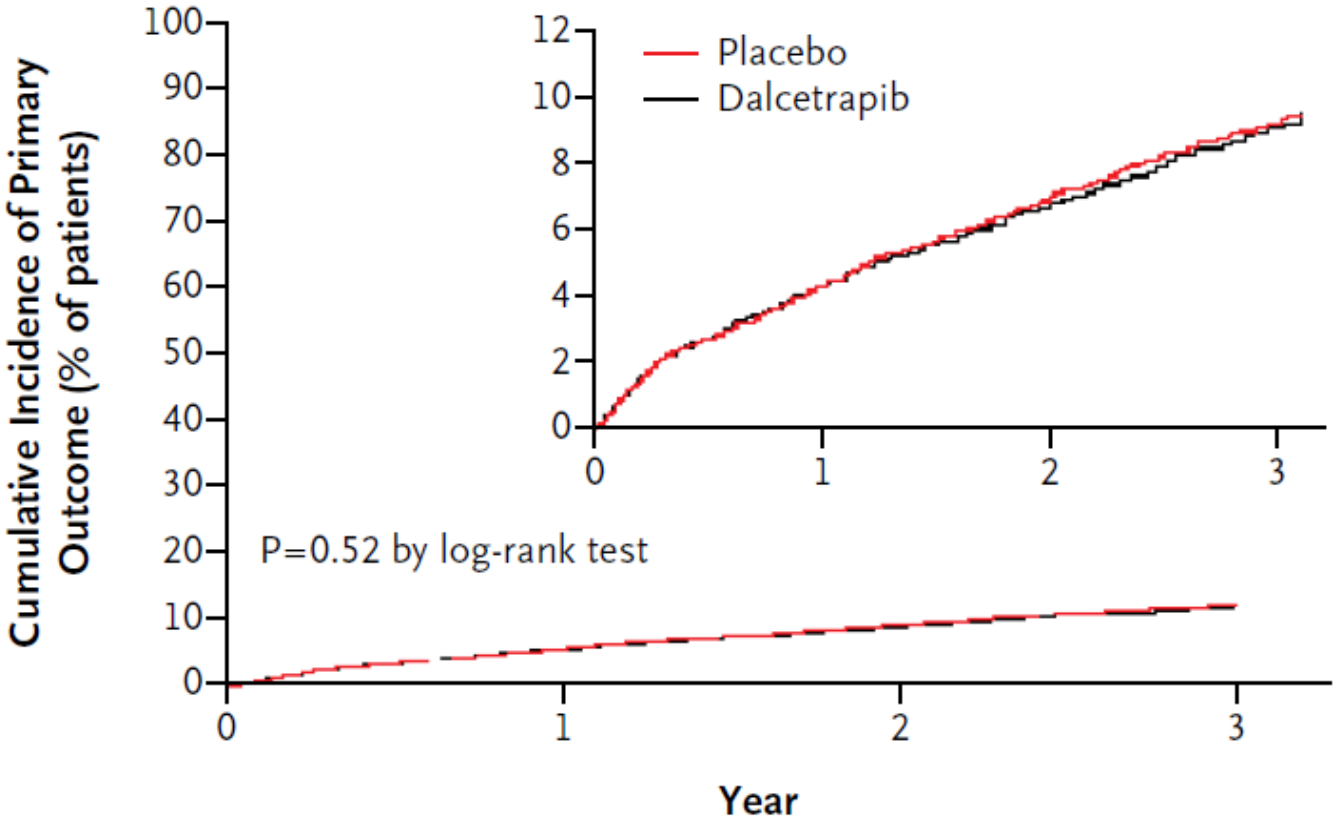
Schwartz G, et al. NEJM 2012;367:2089-99.

Dal-OUTCOMES: Effect on LDL-C



Schwartz G, et al. NEJM 2012;367:2089-99.

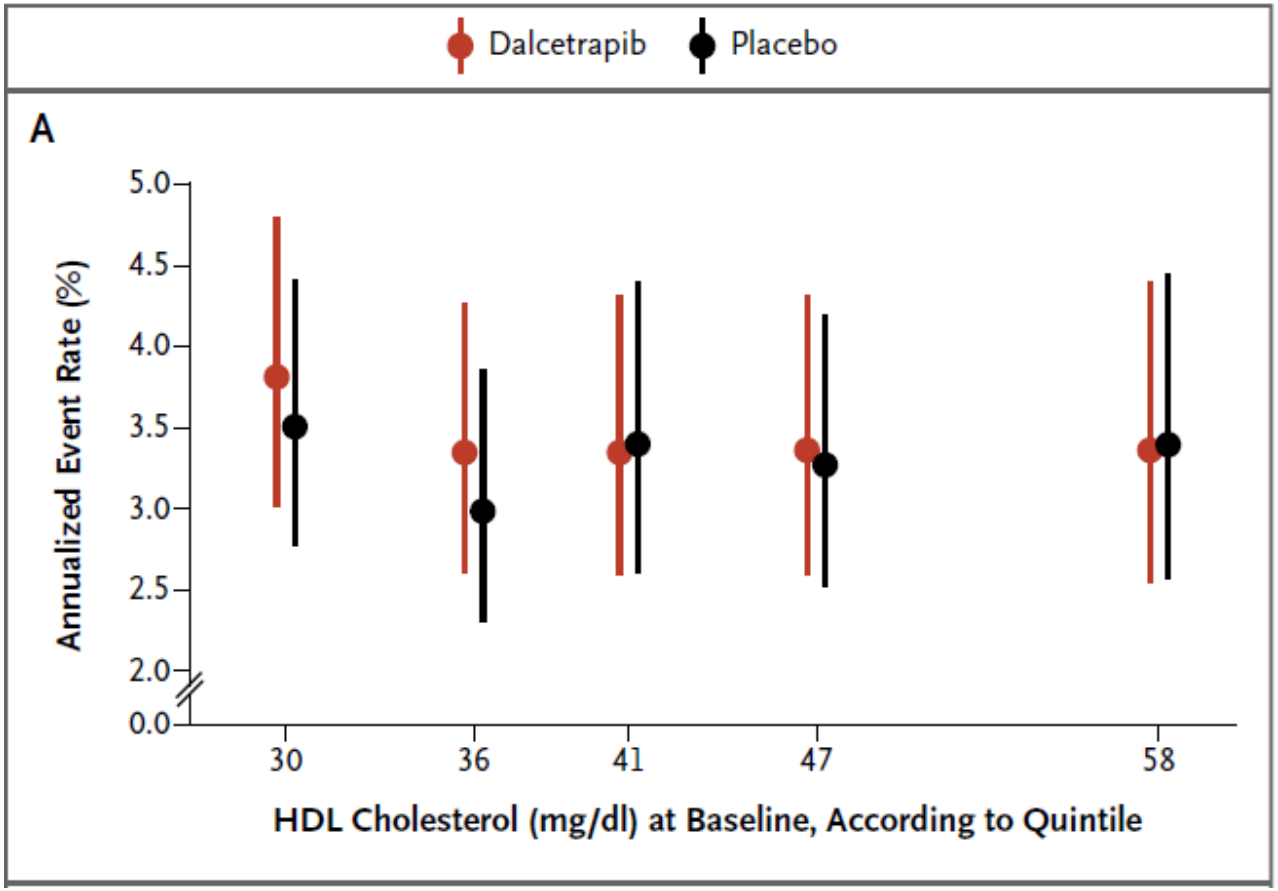
Dal-OUTCOMES: Effect on Primary Outcome



No. at Risk				
Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

Schwartz G, et al. NEJM 2012;367:2089-99.

Dal-OUTCOMES: Events by HDL Quitile



Schwartz G, et al. NEJM 2012;367:2089-99.

REVEAL Heart Protection Study 3

Patients with previous AMI, stroke or Diabetes with CHD

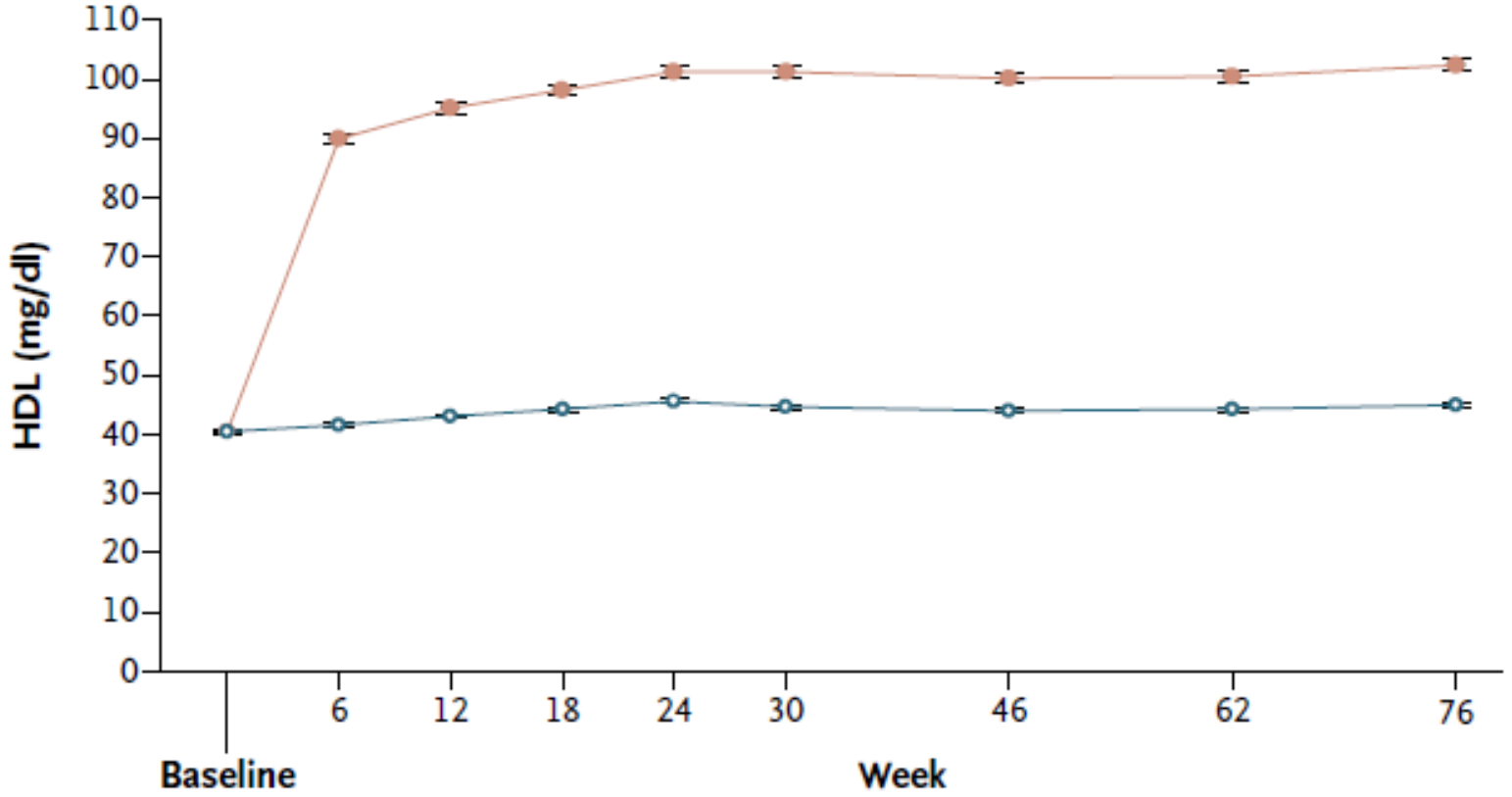
Anacetrapib 100 mg/d or placebo
on top of atorvastatin 20 or 80 mg/d

UK, USA, Canada, Nordic, *Italy,* Germany , China, Japan

N= 30 000

Duration: 4 years
Start Q1, 2012

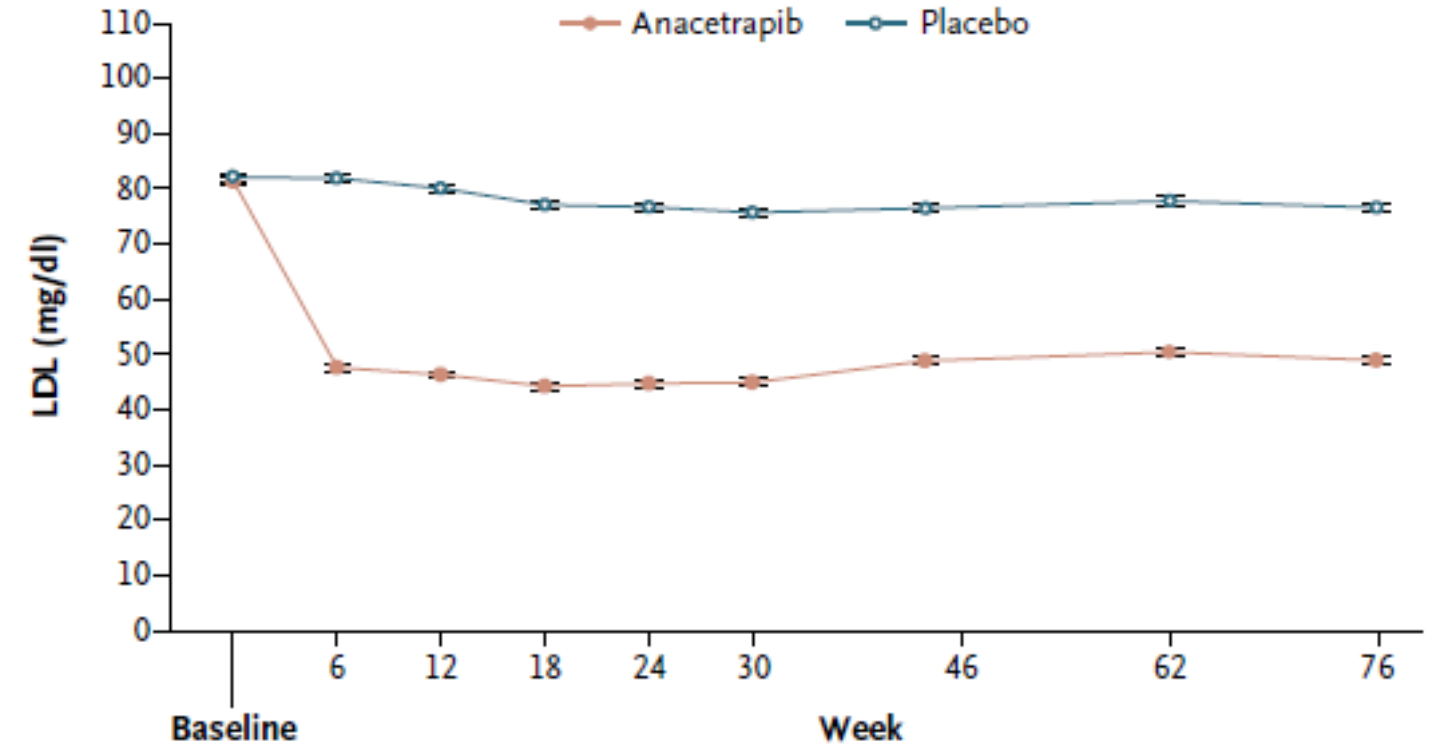
DEFINE
Anacetrapib: HDL-C



No. at Risk									
Anacetrapib	807	776	757	718	687	647	607	572	543
Placebo	804	766	761	741	744	736	711	691	666

Cannon CP, et al. NEJM 2010;363:2406-15

DEFINE
Anacetrapib effect on LDL-C



Cannon CP, et al. NEJM 2010;363:2406-15

Increase HDL-C with drugs = reduce risk

?

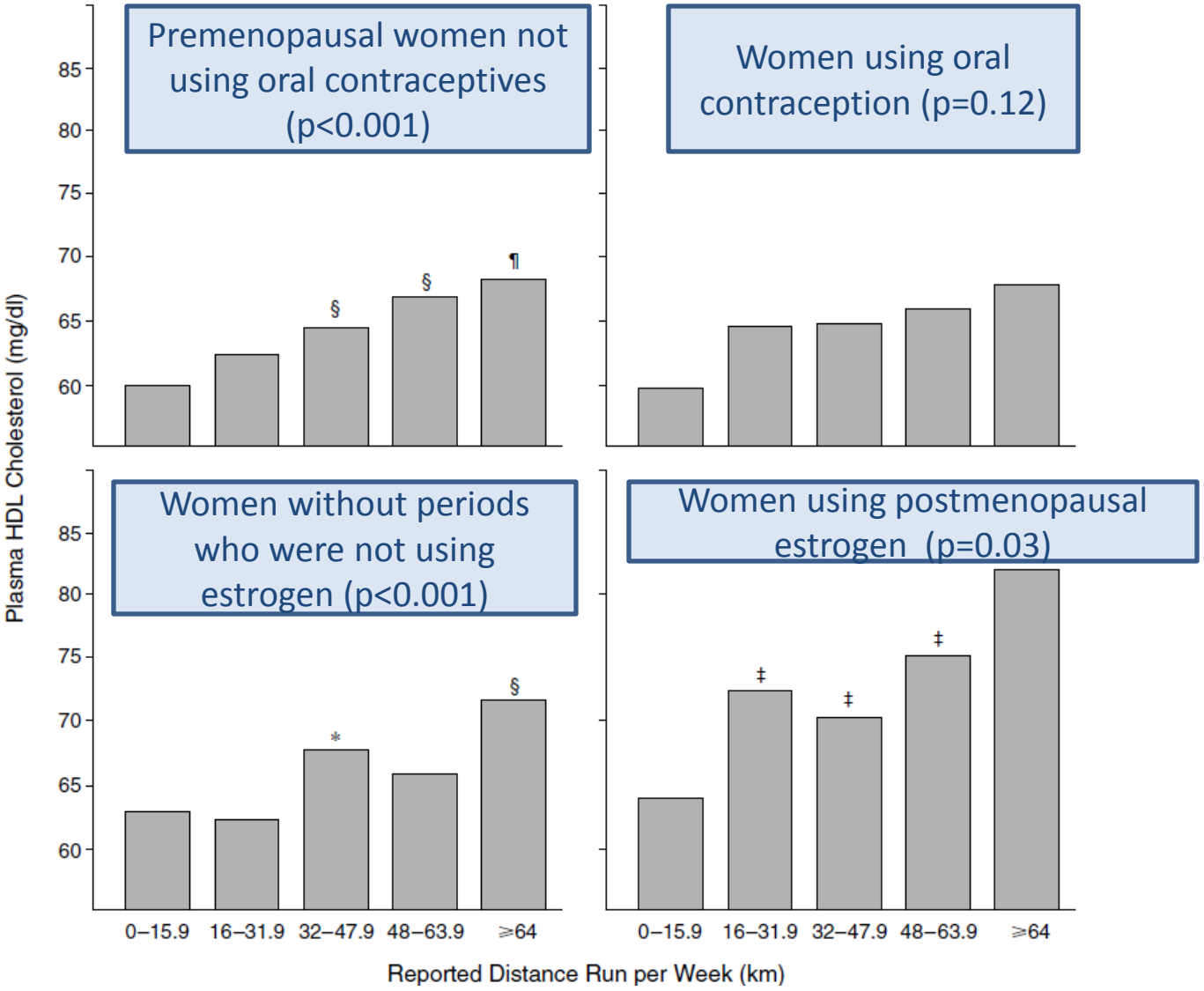
HDL raising strategies

Lifestyle modification

Life Style Modification	**Net HDL % Increase**
Smoking Cessation	**+8.5**
Weight Loss for every kg decrease	+1.0
Dietary Intake:	
- n-3 polyunsaturated fatty acids	+8.0
- Alcohol consumption	+8.3
- Soy protein	+2.4
Exercise: Dose-dependent	+2.6 - +8.5

R. Birjmohun et al, Future Lipidology 2006 (1) 47-55

HDL-C and Distance Run per Week



Williams PT. NEJM 1996;334:1298-1303

Effect of running (women)

For each additional km run per week:

HDL-C were **0.003** mmol/L higher (SD: 0.0005)

0.116 mg/dl higher (SD: 0.0193)

Williams PT. NEJM 1996;334:1298-1303

Conditions With Reduced HDL-C

- Type 2 diabetes
- Metabolic syndrome
- Obesity
- Physical inactivity
- Very high carbohydrate diet
- Mixed dyslipidemia
- Hypertriglyceridemia

- Smoking

- Betablockers
- Anabolic steroids
- Progestational agents

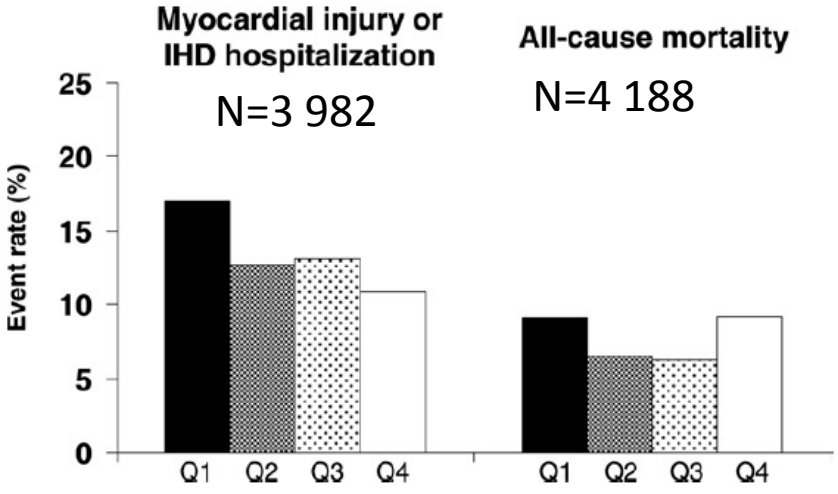
Conclusion

- High levels of HDL-C : Low risk of CVD
- No randomized clinical trial has to date shown that isolated increase of HDL-C is beneficial
  (VA-HIT: decrease in TG)
- New trials use drugs with multiple effects on lipids
  (Dal-OUTCOMES exception?)
- Will we ever find out about HDL ?

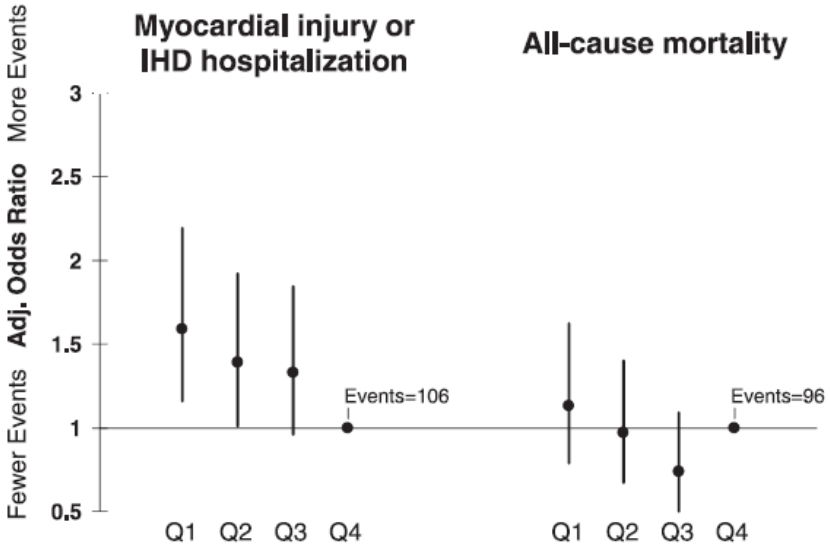
Ischemic Heart Disease Risk by HDL-C
Patients with LDL-C < 60 mg/dl

Palo Alto Veterans Administration Medical Center And Affiliated Clinics

Unadjusted rates



Adjusted odds ratios

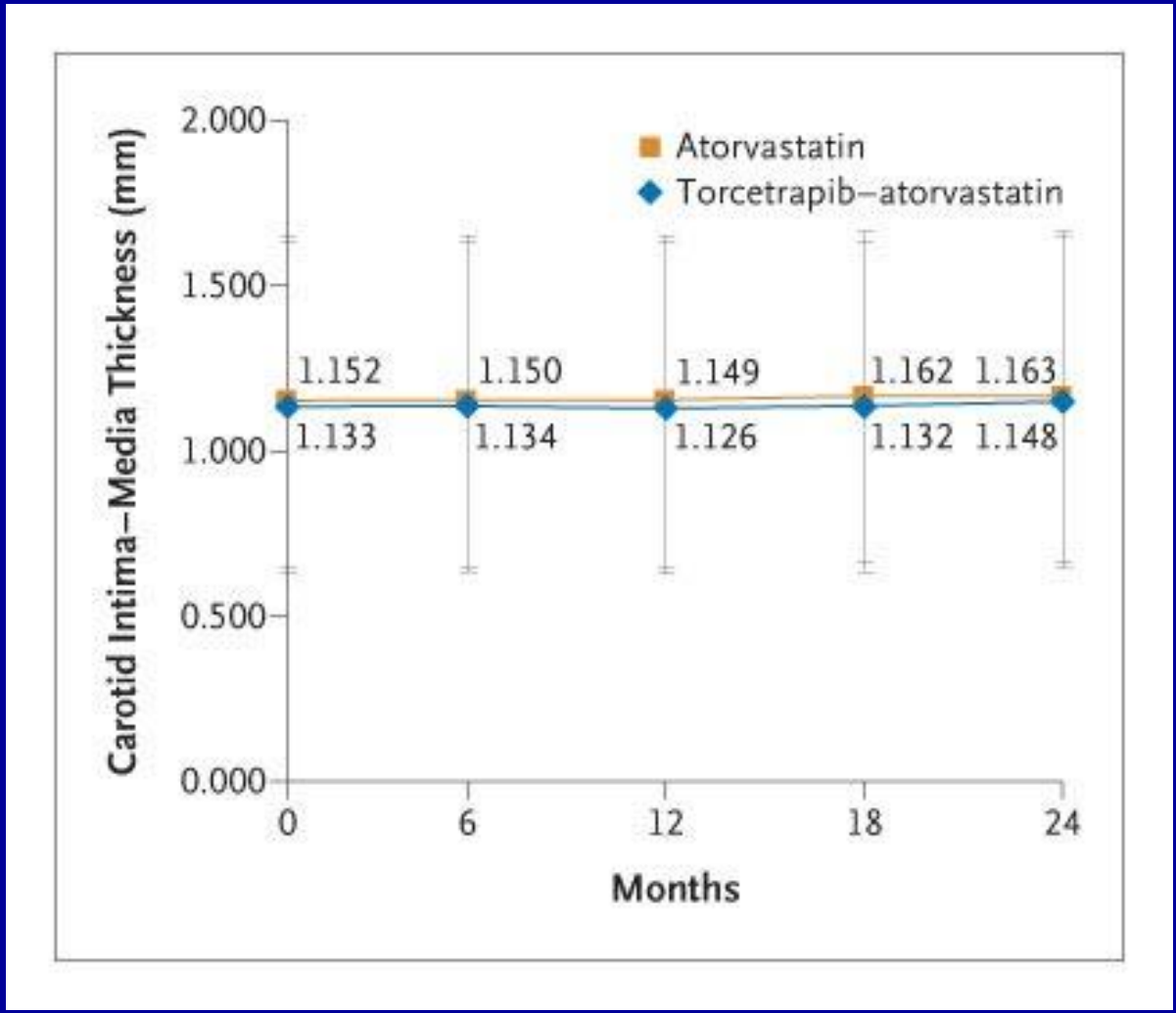


Mean HDL-C

Q1: 28 mg/dl	0.72 mmol/L
Q2: 36 mg/dl	0.93 mmol/L
Q3: 43 mg/dl	1.11 mmol/L
Q4: 63 mg/dl	1.63 mmol/L

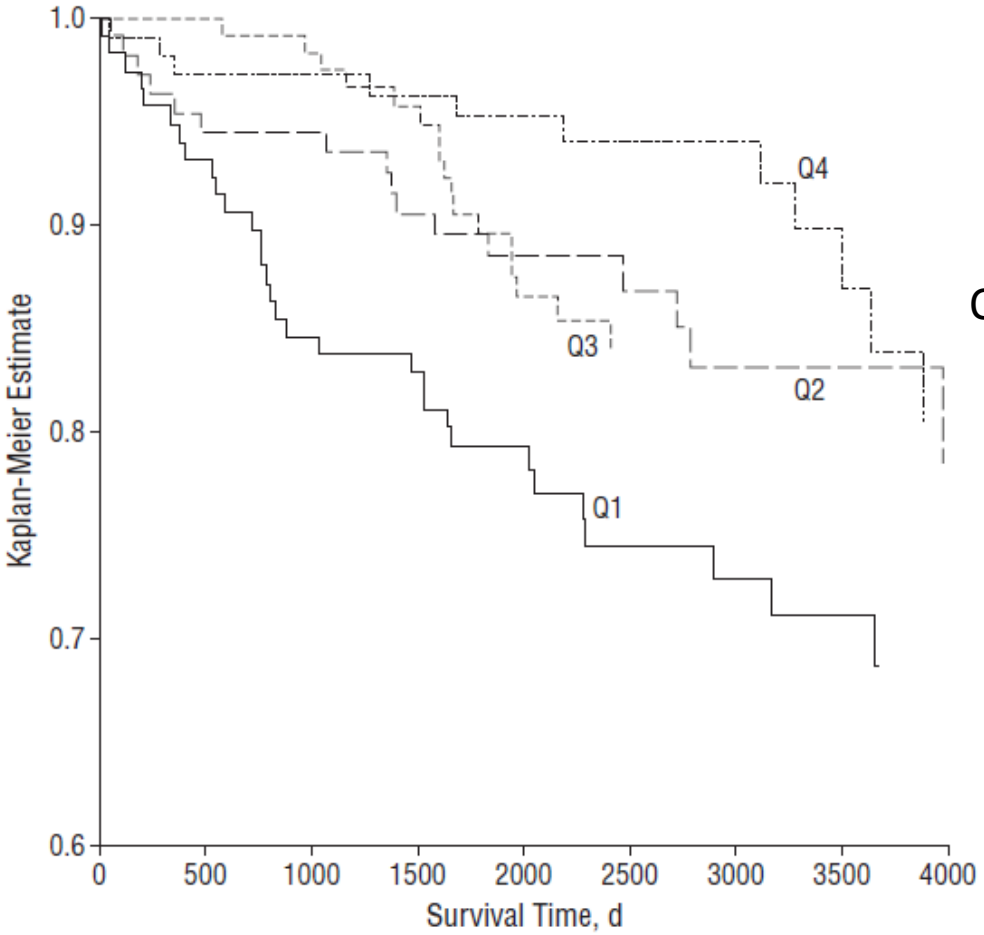
deGokma EM, et al. JACC 2008;51:49-55

Average Maximum Carotid Intima-Media Thickness during 24 Months of Treatment



Kastelein J et al. N Engl J Med 2007;356:1620-1630

Framingham Offspring Study
Prognosis by quartiles of change in HDL-C



	Q1	Q2	Q3	Q4
No. of Patients	117	108	121	108
No. (%) of Events	31 (26.5)	17 (15.7)	19 (15.7)	12 (11.1)

Q4: +7.5 to +35 mg/dl

Q3: +2.5 to +7 mg/dl

Q2: -2.7 to +2.3 mg/dl

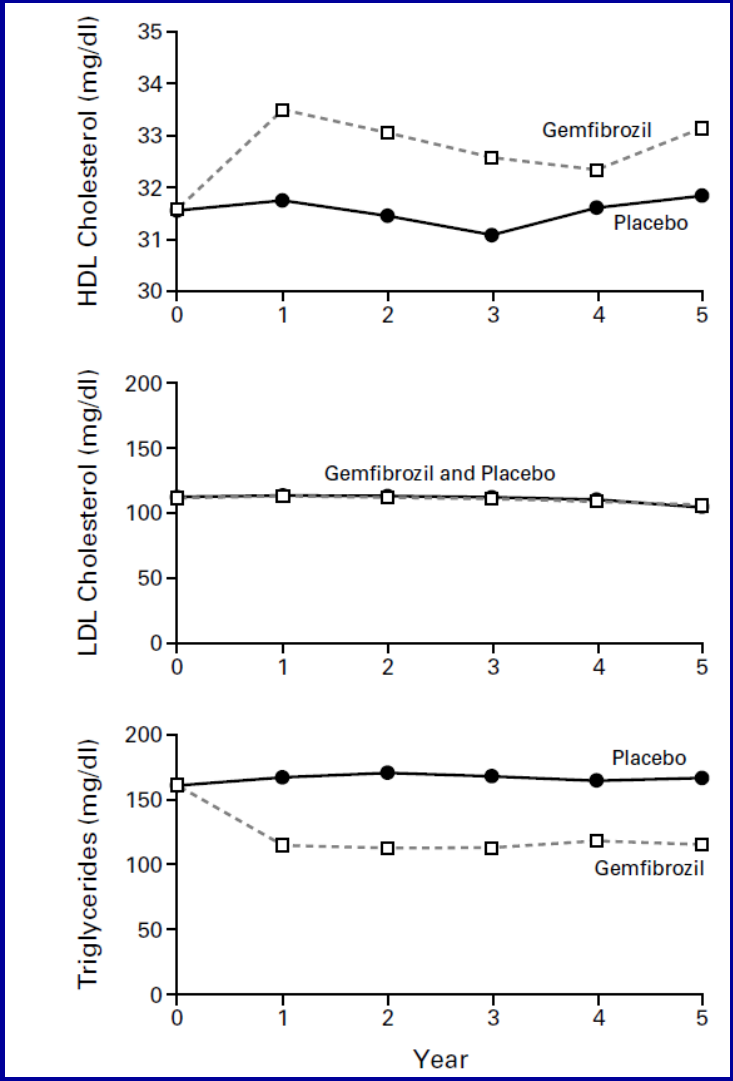
Q1: -37 to -3 mg/dl

VA HIT: Lipids

HDL-C

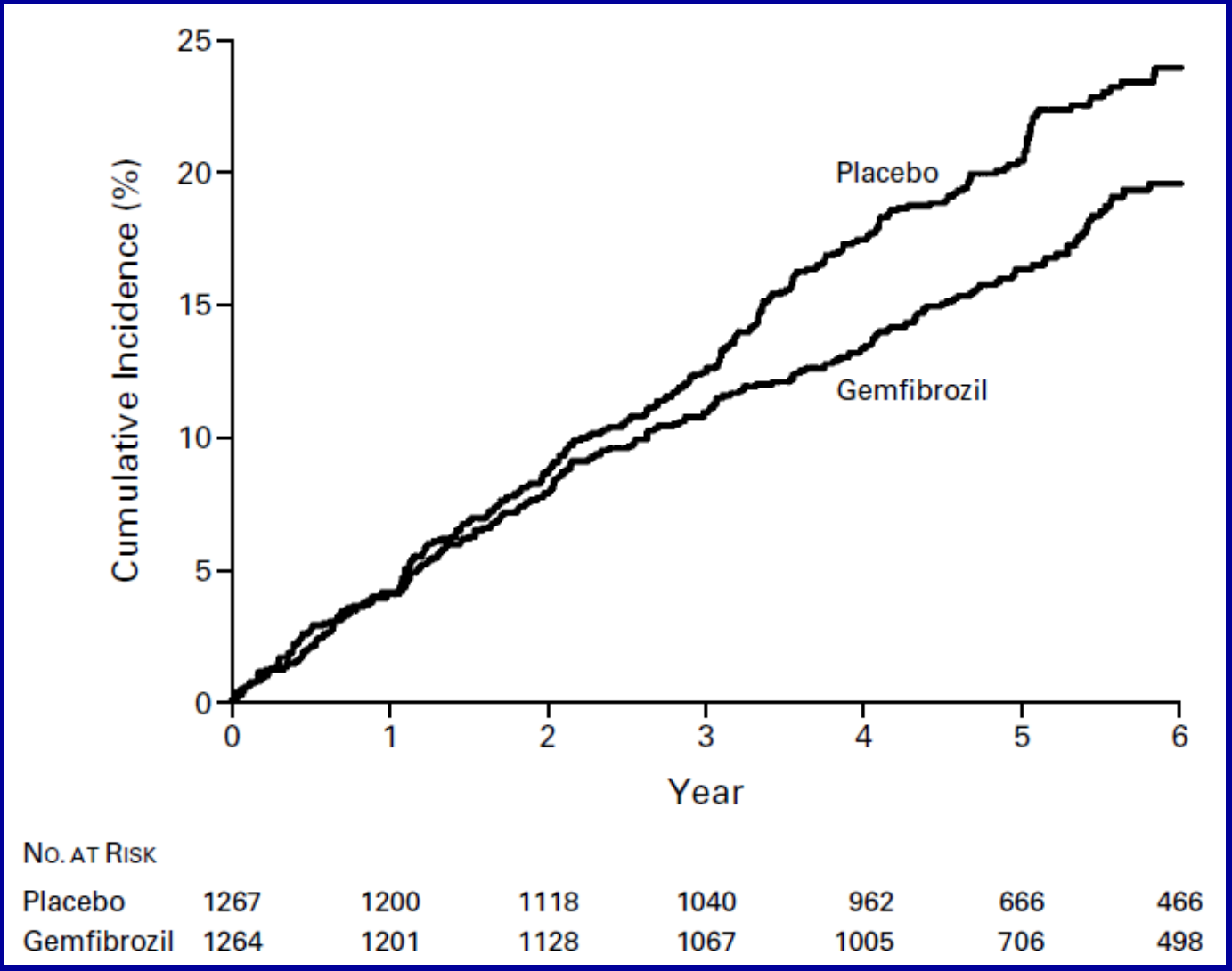
LDL-C

Triglycerides



Rubins HB, et al. NEJM 1999;341:410-418

VA-HIT: CHD Death & Fatal AMI

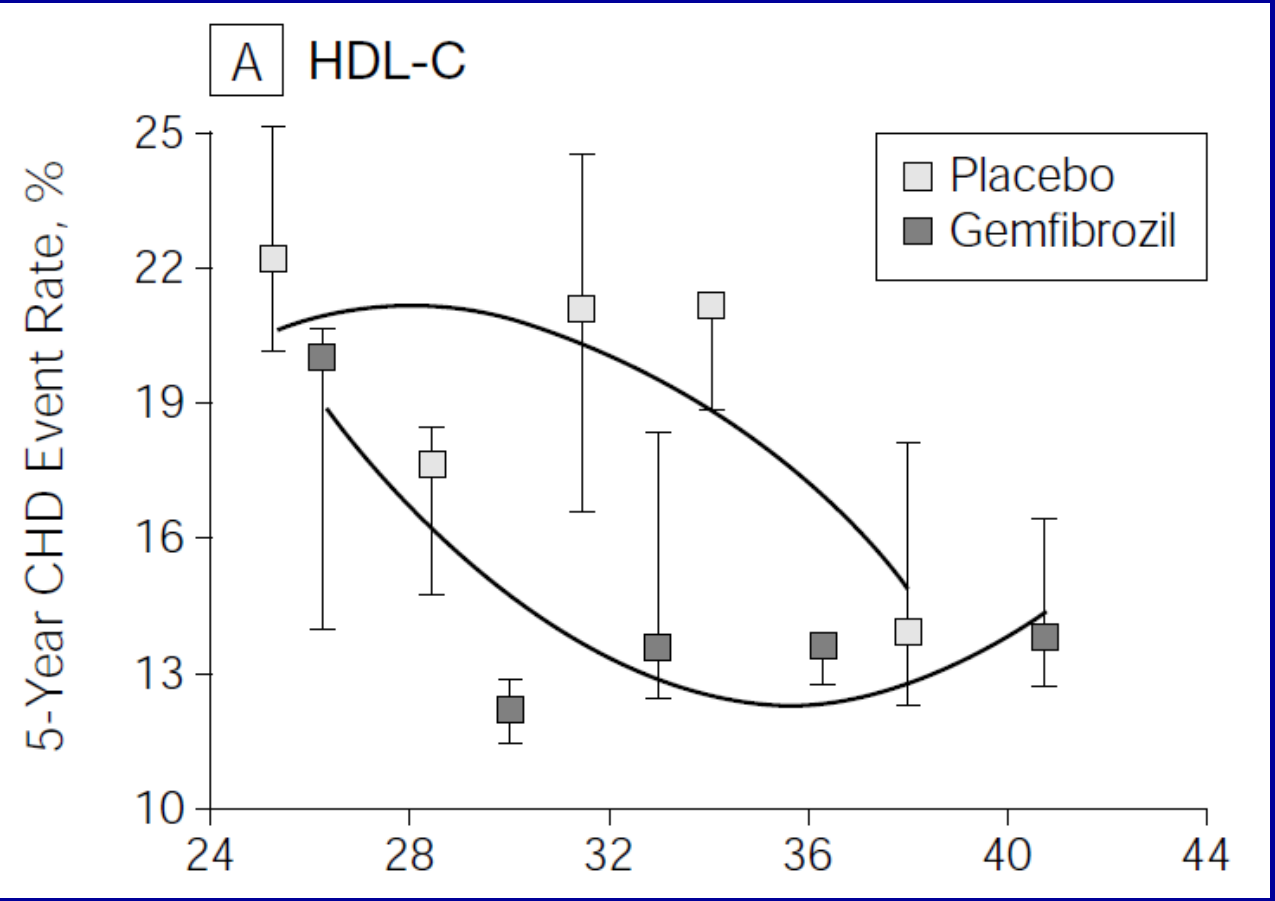


RRR: 22%

p= 0.006

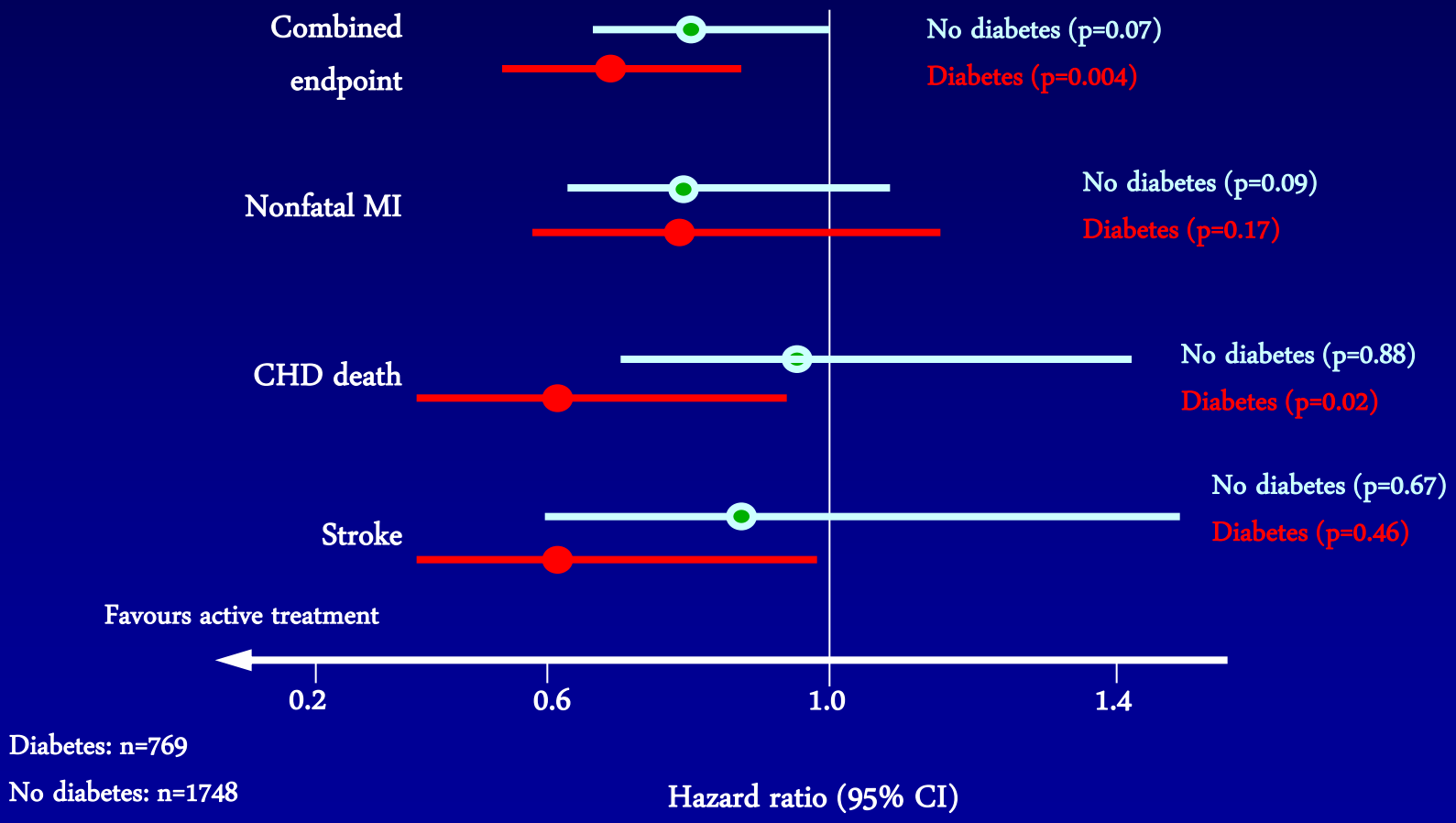
Rubins HB, et al. NEJM 1999:341:410-418

VA-HIT: Relation of CHD to Quintiles of in-trial HDL-C



Robins SJ, et al JAMA 2001;285:1585-1591

Greater benefits from increasing HDL-C in type 2 diabetic subjects in VA-HIT



Rubins HB et al. *Arch Intern Med* 2002;162:2597-604

Meta-regression models of change in HDL-C, LDL-C or both and clinical outcomes

CHD events (CHD death and non-fatal MI)

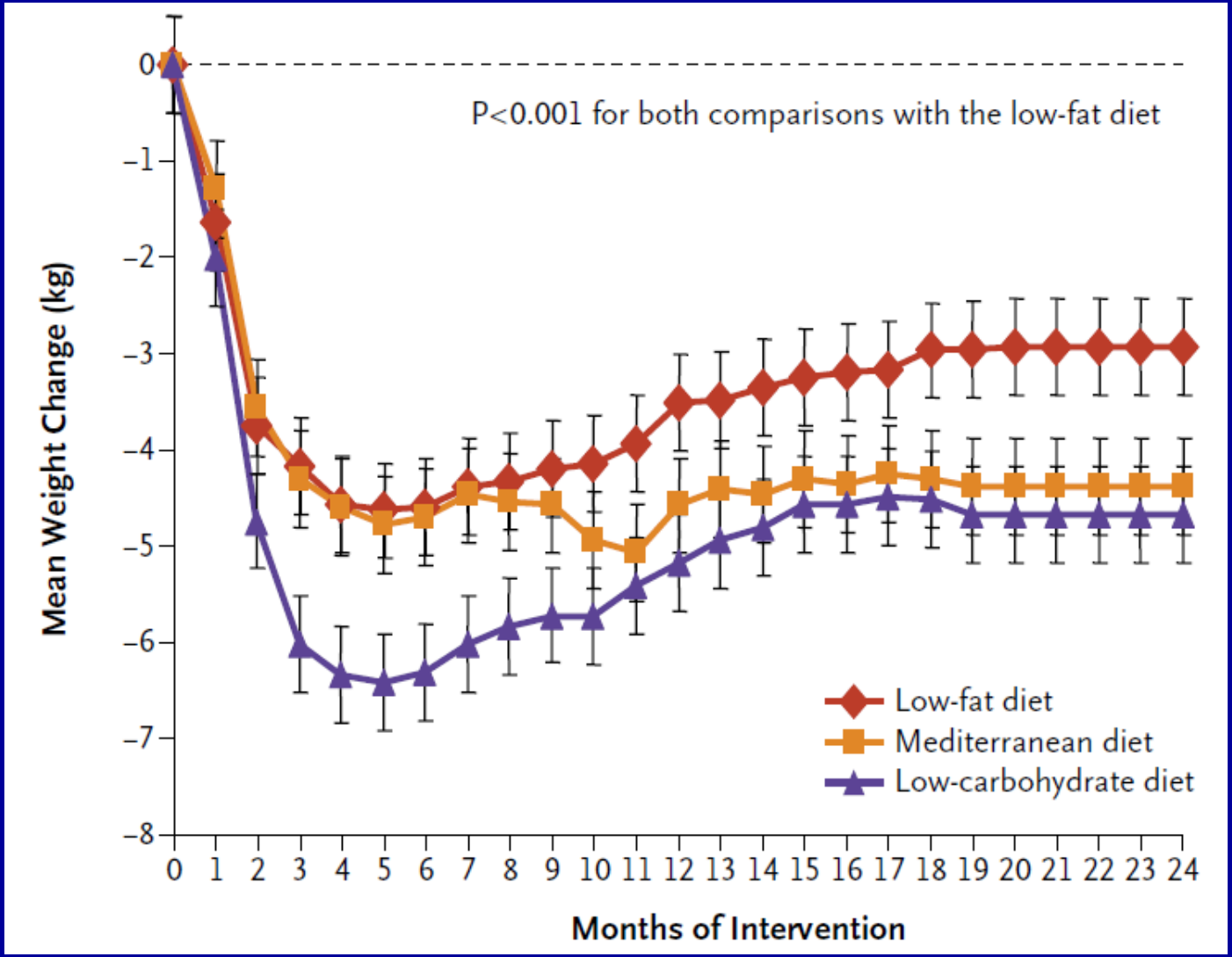
Regression model and predictor	Change in log risk per 10mg/dl increase	P value	R^{2}*
Univariable:			
Change in LDL	4.9 (3.4 to 6.5)	<0.001	0.32
Change in HDL	-8.2 (-24.7 to 8.1)	0.32	0.01
Bivariable:			
Change in LDL	5.1 (3.6 to 6.7)	<0.001	0.33
Change in HDL	6.4 (-7.8 to 20.4)	0.37	
Multivariable┼			
Change in LDL	7.1 (4.5 to 9.8)	<0.001	0.46
Change in HDL	16.0 (-4.2 to 36.9)	0.12	

*Proportion of total variability in log risk ratio of outcome explained by model

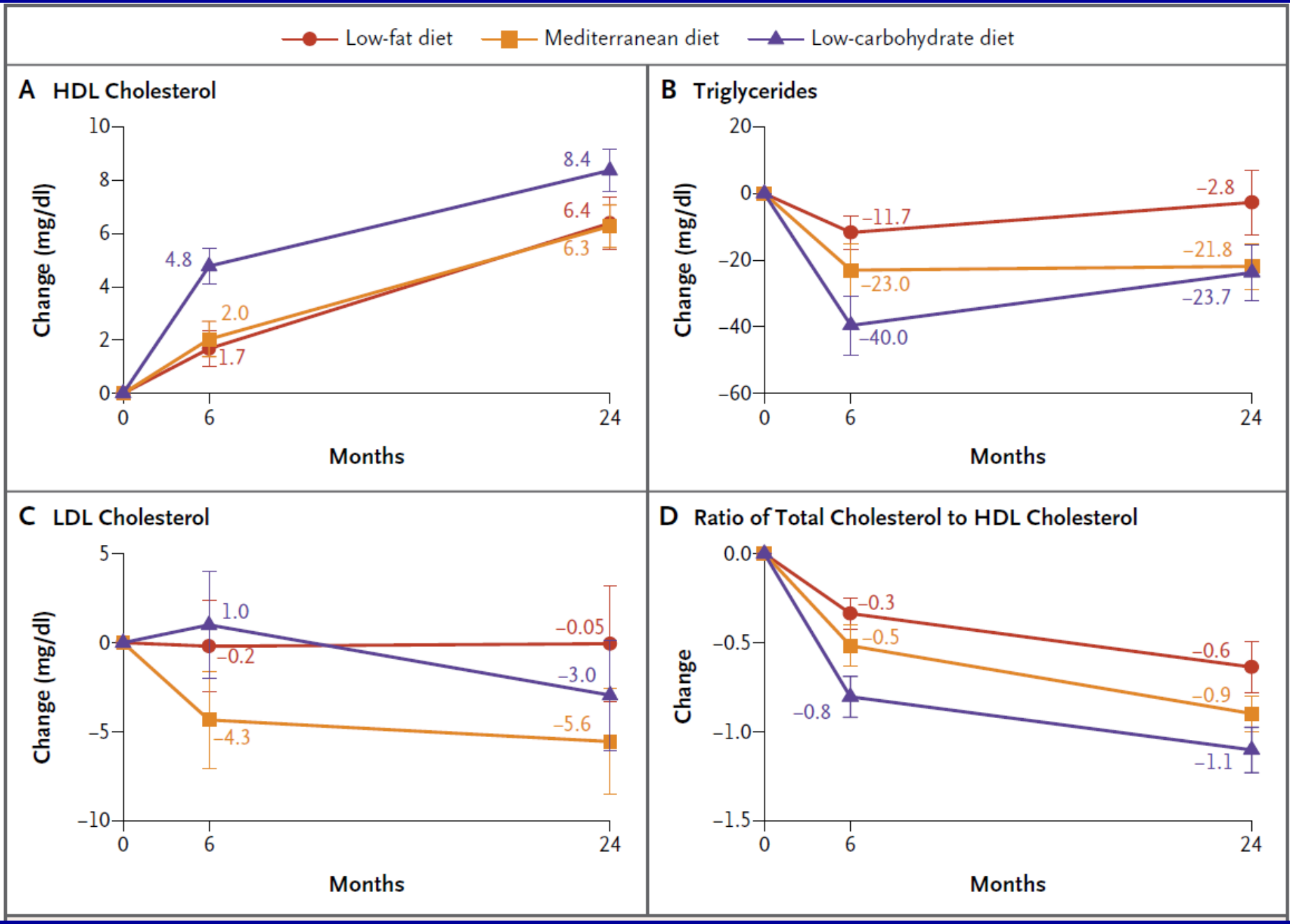
┼Models include adjustment for drug class in addition to variables of lipid subfractions

M Briel et al. BMJ 2009; 338: b92

Weight loss in moderately 322 obese adults

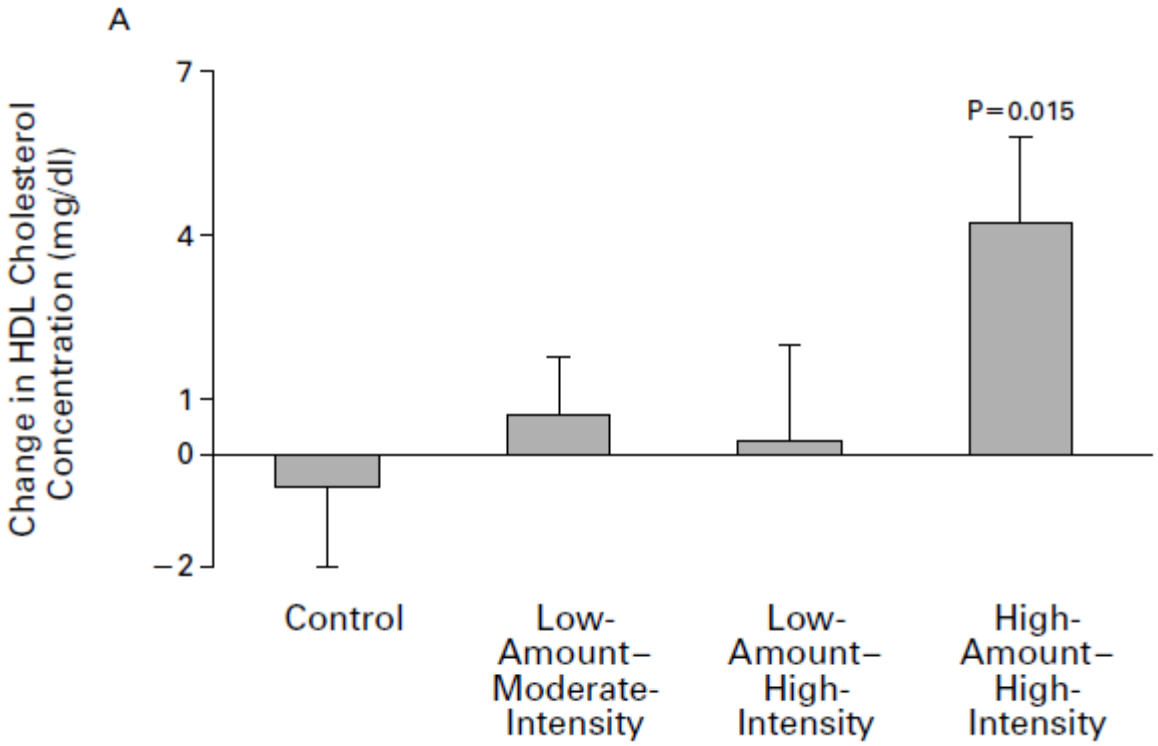


Shai I, et al. NEJM 2008;359:229-241



Shai I, et al. NEJM 2008;359:229-241

HDL-C concentration according to exercise



Kraus WE, et al. NEJM 2002;347:786-789

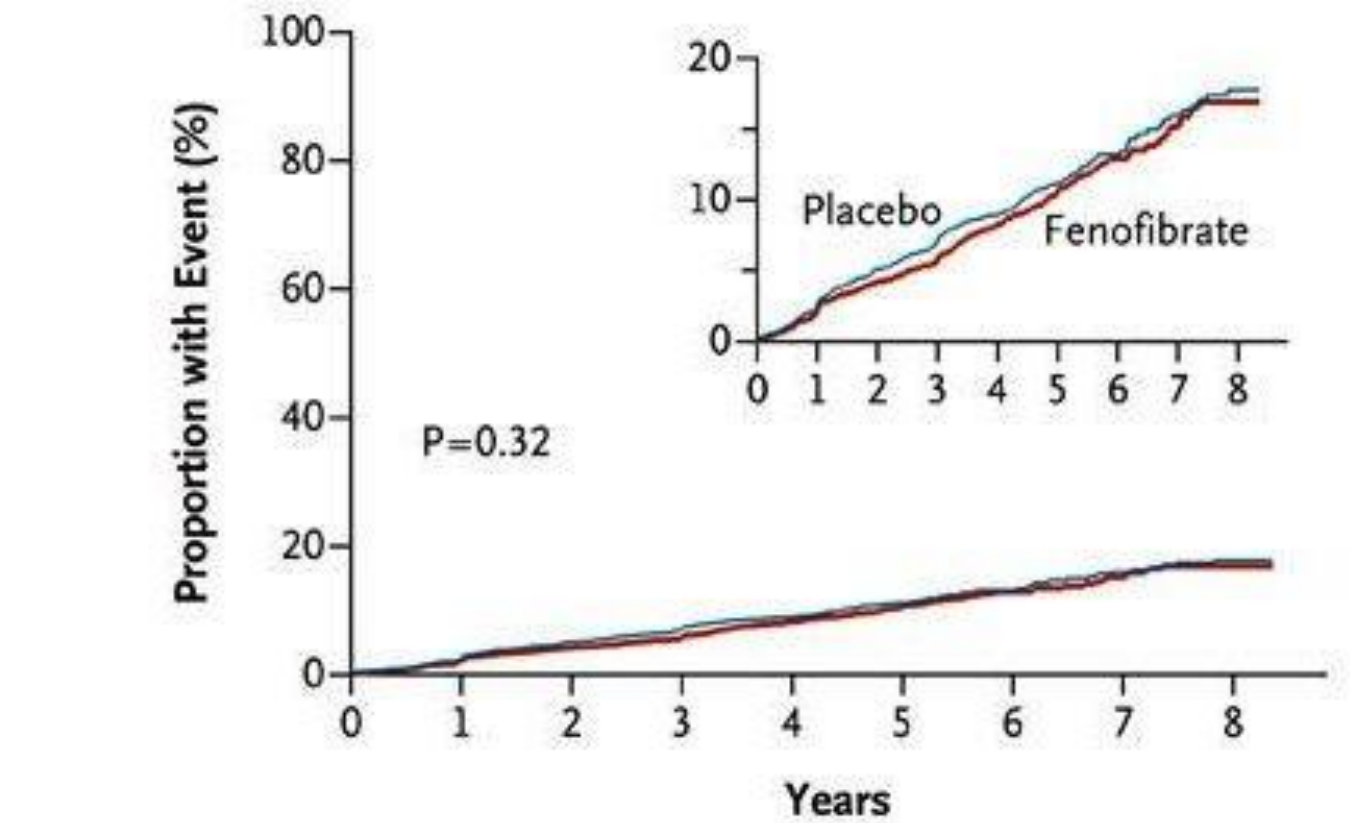
Currently available drugs to raise HDL-C

Drugs	HDL-C change
• Statins	+ 5 % (+ 15%)
• Fibrates	+ 15 %
• (Rimonabant	+ 16 %)
• Glitazones	+ 20 %
• Nicotinic acid	+ 25 %

Currently available drugs to raise HDL-C

Drugs	HDL-C change
• Statins	+ 5 % (+ 15%)
• Fibrates	+ 15 %
• ~~(Rimonabant~~	~~+ 16 %)~~
• Glitazones	+ 20 %
• Nicotinic acid	+ 25 %

ACCORD: Major Vascular Events*



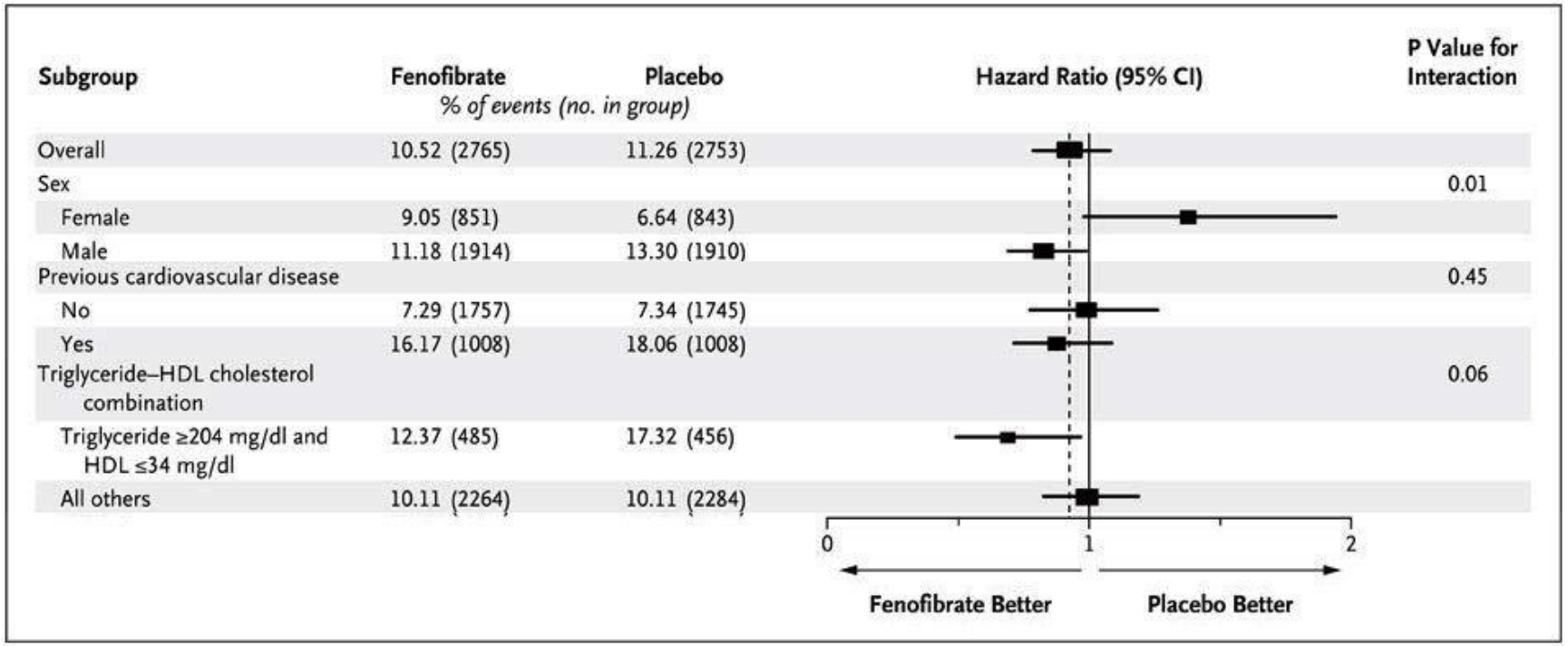
No. at Risk

Fenofibrate	2765	2644	2565	2485	1981	1160	412	249	137
Placebo	2753	2634	2528	2442	1979	1161	395	245	131

***nonfatal MI, nonfatal Stroke, or CVD Death**

The ACCORD Study Group. NEJM 2010; 362: 1563-1574

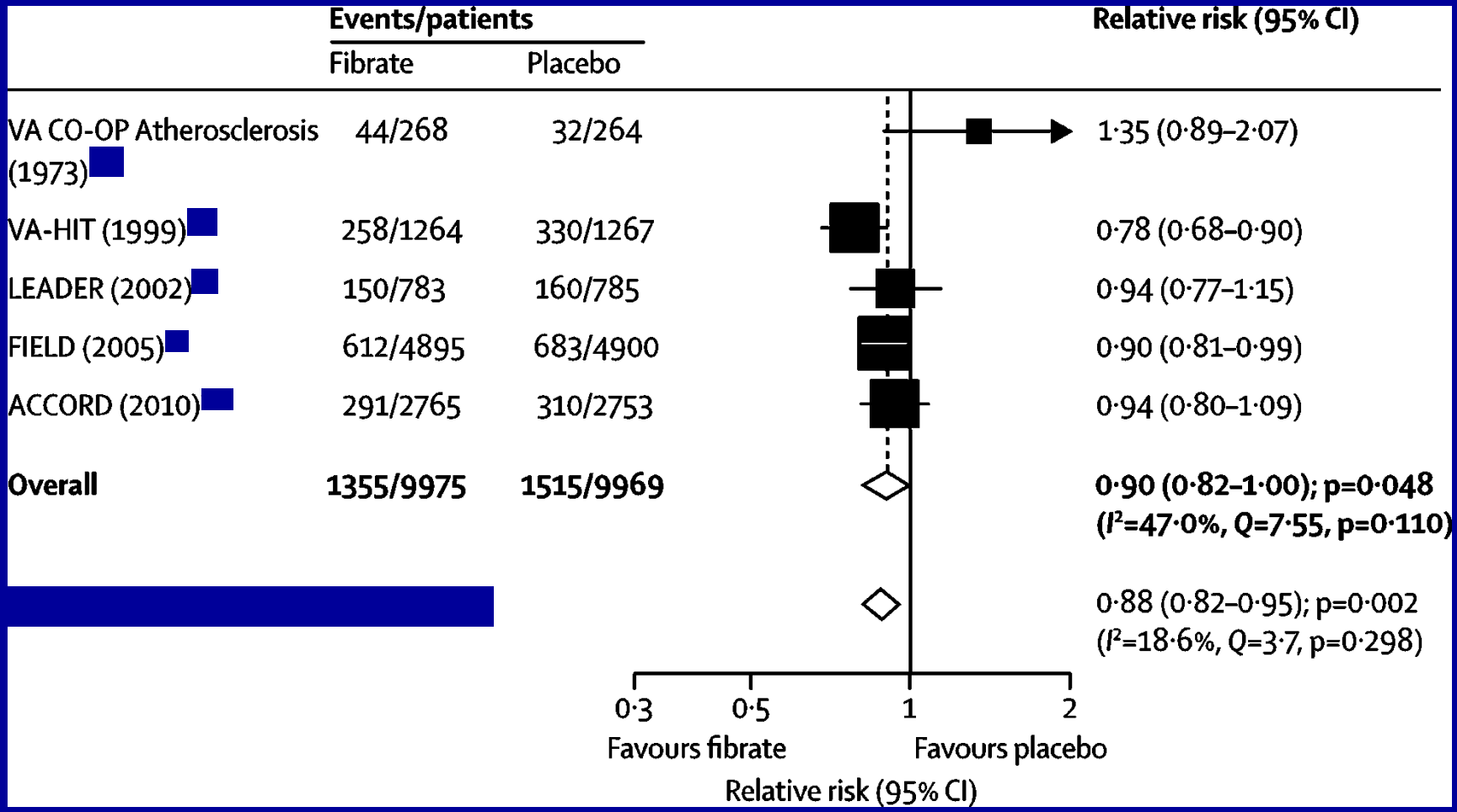
ACCORD: Primary Outcomes in Prespecified Subgroups



Subgroup	Fenofibrate	Placebo	P Value for Interaction
	% of events (no. in group)		
Overall	10.52 (2765)	11.26 (2753)	
Sex			0.01
Female	9.05 (851)	6.64 (843)	
Male	11.18 (1914)	13.30 (1910)	
Previous cardiovascular disease			0.45
No	7.29 (1757)	7.34 (1745)	
Yes	16.17 (1008)	18.06 (1008)	
Triglyceride–HDL cholesterol combination			0.06
Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl	12.37 (485)	17.32 (456)	
All others	10.11 (2264)	10.11 (2284)	

The ACCORD Study Group. NEJM 2010; 362: 1563-1574

Effect of Fibrates on Risk of Major CVD Outcomes



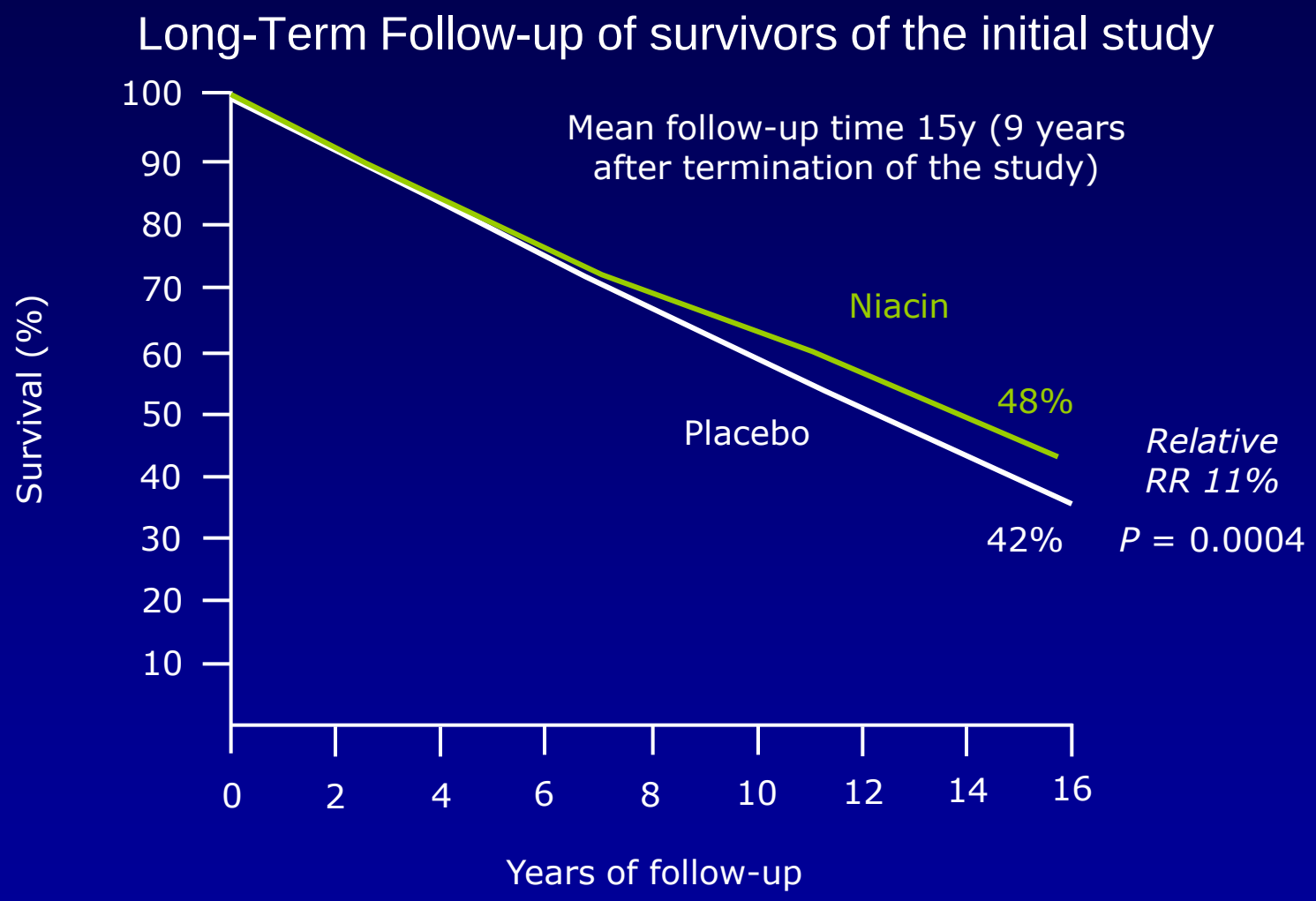
M Jun et al. Lancet 2010; 375: 1875-1884

Coronary Drug Project

- Long-term efficacy and safety of five lipid-influencing drugs
- Study population: post-MI aged 30–64 y
- 1119 pts allocated to 3g/day Niacin, 2789 to placebo
- Initial study conducted between 1966 and 1975
- Mean follow-up: 6.2 years

	Niacin (1119)	Placebo (2789)	Odds Ratio	95% CI
Coronary death/ nonfatal MI	287 (25.6%)	839 (30.1%)	0.81	0.69-0.94
Stroke	95 (8.5%)	311 (11.2%)	0.75	0.6-0.94
CV death	238 (21.3%)	633 (22.7%)	0.92	0.78-1.09

Coronary Drug Project



Canner PL et al. *J Am Coll Cardiol* 1986;8:1245–1255

THRIVE – Heart Protection Study 2

Patients with previous AMI or Stroke

UK, Nordic countries, China

Placebo vs. Niacin 2000 mg + laropiprant
on top of statins ± ezetimibe

n= 25 000

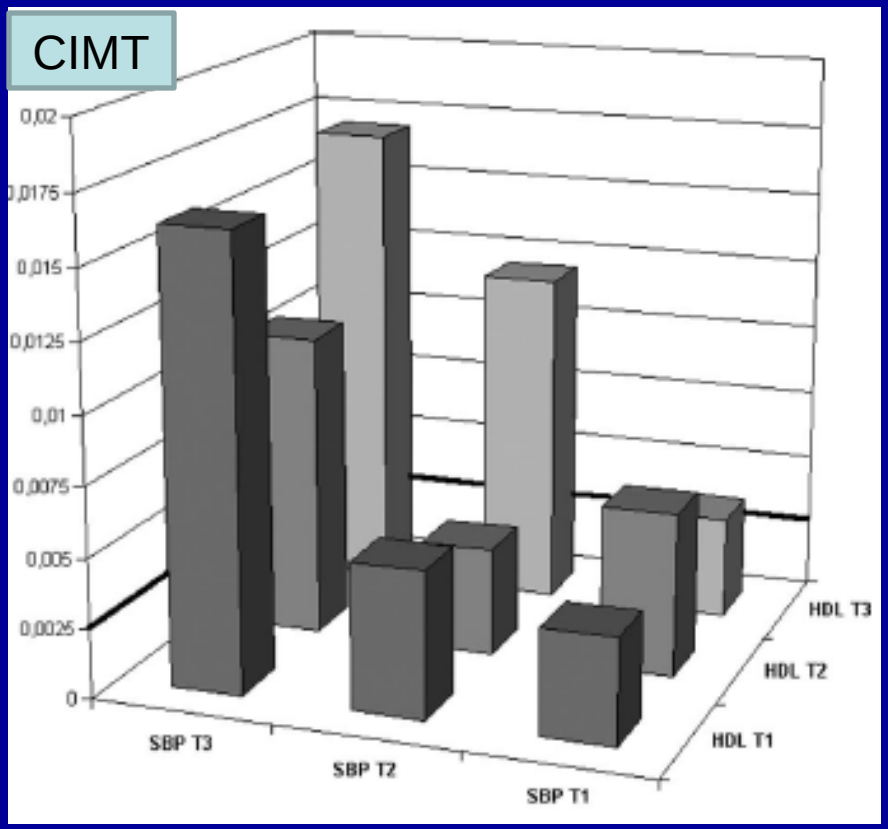
Duration: 4 years

Planned reporting: ACC 2013 (?)

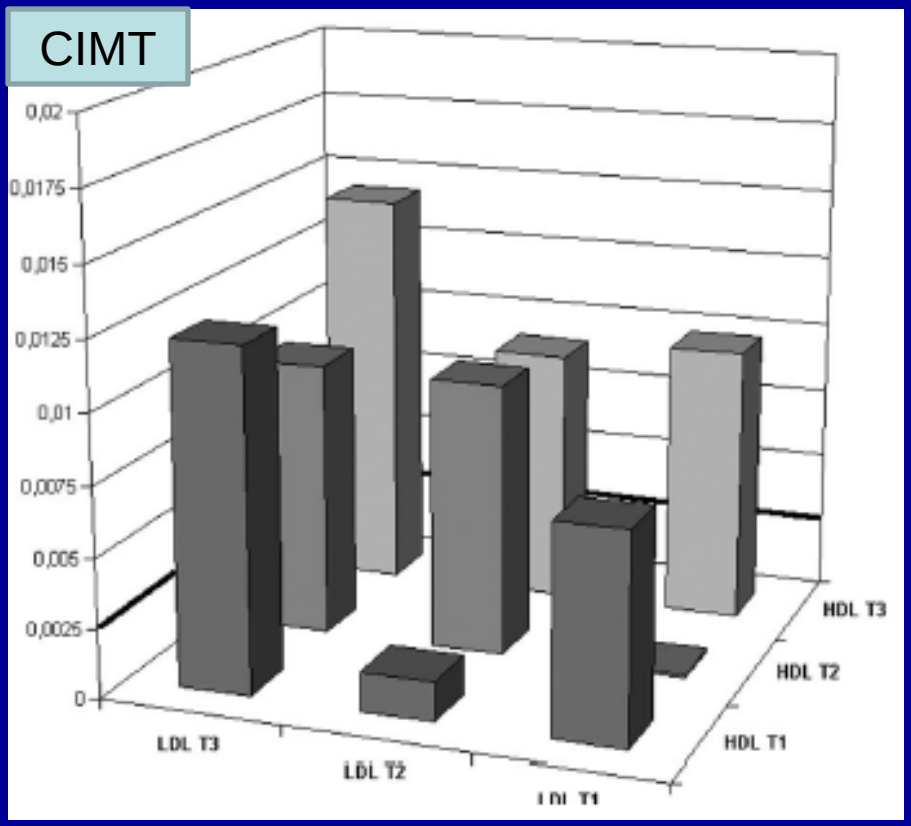
RADIANCE

Relationships between CIMT and tertiles of changes in SBP, HDL and LDL

Tertiles of SBP and HDL-C changes



Tertiles of LDL-C and HDL-C changes



Vergeer M, et al. Circualtion2008;118:2512-2522

Conditions With Reduced HDL-C

- Type 2 diabetes
- Metabolic syndrome
- Obesity
- Physical inactivity
- Very high carbohydrate diet
- Mixed dyslipidemia
- Hypertriglyceridemia

- Smoking

- Betablockers
- Anabolic steroids
- Progestational agents

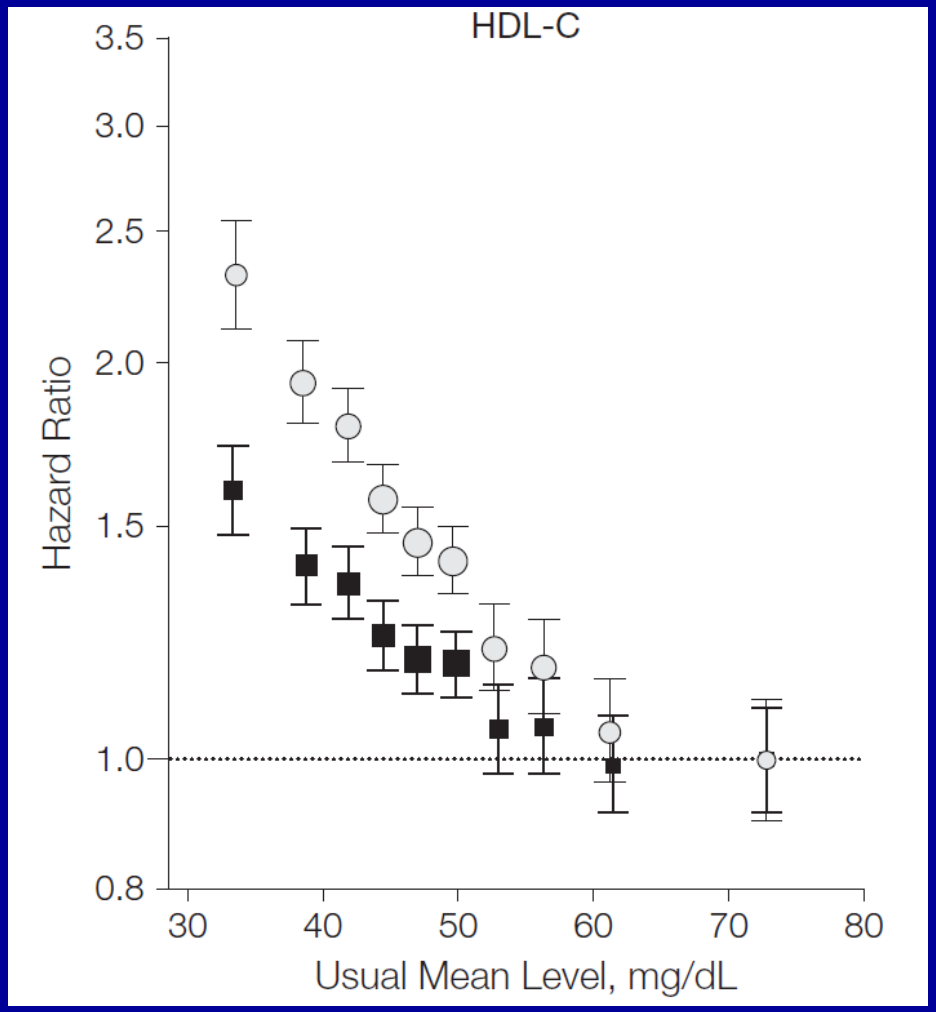
Mutations or Deficiencies With Reduced HDL-C

- Apo A-I
- ABCA-1
- LCAT
- CETP

- May account for 40 % of HDL-C variation

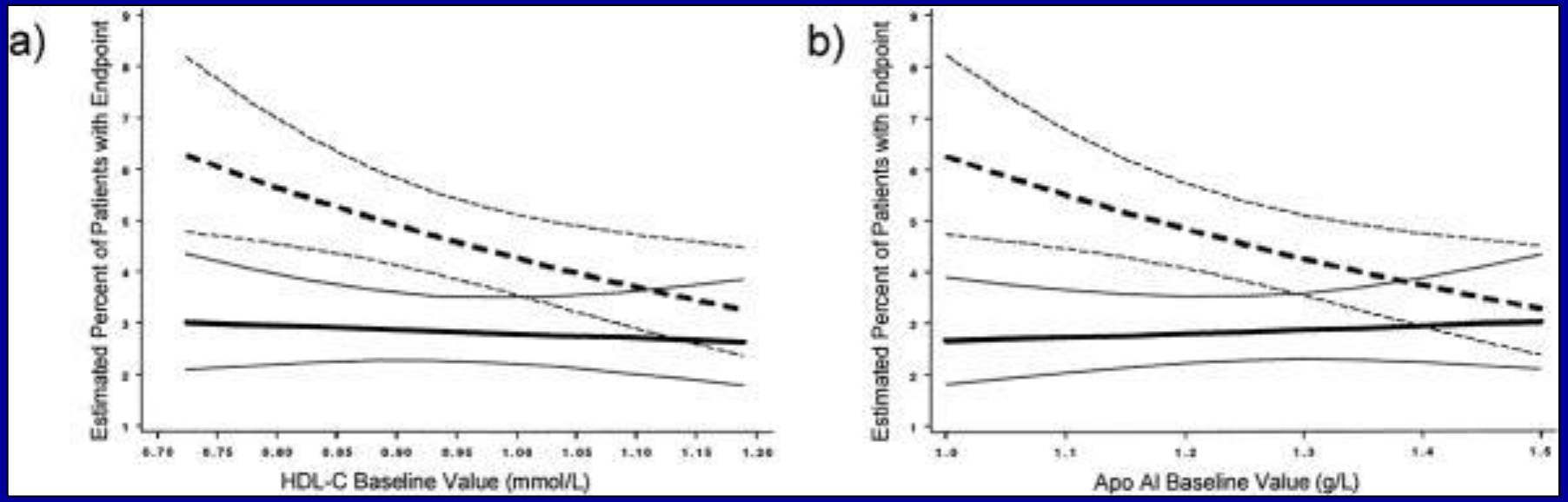
Chapman MJ. Pharmacology & Therapeutics 2006

CHD Risk and HDL-C: (n=302, 430 (12785 cases), 68 studies



The Emerging Risk Factors Collaboration; JAMA 2009; 302: 1993-2000

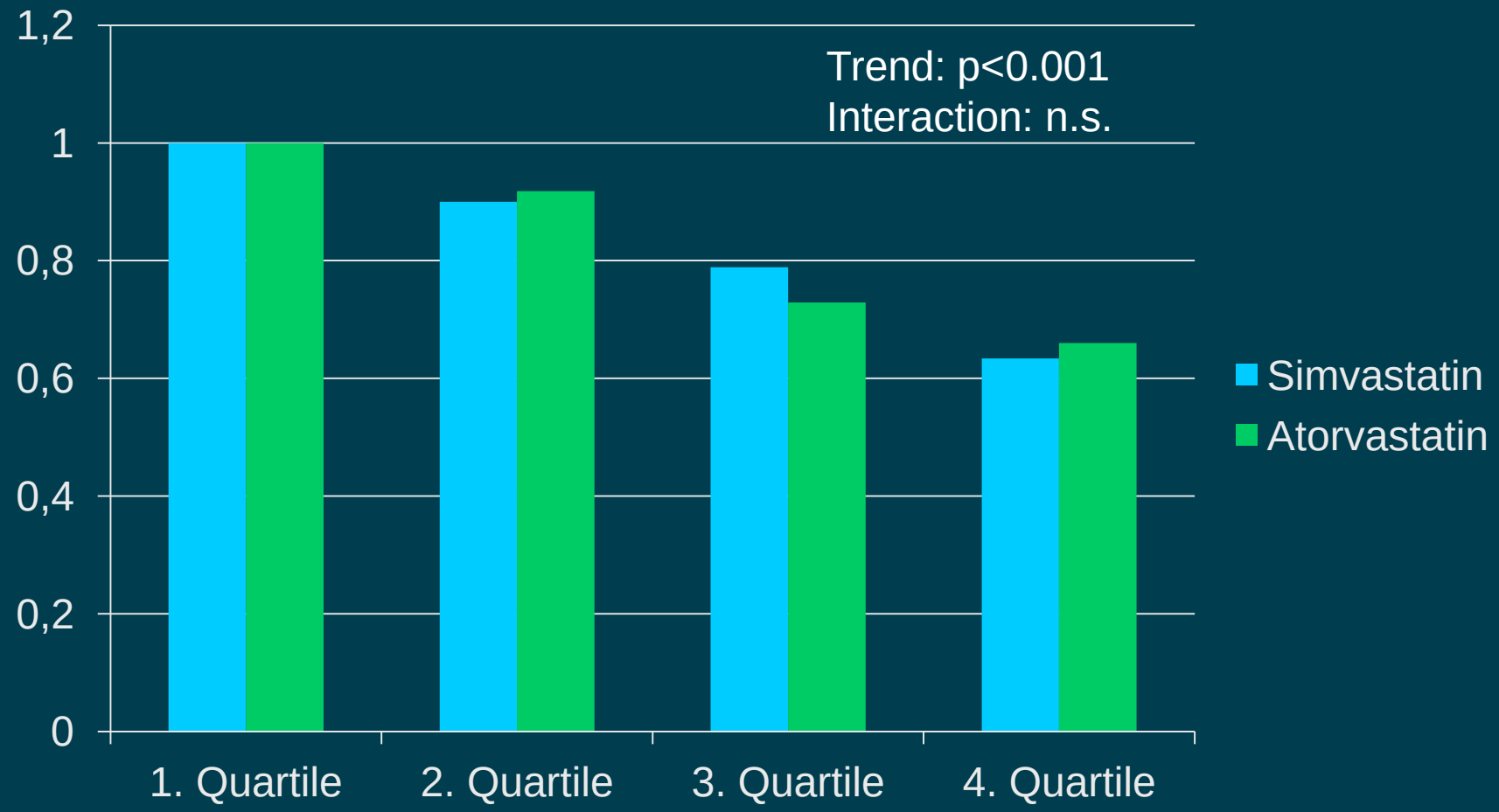
AFCAPS/TexCAPS
Relation of Baseline HDL-C and Apo A1Acute coronary events



Logistic regression models adjusted for age, sex, marital status, hypertension, smoking, and family history of relation between AMCEs and (a) baseline HDL-C or (b) baseline apoAI, with 95% CI. Dashed line represents placebo; solid line, lovastatin.

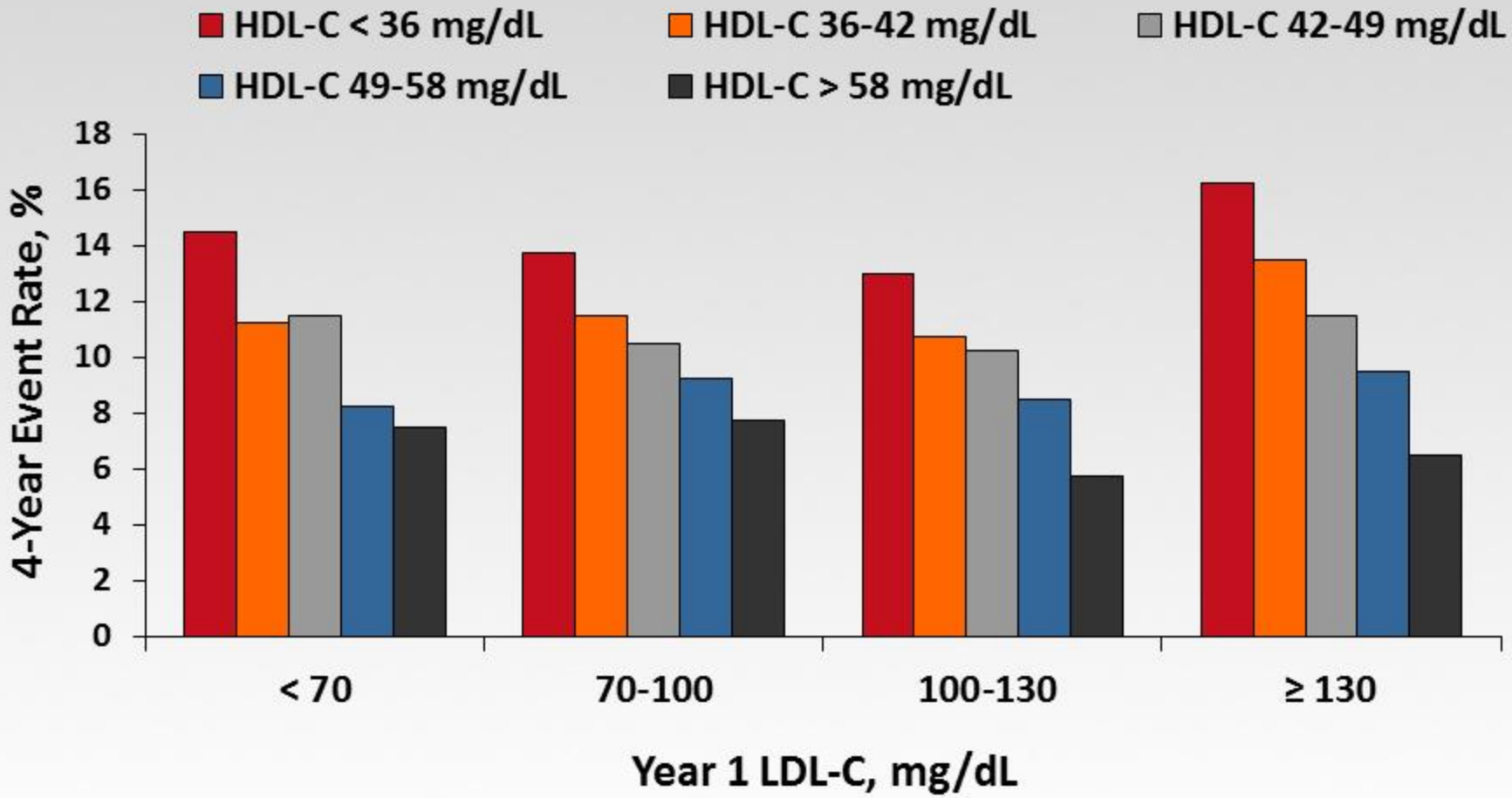
Gotto, AM, et al. Circulation 2000;101:477-484

Relative Risk of CHD by on-treatment Apo A1



Holme I 2012 Data on file

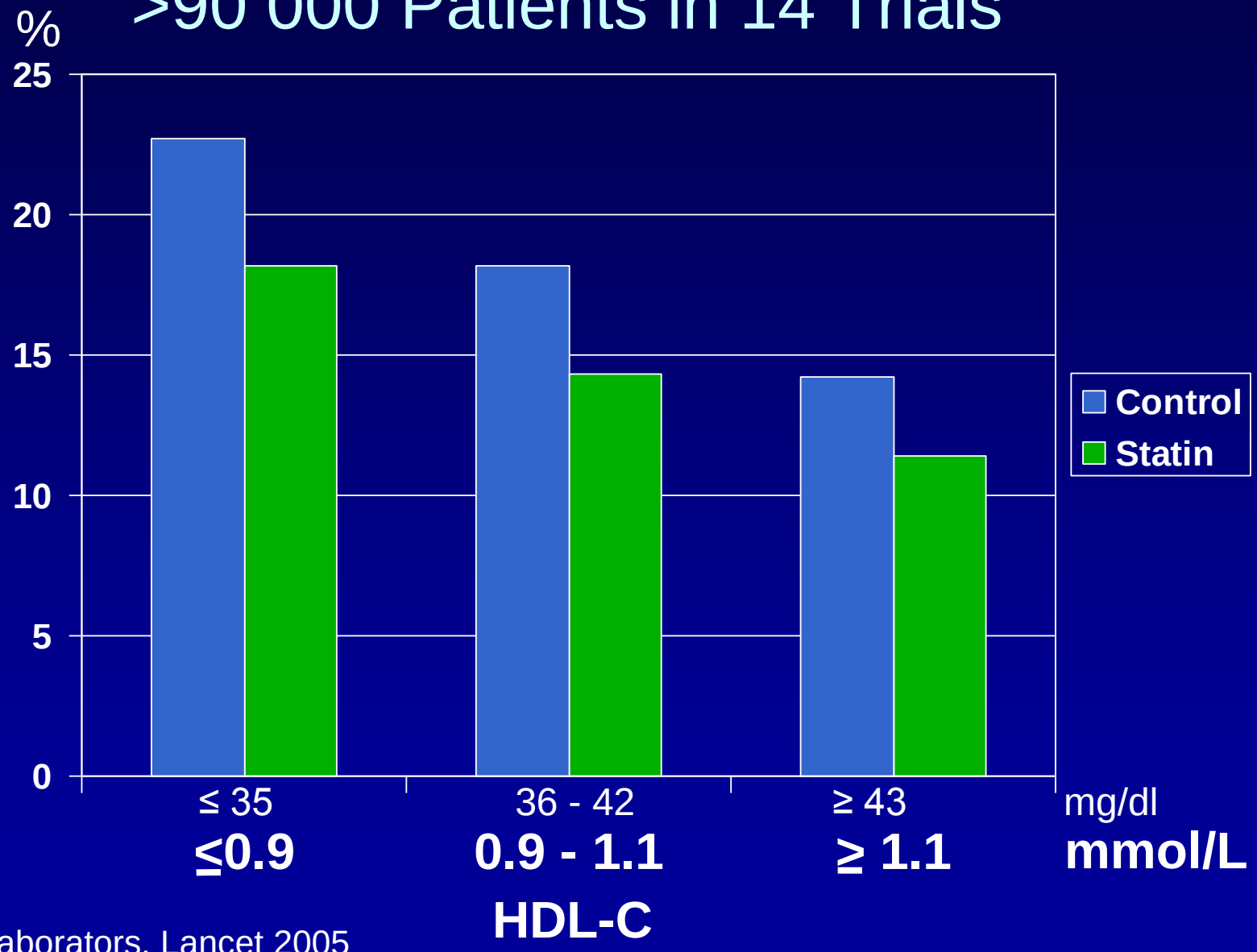
Cholesterol Treatment Trialists' Collaboration: LDL-C, HDL-C, and Major Vascular Events on Statin Treatment



Keech AC, et al. AHA 2011.

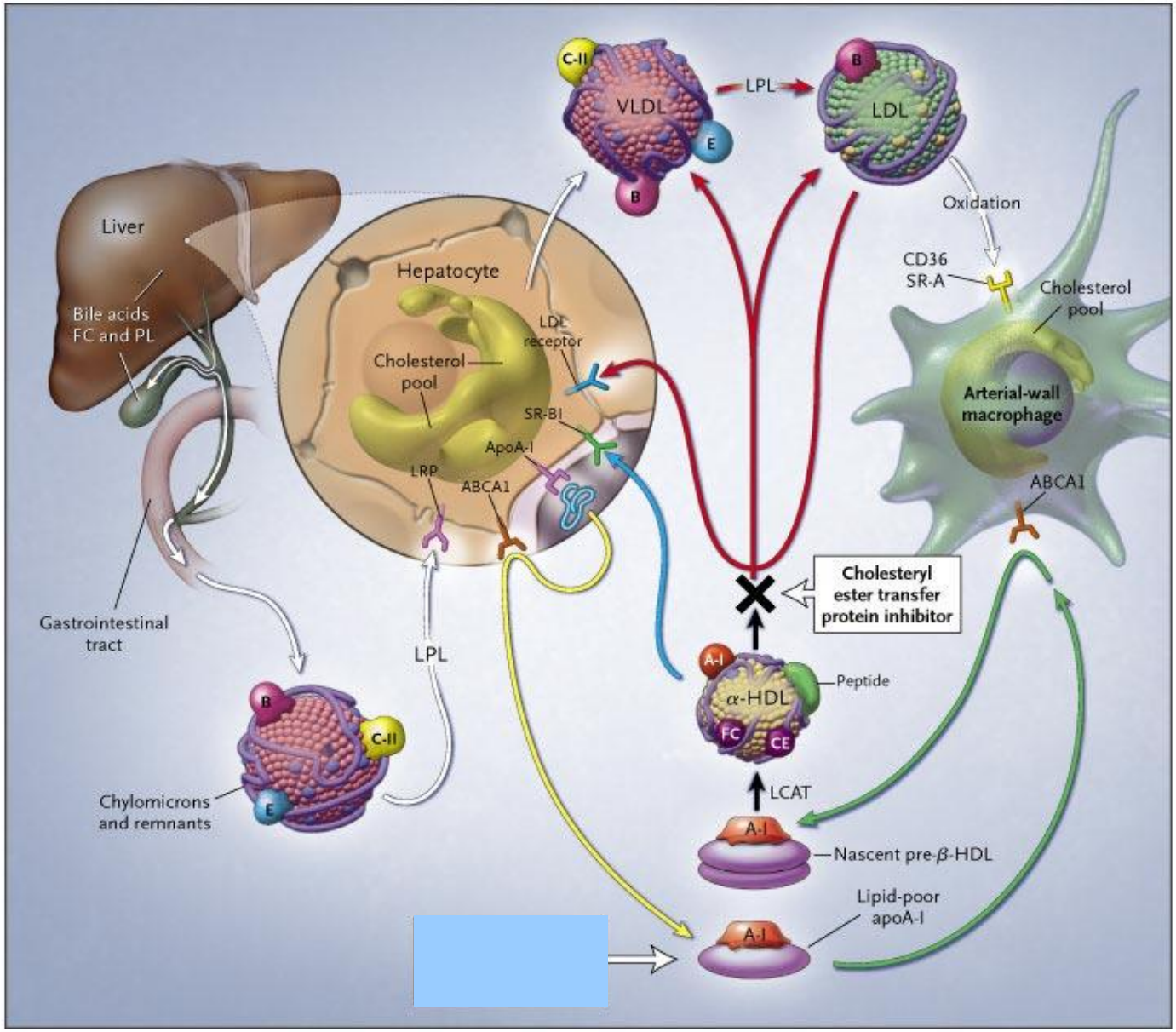
HDL-C and Risk in CTT Metaanalysis

>90 000 Patients in 14 Trials



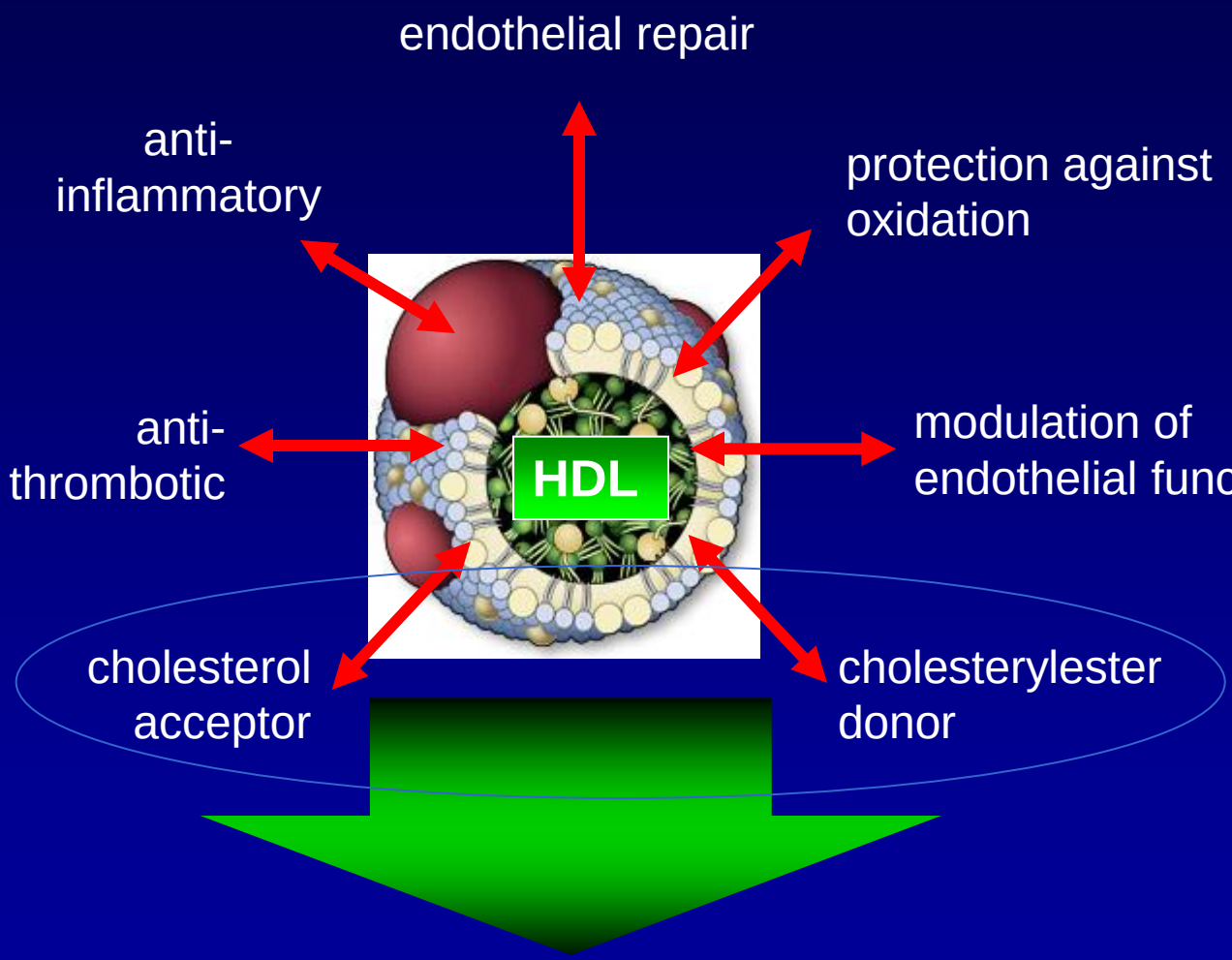
CTT Collaborators. Lancet 2005

Reverse Cholesterol Transport by HDL



Brewer HB,
NEJM 2004

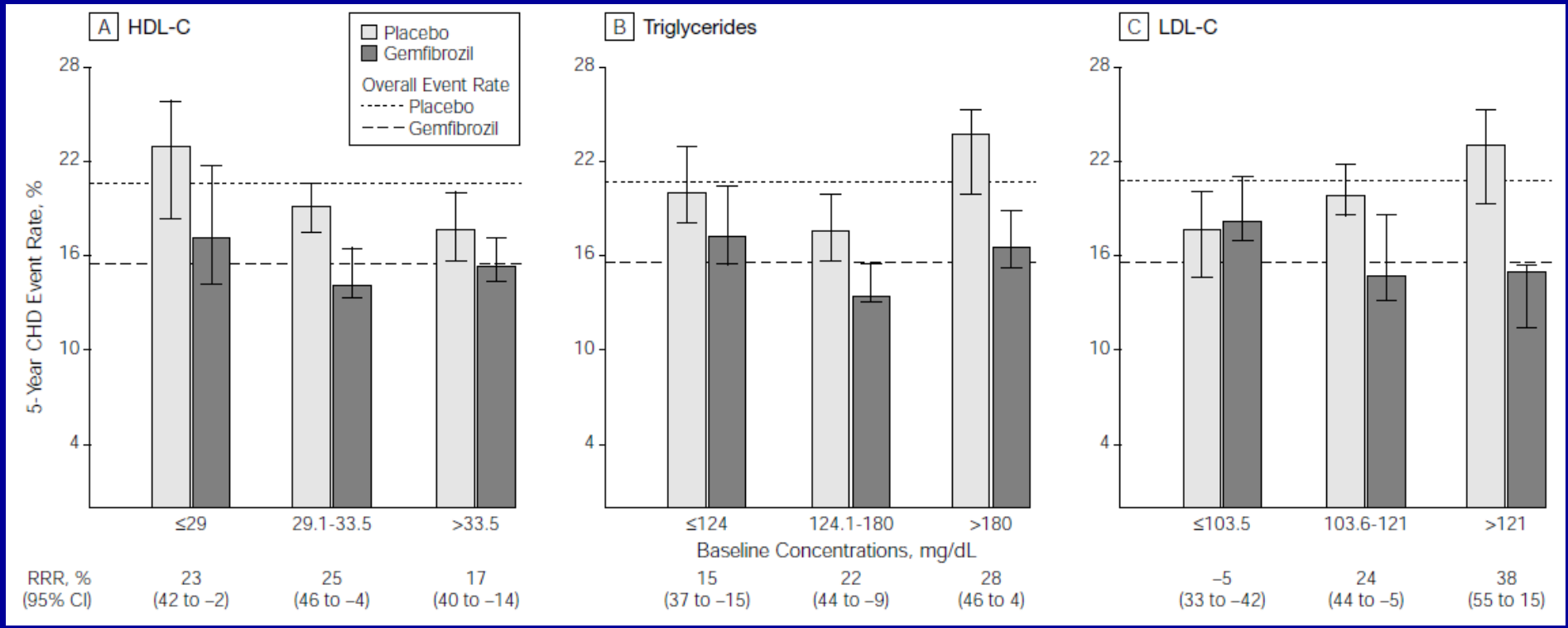
Why Does HDL Protect?



Reverse Cholesterol Transport (RCT)

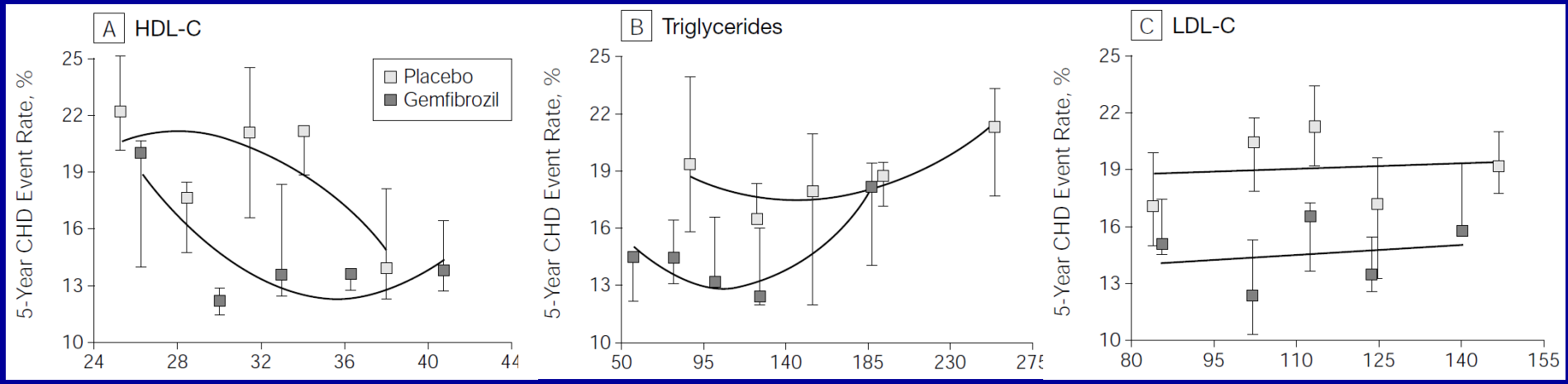
Protection of the vessel wall

VA-HIT: Relation of CHD Incidence to Baseline Lipids



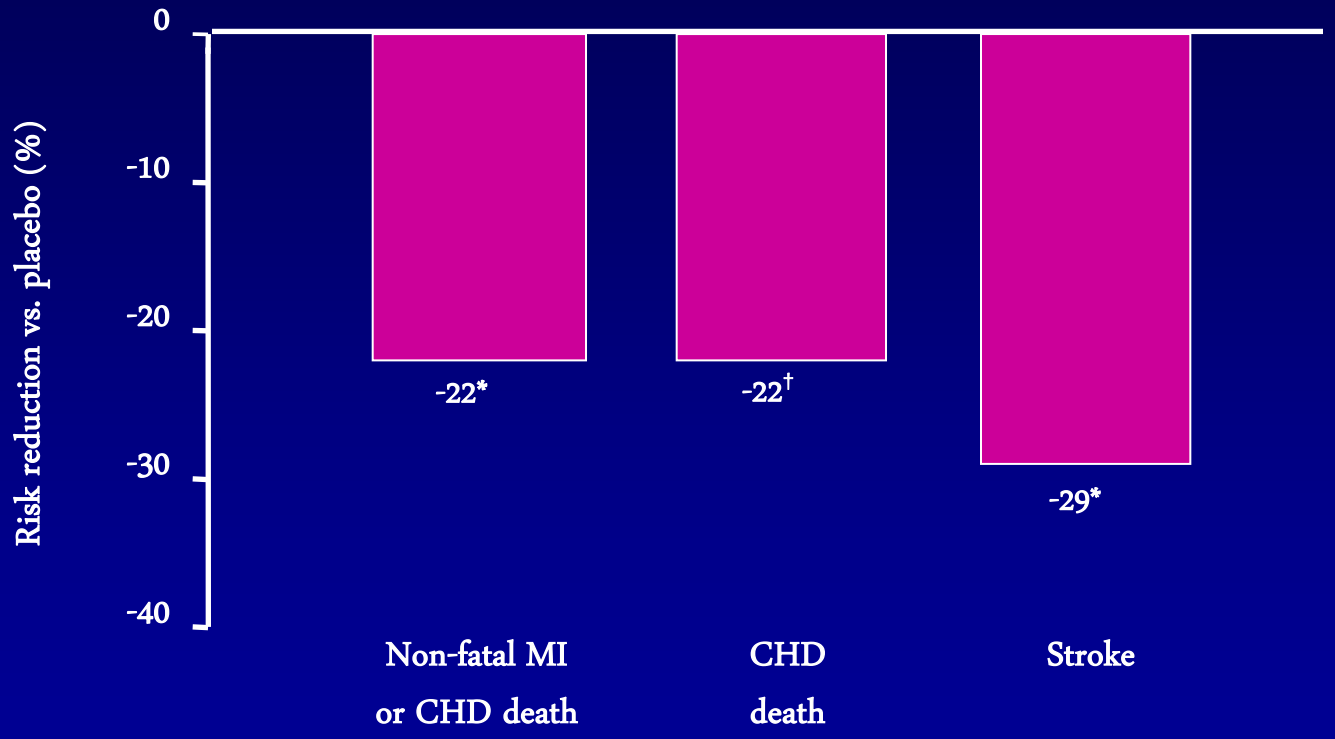
Robins SJ, et al. JAMA 2001;285:1585-1591

VA-HIT: Relation of CHD to Quintiles of in-trial Lipids



Robins SJ, et al JAMA 2001;285:1585-1591

Outcome benefits from raising HDL-C with gemfibrozil in the VA-HIT study



*p≤0.05; †p=0.07

Rubins HB et al. *N Engl J Med* 1999;341:410-8

New HDL Therapies

Acute

- Apo A_1 regulators – Apo A_1 Milano
- Delipidated HDL
- Apo A, mimetic peptides

Chronic

- Selective increase in Apo A_1 synthesis
- Increase LCAT
- Reduced flushing with niacin
  a. Tredaptive (DPI antagonist)
  b. I-methyl nicotinic acid
- CETP inhibitors
  a. Torcetrapib (off-target toxicity)
  b. Dalcetrapib
  c. Anacetrapib

Effect of Mipomersen on Lipids & lipoproteins

	Placebo	Mipomersen	P-value
LDL-cholesterol	- 3.3 %	- 24.7%	0.0003
Apo-B	- 2.5 %	-26.8 %	<0.0001
HDL-cholesterol	+3.9 %	+15.1 %	0.0326
Apo A1	+ 5.4 %	+ 9.3 %	0.3284
Triglycerides	+0.4 %	-17.4 %	0.0133

Raal FJ, et al. Lancet 2010; 375:996-1006

HDL-C and AIM-HIGH: Does Increasing HDL-C Reduce Cardiovascular Risk?

Michael H. Davidson, MD
Clinical Professor of Medicine
Director, Preventive Cardiology
Pritzker School of Medicine
The University of Chicago
Chicago, Illinois

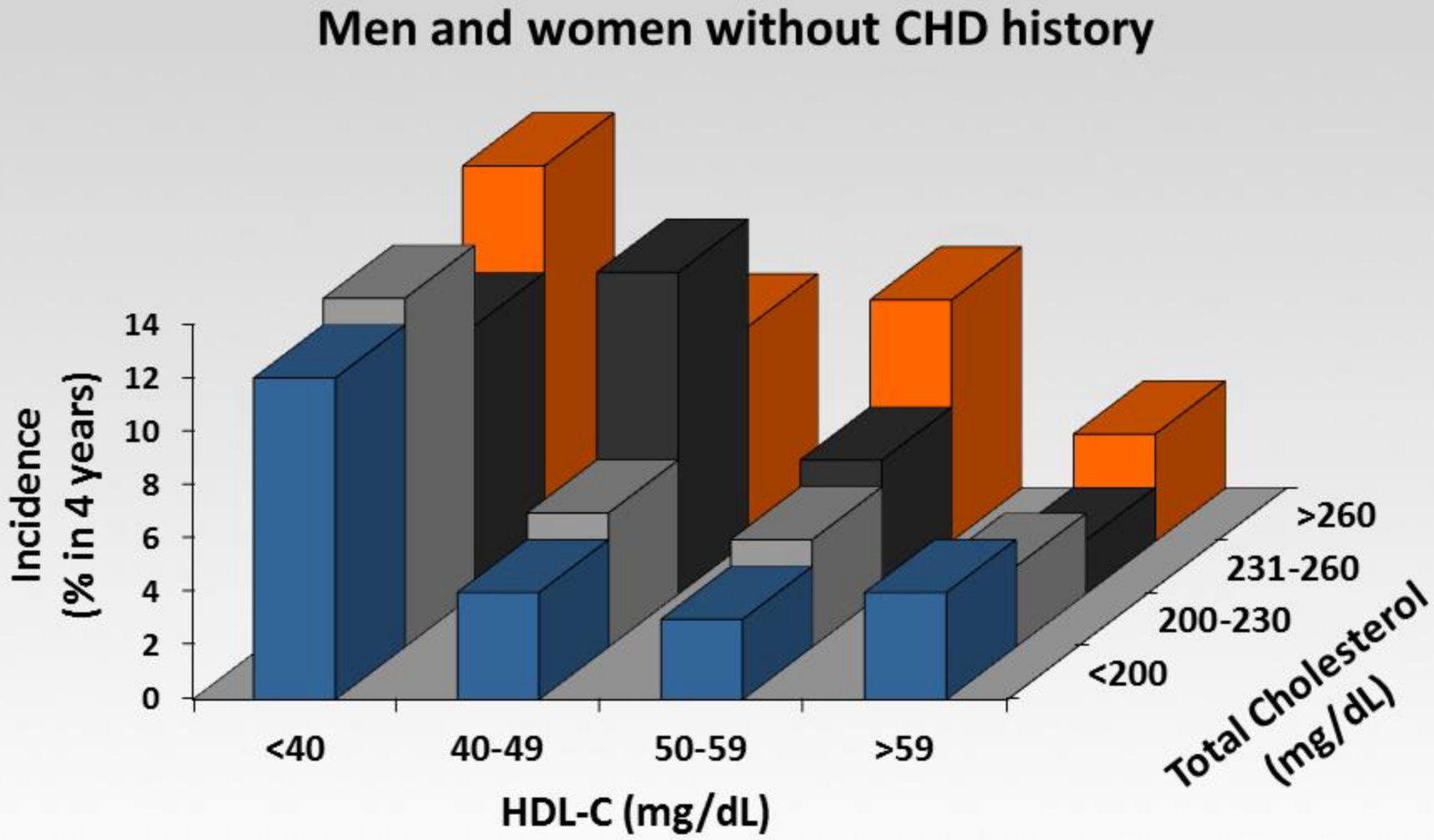
LIPID & METABOLIC
theheart.org from WebMD
Medscape EDUCATION

Panelists

Peter P. Toth, MD, PhD
Director of Preventive Cardiology
CGH Medical Center
Sterling, Illinois
Professor of Clinical Family and Community Medicine
University of Illinois College of Medicine
Peoria, Illinois

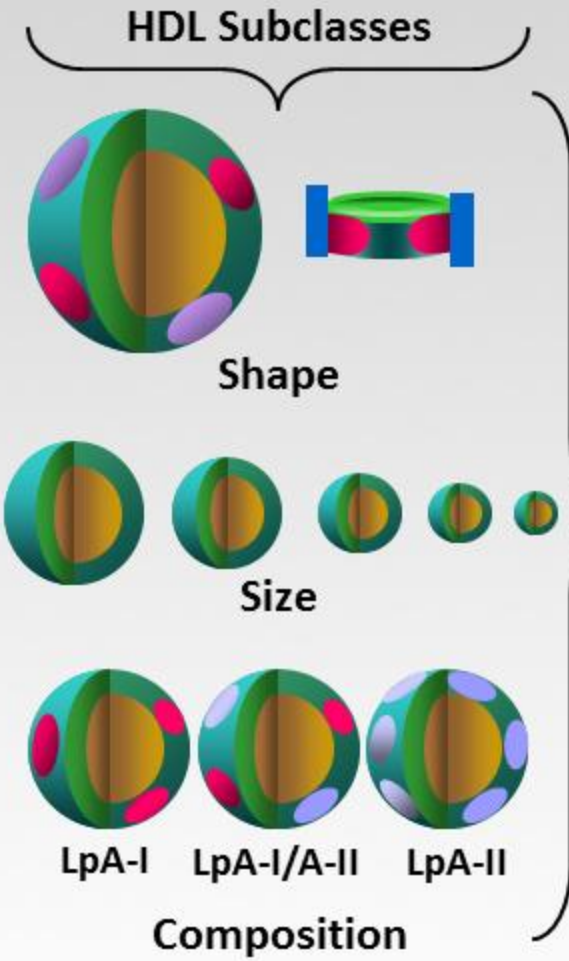
William E. Boden, MD
Clinical Chief
Division of Cardiovascular Medicine
Professor of Medicine and Preventive Medicine
University at Buffalo Schools of Medicine & Public Health
Buffalo, New York

Predictive Value of HDL-C



Castelli W. *Can J Cardiol*. 1988;4(supplA):5a-10a.

Heterogeneity of HDL



Proteins or peptides > 80

Apolipoproteins: ApoA-I, ApoA-II, ApoA-IV, ApoA-V, ApoC-I, ApoC-II, ApoC-III, ApoC-IV, ApoD, ApoE, ApoF, ApoH, ApoJ, ApoL1, ApoM, ApoO?

Enzymes: LCAT, CETP, PLTP, PON1, PON3, GPx, LpPLA2, MPO
Other proteins: SAA1, SAA2, SAA4, Coe, Hp, Hb,HRP, hPBP, PSP, C3, C4, C4B, lipocalin2? Oro, a1-AT, a2-HS-GP, a2-AP, PBP, TTR, aFib a1-PI

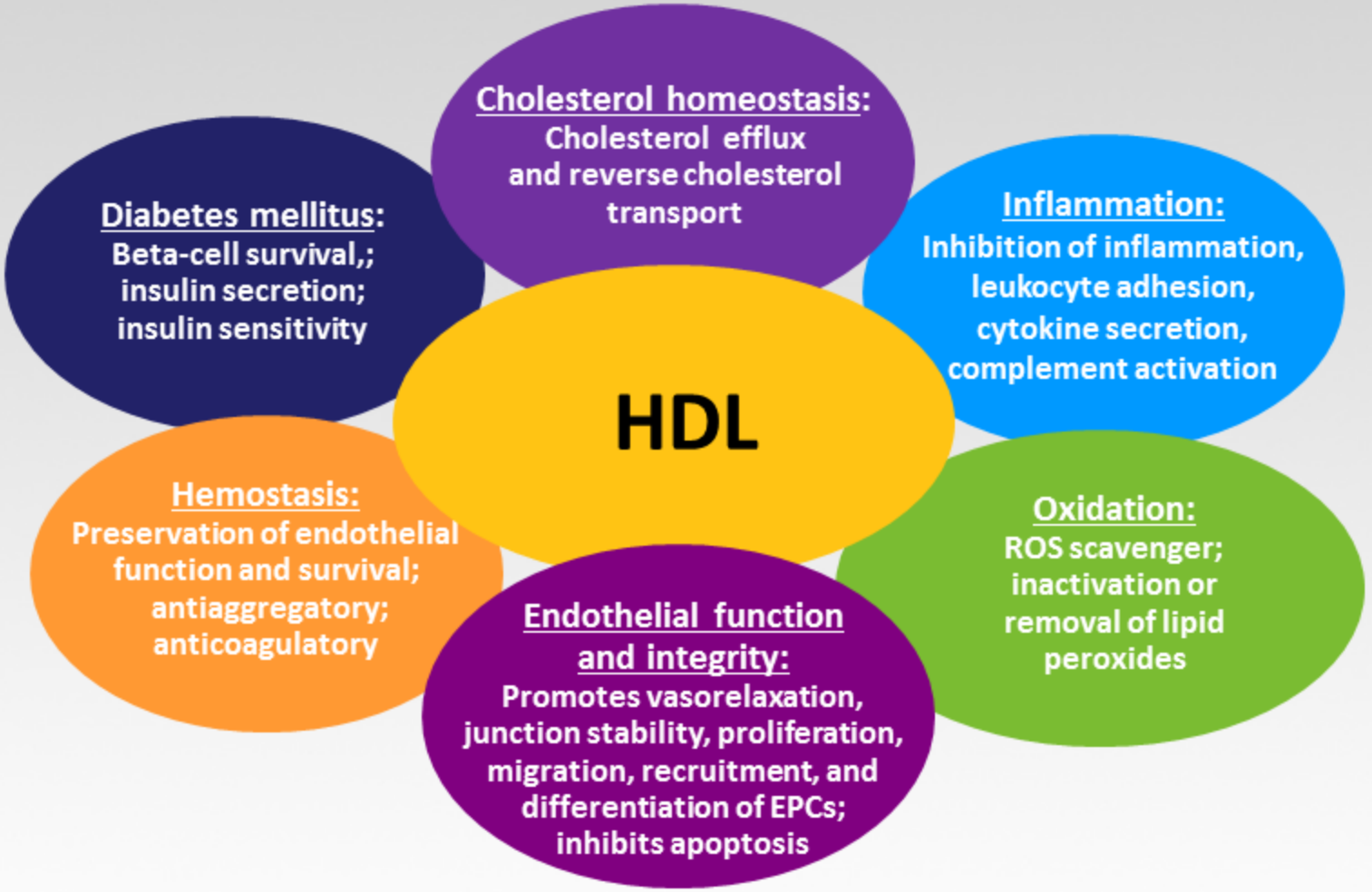
Lipids 100s

Steroids: FC, CE, E2, Prg, Pgn, 24OHC, 27OHC
Phospholipids: PC, SM, PS, PE, PI, CLP, Cer
Etherphospholipids: Plasmalogen
Glycolipids: Glc-Cer, Gal-Cer, Lac-Cer, sulfatides, gangliosides (GM3), globosides
Lysophospholipids: LPC, SPC, LSF, S1P
Vitamins: a-tocopherol, carotenoids (lutein, canthaxanthin, b-cryptoxanthin), retinoids

microRNAs

von Eckardstein A. *Drug Discov Today Dis Mech.* 2008;5:e305-e324.

Pleiotropic Functions of HDL



EPC = endothelial progenitor cell

von Eckardstein A. *Expert Rev Cardiovasc Ther.* 2010;8:345-358.

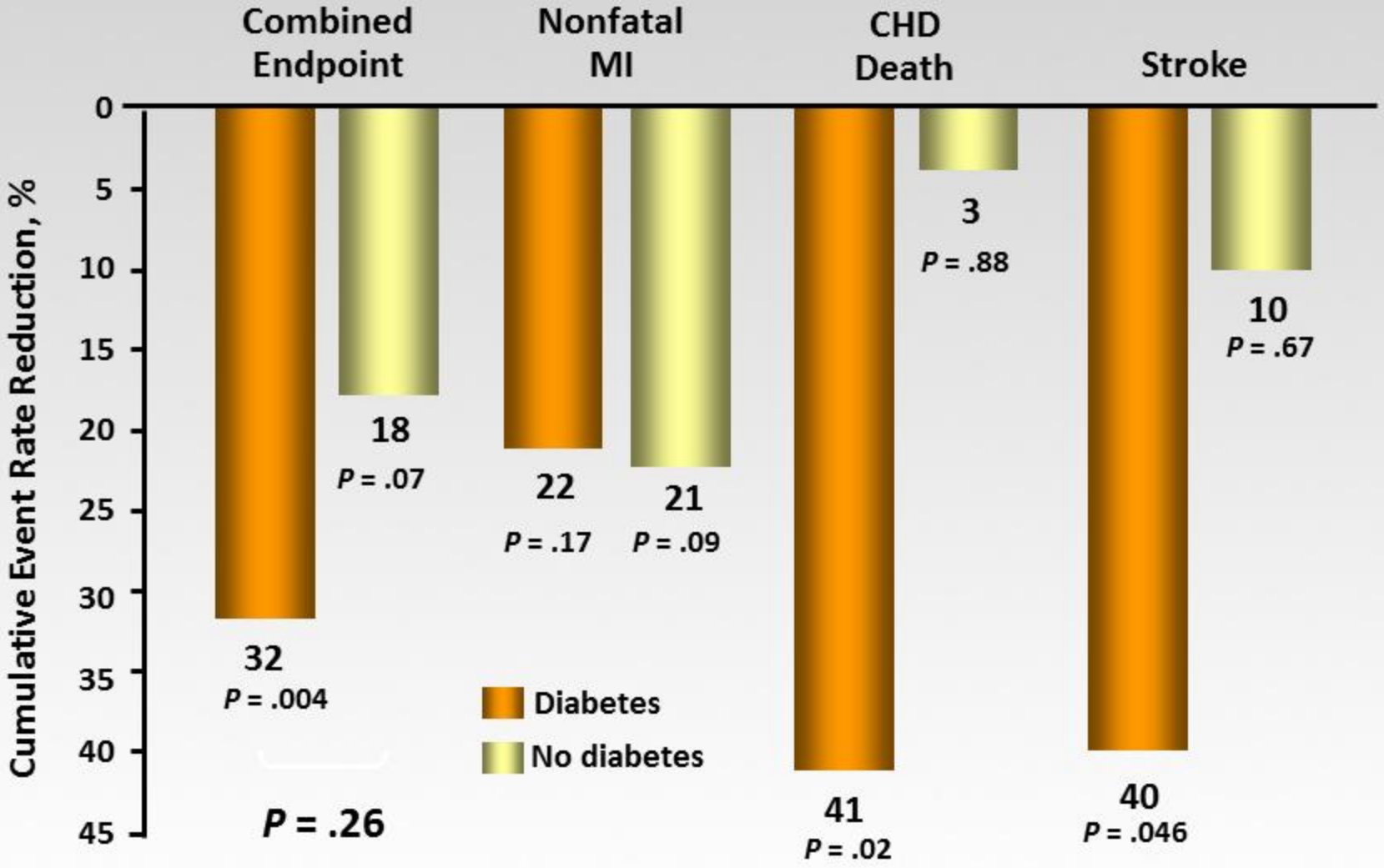
Evidence From Prior Placebo-Controlled Trials Supporting Niacin or Fibrate Benefit

- **Coronary Drug Project (1975) 5-year follow-up**
  - Immediate-release niacin (3000 mg/day)
  - Reduced CHD death/MI by 14%
  - Reduced nonfatal MI by 26%
  - Reduced stroke/TIA by 21%
- **HATS (2001) 3-year follow-up**
  - Niacin + simvastatin
  - Regression of angiographic coronary stenosis and reductions in clinical events

TIA = transient ischemic attack

Schlant RC, et al. *Circulation*. 1982;66:401-414.
Matthan NR, et al. *J Lipid Res*. 2003;44:800-806.

VA-HIT: CV Disease Risk Reduction in Patients With and Without Type 2 Diabetes



Rubins HB, et al. *Arch Intern Med*. 2002;162:2597-2604.

BIP: Bezafibrate Infarction Prevention Trial

Effect of lipid and TG change on the risk for cardiac death or nonfatal MI by baseline LDL-C tertile

7.9-year follow-up period in 3020 patients with CAD

	Overall	By Baseline LDL-C Level (mg/dL)		
Lipid Change	All patients (n=3020)	≤ 129 (n=413)	130-159 (n=1804)	≥ 160 (n=803)
HDL-C (per 5-mg/dL increase)	0.87 (0.79-0.95)	0.71 (0.53-0.95)	0.87 (0.77-0.98)	0.94 (0.75-1.17)
TG (per 50-mg/dL reduction)	0.88 (0.82-0.96)	0.81 (0.66-1.00)	0.84 (0.76-0.93)	0.96 (0.80-1.15)
LDL-C (per 20-mg/dL reduction)	0.79 (0.71-0.88)	1.01 (0.51-1.37)	0.75 (0.65-0.85)	0.81 (0.64-1.03)

Data are hazard ratios and 95% confidence intervals.

Goldenberg I, et al. *Am J Cardiol.* 2009;103:41-45.

AIM-HIGH Trial

Atherothrombosis
Intervention in
Metabolic Syndrome With Low
HDL/High TG and
Impact on
Global
Health Outcomes

AIM-HIGH: Hypothesis

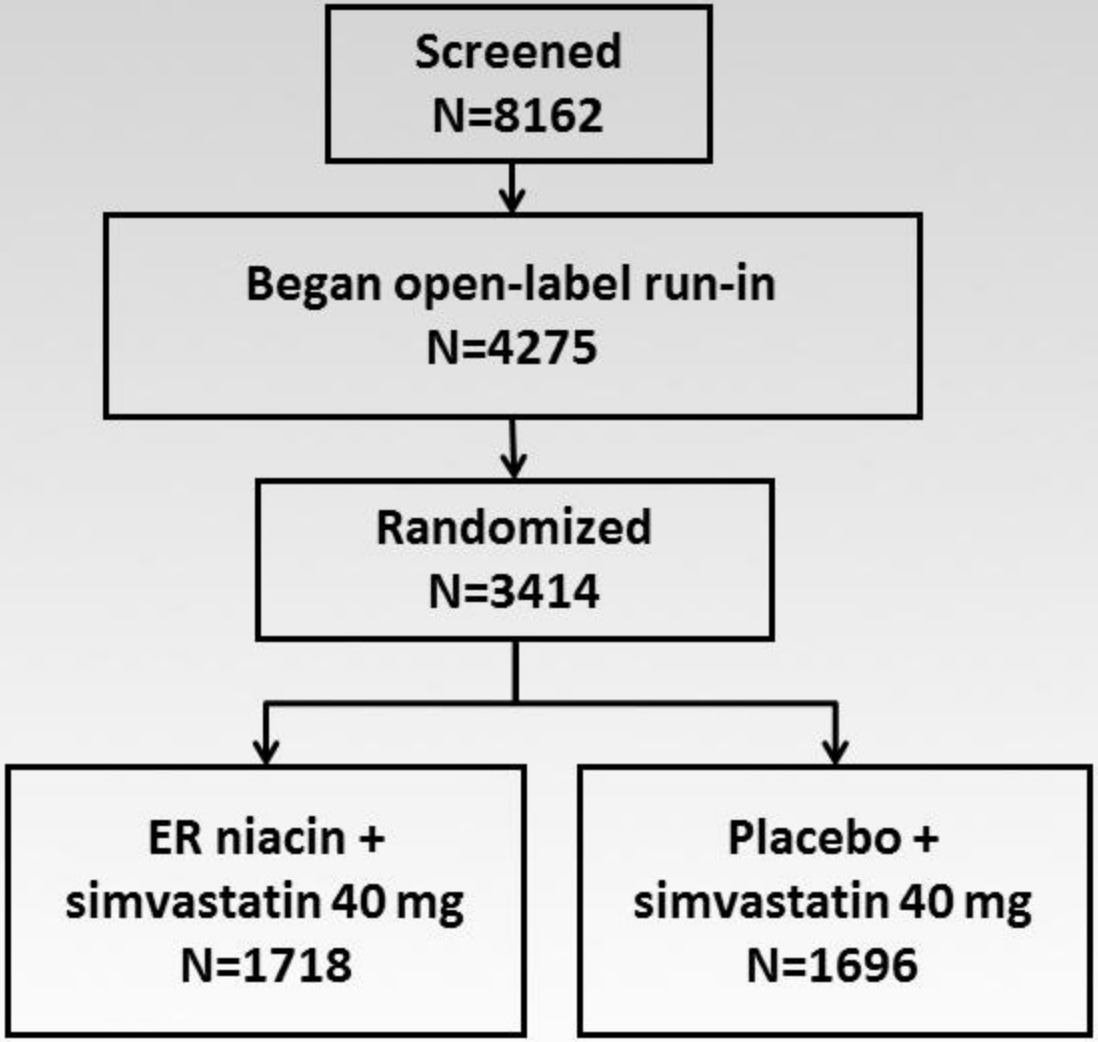
- Combination dyslipidemic therapy with high-dose ER niacin (1500-2000 mg/day), when added to intensive LDL-C-lowering therapy, will be superior to intensive LDL-C-lowering therapy alone in reducing the risk for CV events in patients with established atherosclerotic CV disease and low baseline levels of HDL-C.

Boden WE, et al. AHA 2011.

AIM-HIGH: Entry Criteria

- Patients aged ≥ 45 years with
  - CHD,
  - CV disease, or
  - Peripheral arterial disease
- …and dyslipidemia
  - Low levels of baseline HDL-C
    - < 40 mg/dL for men; < 50 mg/dL for women
  - TG 150-400 mg/dL
  - LDL-C < 180 mg/dL

AIM-HIGH: Study Flow



Boden WE, et al. AHA 2011.

AIM-HIGH: Endpoints

- Primary outcome composite (time to first occurrence):
  - CHD death
  - Nonfatal MI
  - Ischemic (nonhemorrhagic) stroke
  - Hospitalization for ACS
  - Symptom-driven revascularization
- Secondary composite endpoints included:
  - CHD death, nonfatal MI, ischemic stroke, or hospitalization for high-risk ACS
  - CHD death, nonfatal MI, or ischemic stroke; and CV mortality

AIM-HIGH: Statistical Analyses

- Event-driven trial with projected 800 primary outcomes; 2.5- to 7-year follow-up (mean 4.6 years)
- 85% power to detect a 25% reduction in the revised 5-component primary endpoint (1-sided test of significance; alpha level = .025)
- Prespecified, conservative asymmetric boundaries for potential early stopping based on efficacy or lack of efficacy
- Trial stopped on 5/25/11: lack of efficacy and concern of ischemic stroke imbalance with ER niacin after a 36-month average follow-up

Boden WE, et al. AHA 2011.

AIM-HIGH: Baseline Characteristics

Number randomized	3414
Mean (SD) age	64 ± 9
Male	85%
White	92%
Current smoker	20%
History of hypertension	71%
History of diabetes	34%
Metabolic syndrome	81%
History of MI	56%
History of cerebrovascular disease	21%

All baseline characteristics balanced between treatment groups

AIM-HIGH: Concomitant Medications

Statin use at baseline	94%
Duration of statin therapy*	
≥ 1 year	76%
≥ 5 years	40%
Prior niacin use	20%
Aspirin/antiplatelet therapy	98%
Beta-blocker	80%
ACEI/ARB	74%

Use of all secondary prevention therapies wase well balanced between treatment groups.

***Duration of statin therapy not ascertained in 6%**

AIM-HIGH: Baseline Lipids (mg/dL)

	On Statin (n=3196)	Off Statin (n=218)
LDL-C (mean)	71	119
HDL-C (mean)	35	33
TG (median)	161	215
Non-HDL-C (mean)	107	165
Apo B (mean)	81	111

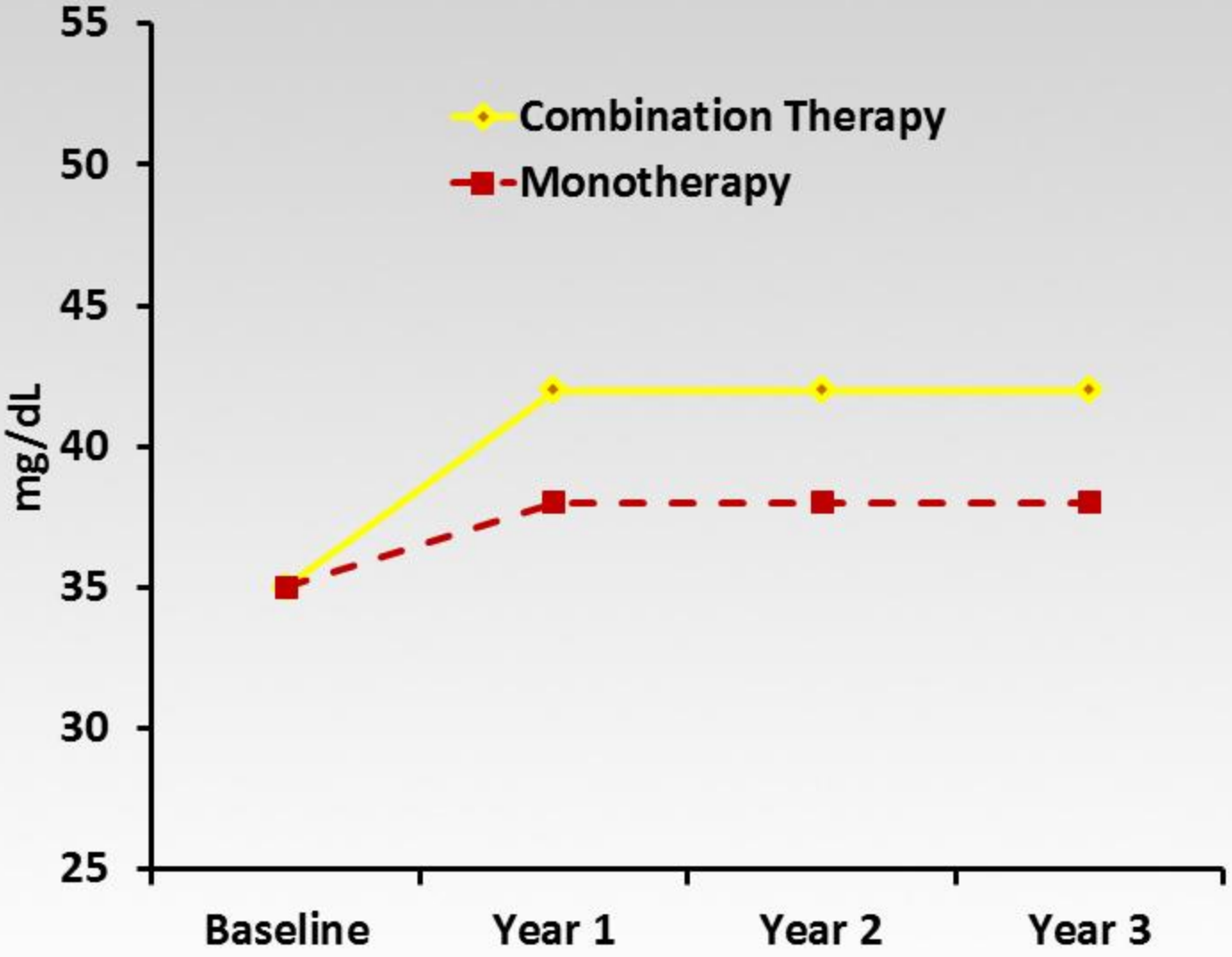
Boden WE, et al. AHA 2011.

AIM-HIGH: Simvastatin Dose and Ezetimibe Use Across the 2 Cohorts

	Monotherapy	Combination Therapy	*P* Value
Simvastatin dose:			
< 40 mg/day	11%	19%	
40 mg/day	50%	50%	.018
> 40 mg/day	25%	18%	
On ezetimibe	22%	10%	< .001

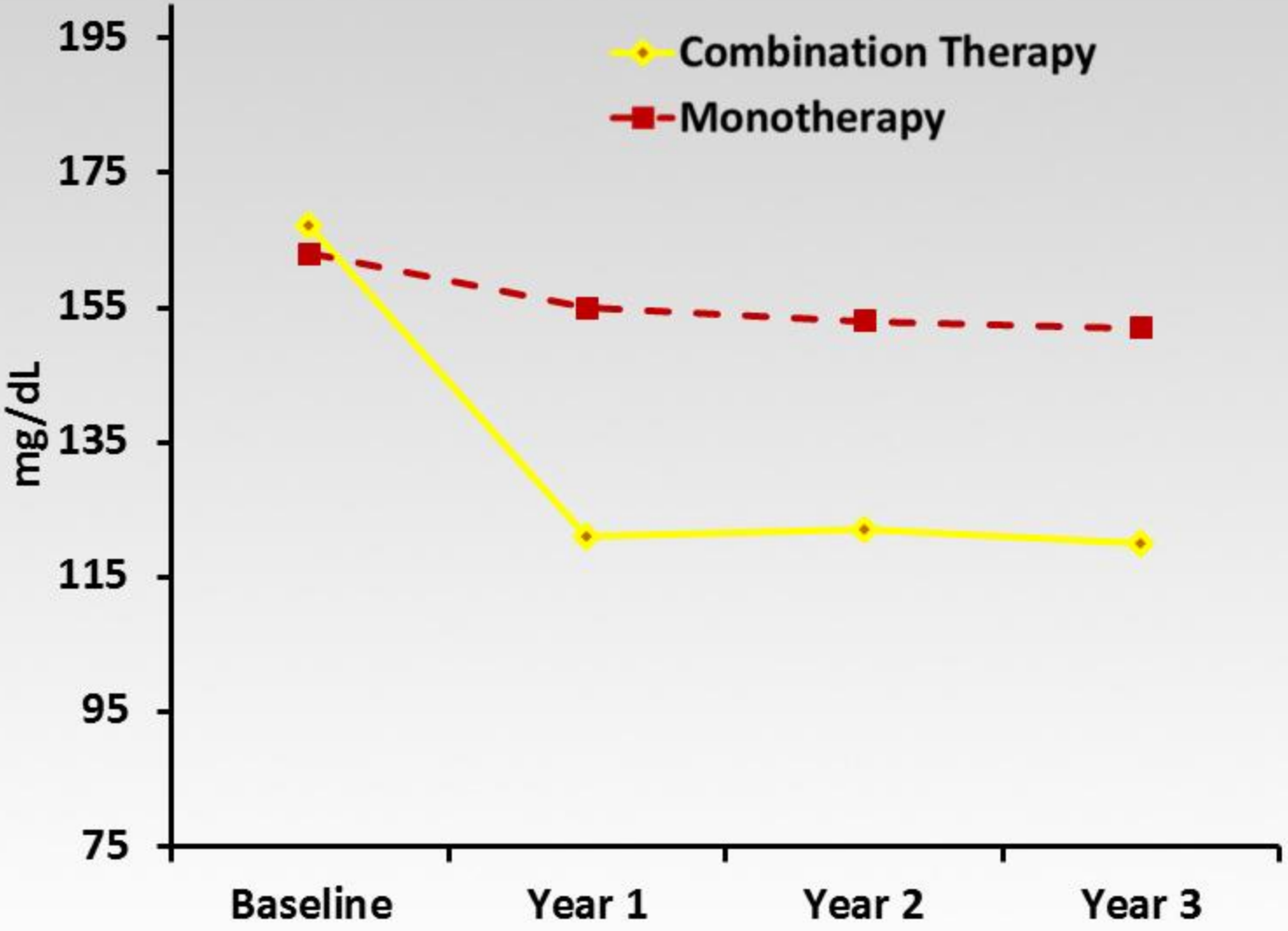
Boden WE, et al. AHA 2011.

AIM-HIGH: HDL-C After 36 Months of Follow-up



Boden WE, et al. AHA 2011.

AIM-HIGH: TG After 36 Months of Follow-up



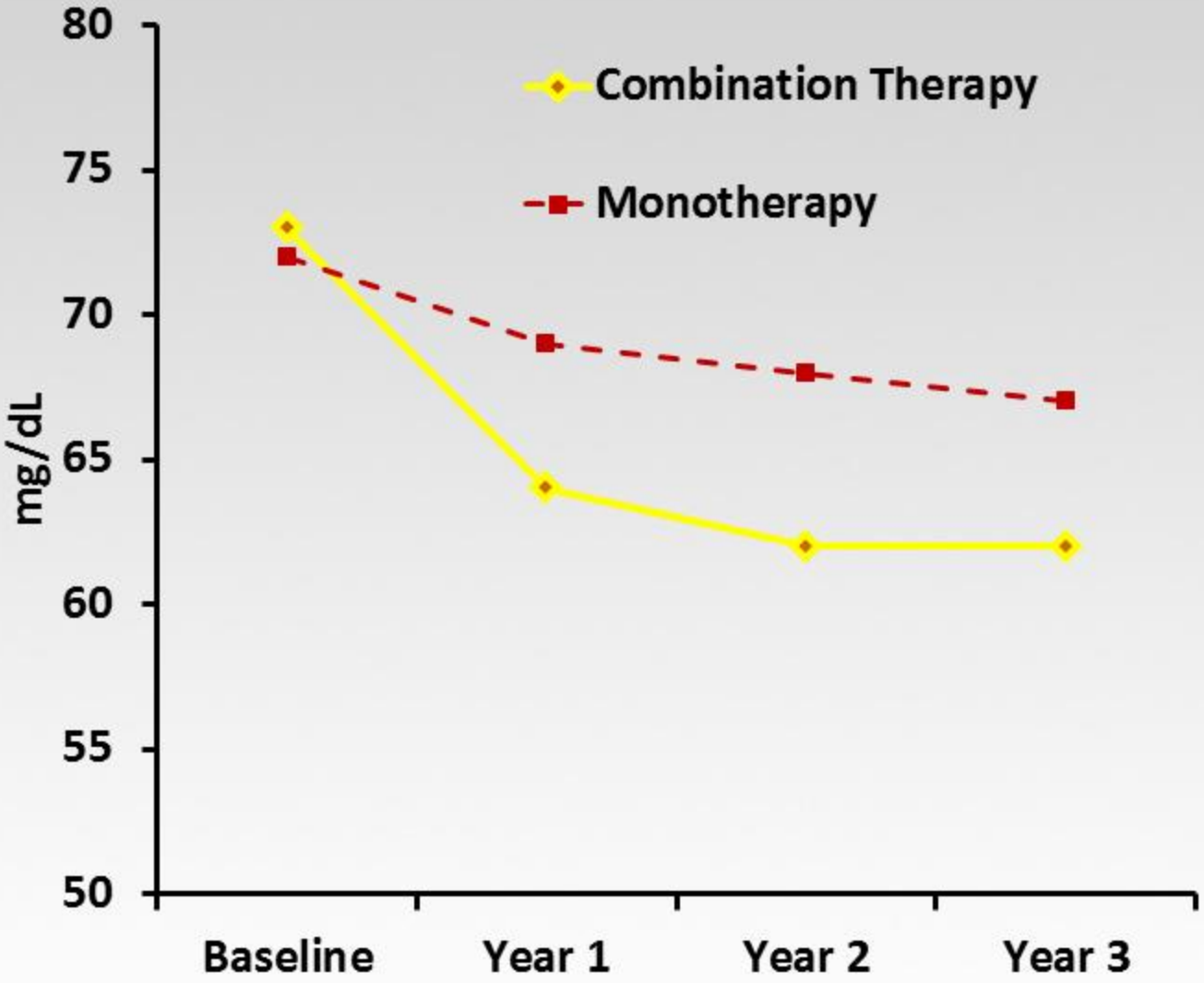
LIPID & METABOLIC

Boden WE, et al. AHA 2011.

theheart.org from WebMD

Medscape EDUCATION

AIM-HIGH: LDL-C After 36 Months of Follow-up



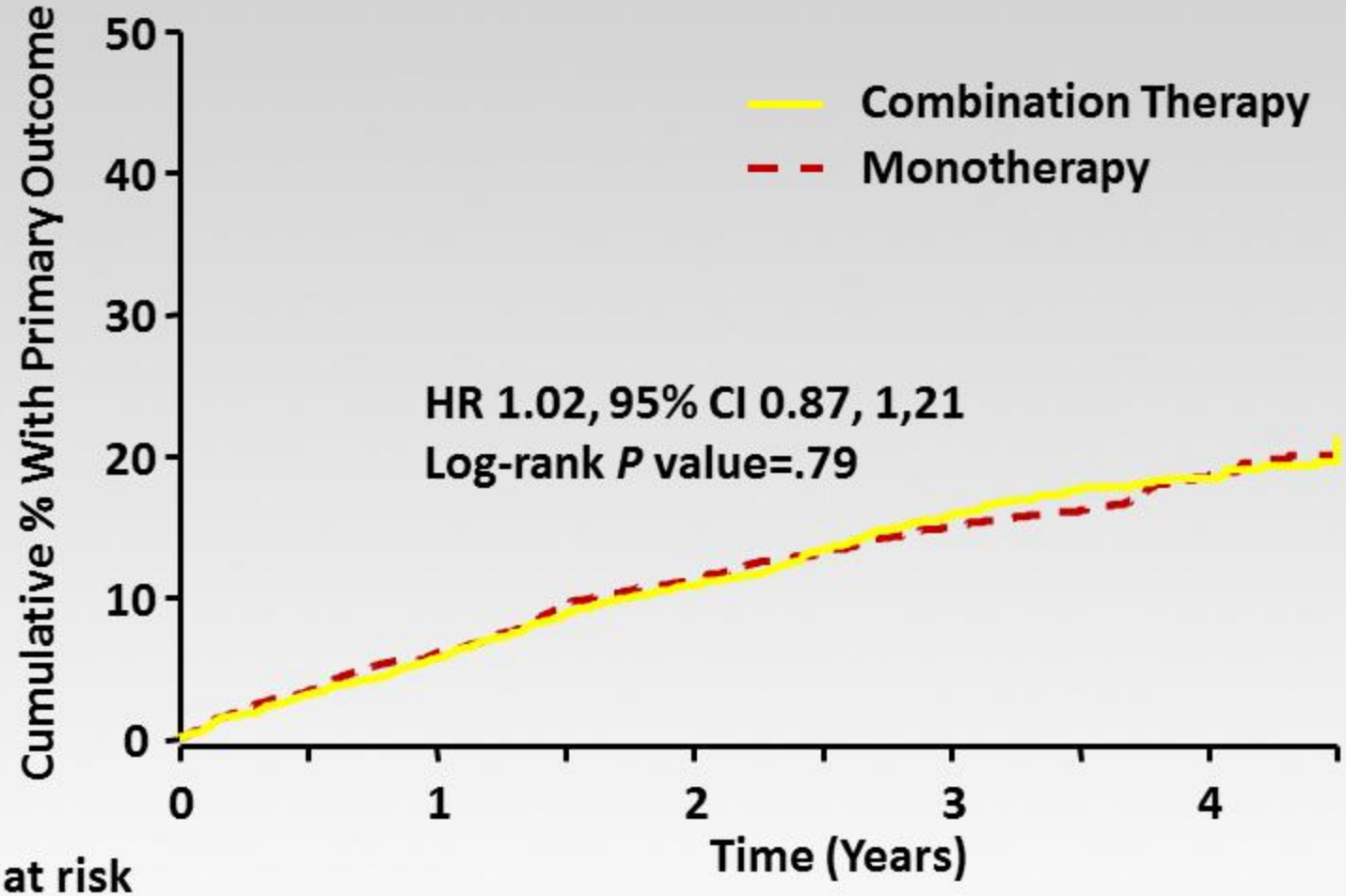
Boden WE, et al. AHA 2011.

AIM-HIGH: Primary and Secondary Endpoints

	Hazard Ratio	95% CI
Primary endpoint	1.02	0.87, 1.21
Secondary endpoints		
CHD death, MI, ischemic stroke, high-risk ACS	1.08	0.87, 1.34
CHD death, MI, ischemic stroke	1.13	0.90, 1.42
CV death	1.17	0.76, 1.80

Boden WE, et al. AHA 2011.

AIM-HIGH: Primary Outcome

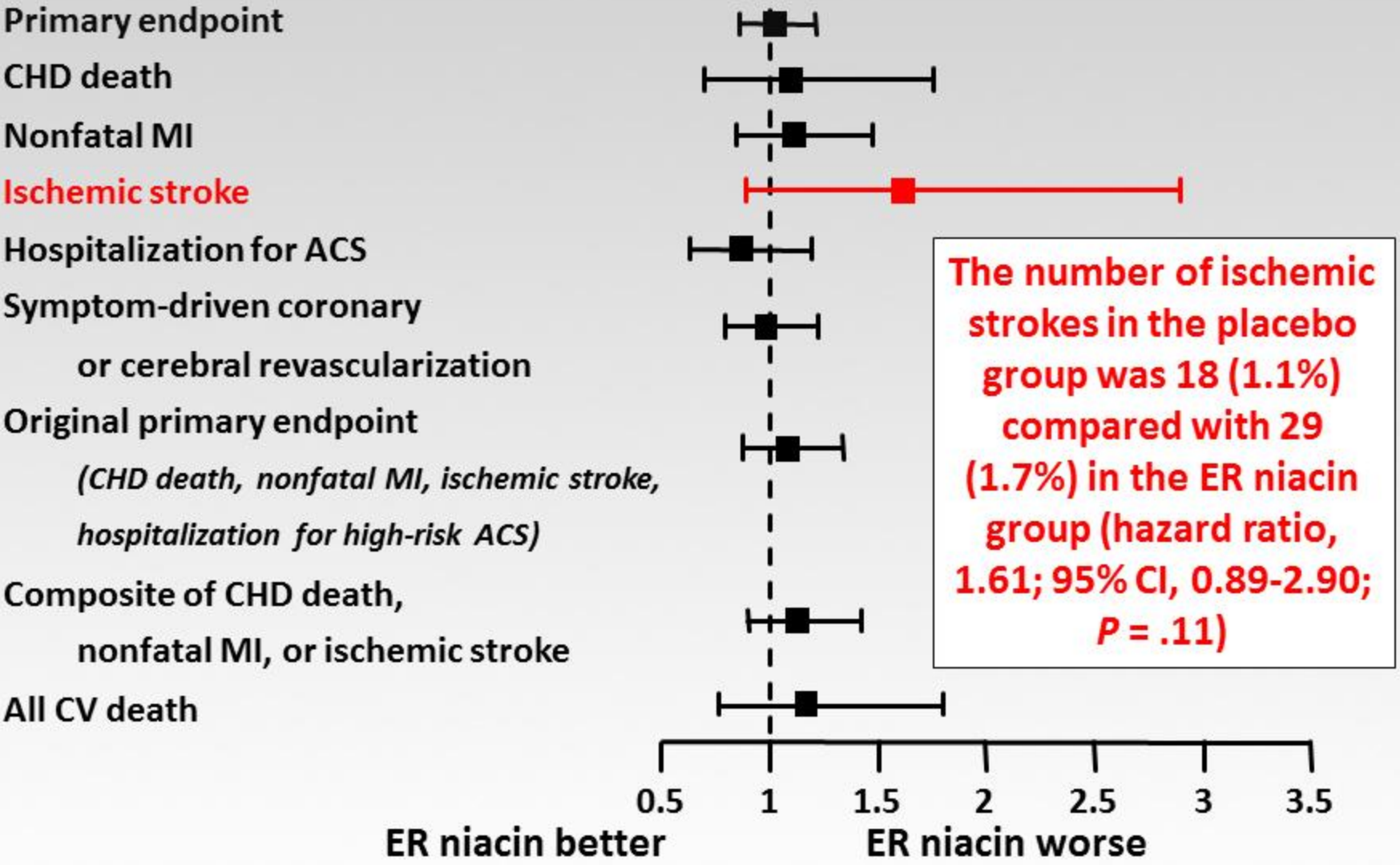


Number at risk					
Monotherapy	1696	1581	1381	910	436
Combination Therapy	1718	1606	1366	903	428

LIPID & METABOLIC

Boden WE, et al. AHA 2011.

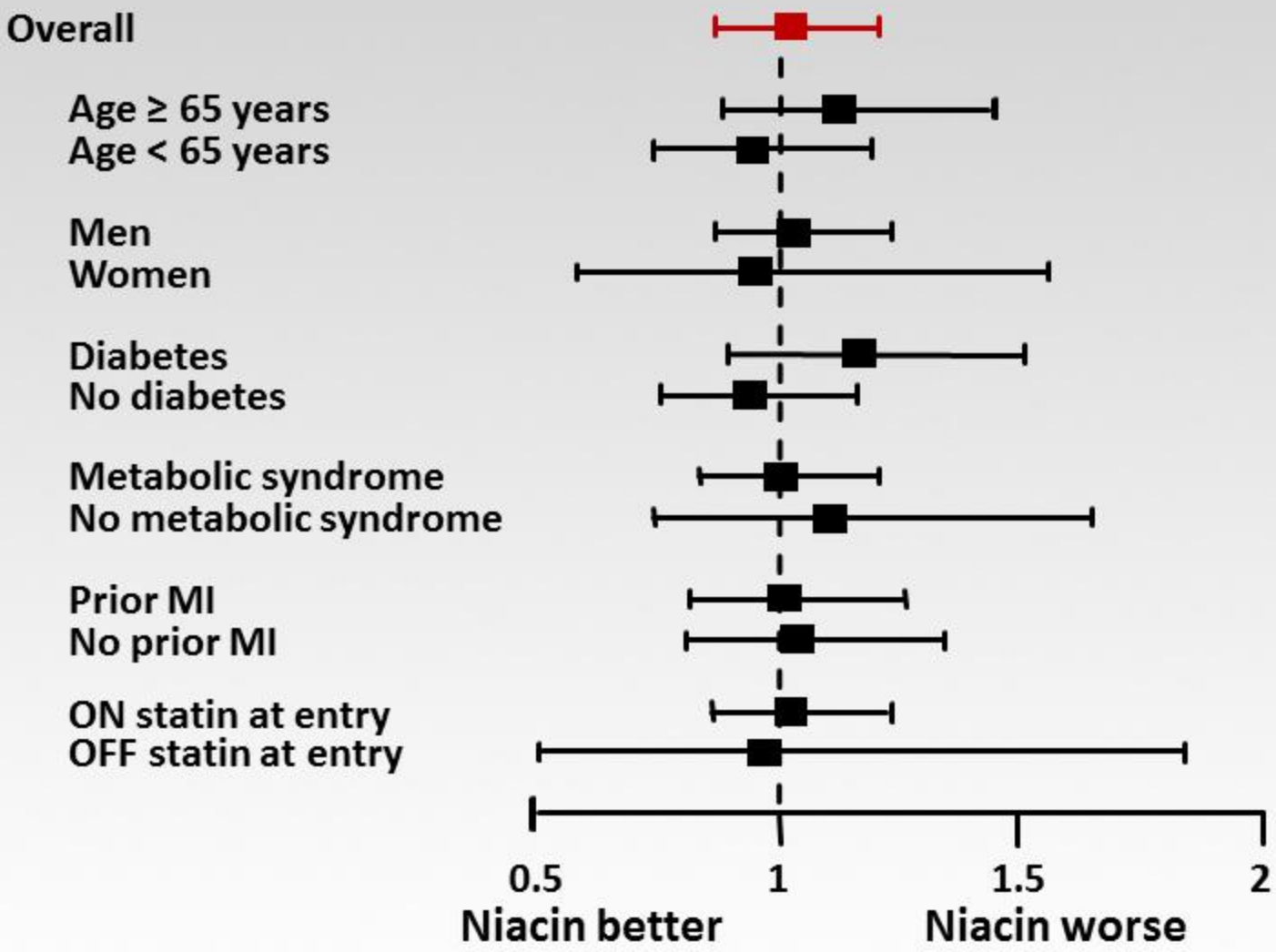
AIM-HIGH: CV and Stroke Endpoints



The number of ischemic strokes in the placebo group was 18 (1.1%) compared with 29 (1.7%) in the ER niacin group (hazard ratio, 1.61; 95% CI, 0.89-2.90; *P* = .11)

Boden WE, et al. AHA 2011.

AIM-HIGH: Prespecified Subgroups



Boden WE, et al. AHA 2011.

Conclusions

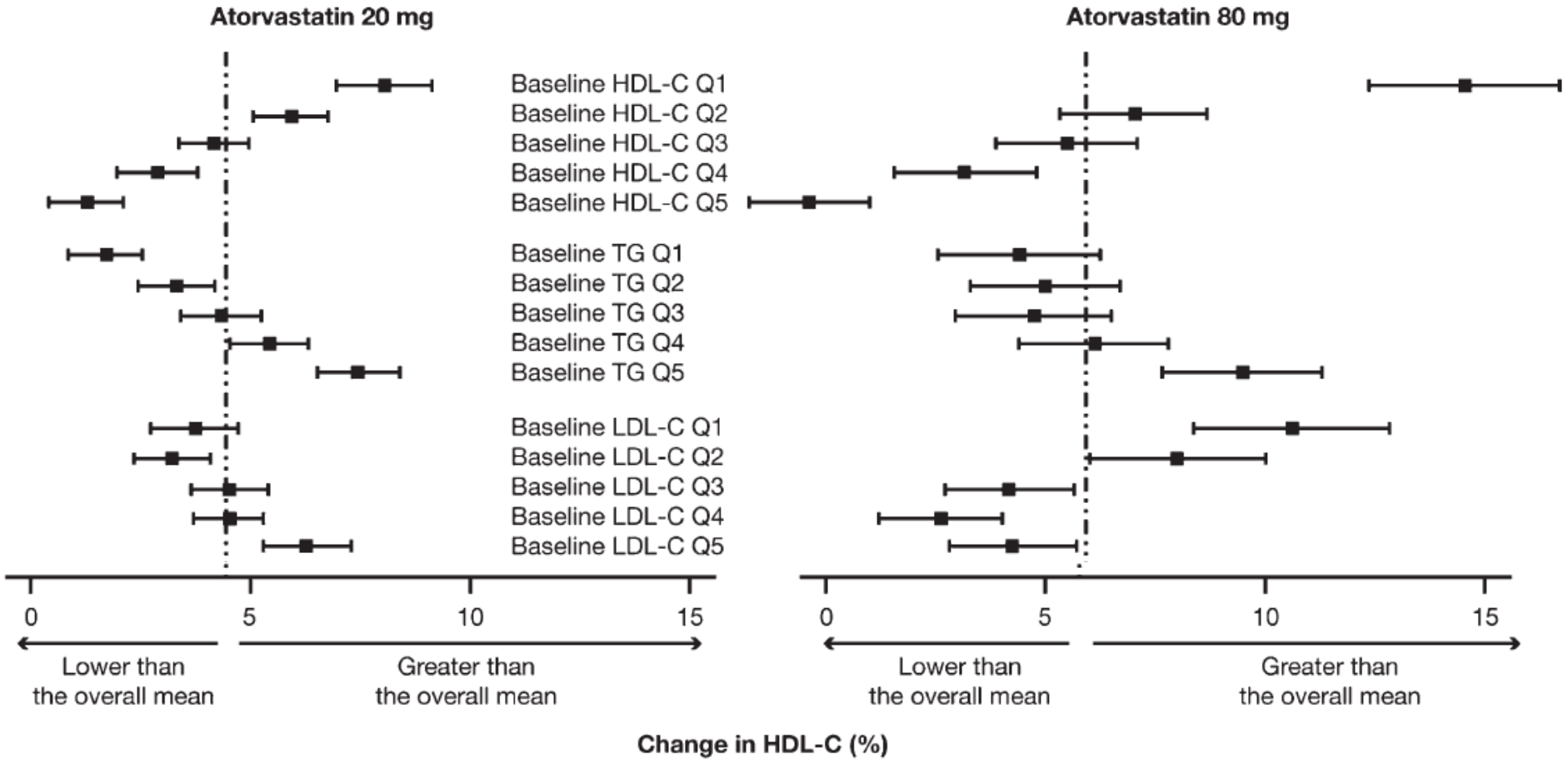
- Among patients with stable, nonacute CV disease and LDL-C < 70 mg/dL, there was no incremental clinical benefit from the addition of ER niacin to statin therapy during a 36-month follow-up, despite significant improvements in HDL-C and TG.
- AIM-HIGH reaffirms current NCEP ATP-III treatment guidelines for LDL-C lowering as the principal target of lipid treatment.
- Additional analyses will be required to determine if certain subsets of patients with low HDL-C in AIM-HIGH may benefit from ER niacin treatment.

Program Summary

Thank you for participating in this activity.

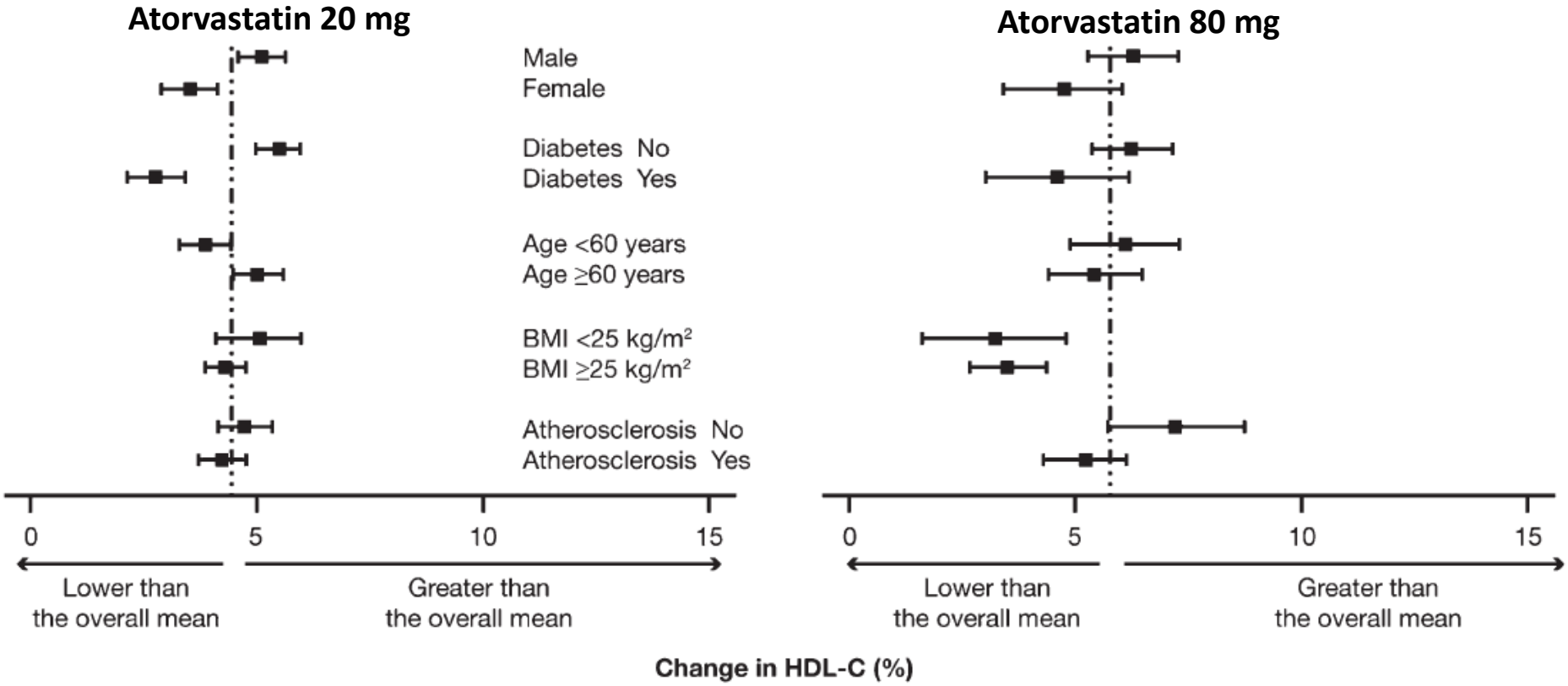
To proceed to the CME post-test, click the Earn CME Credit link on this page.

HDL-C – raising effect of Atorvastatin by baseline lipoprotein and triglyceride



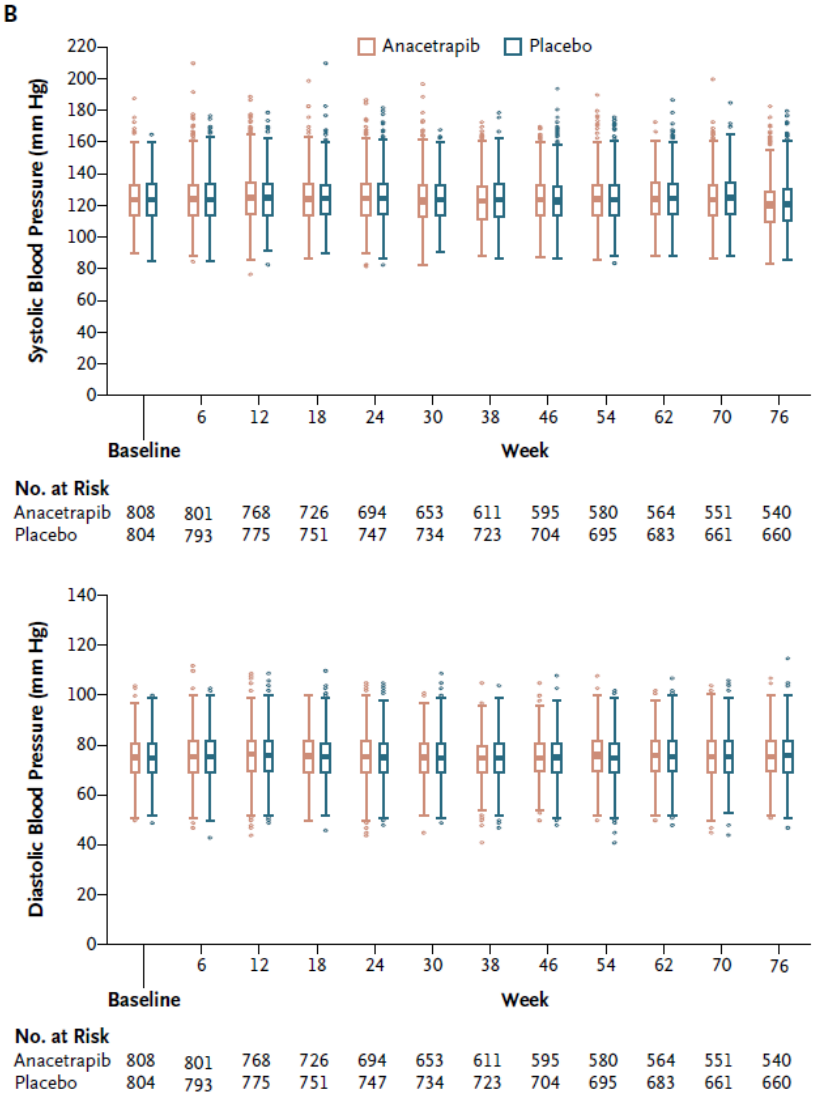
Barter PJ, et al. J Lipid Res 2010;51:1546-53

HDL-C – raising effect of Atorvastatin by baseline characteristics



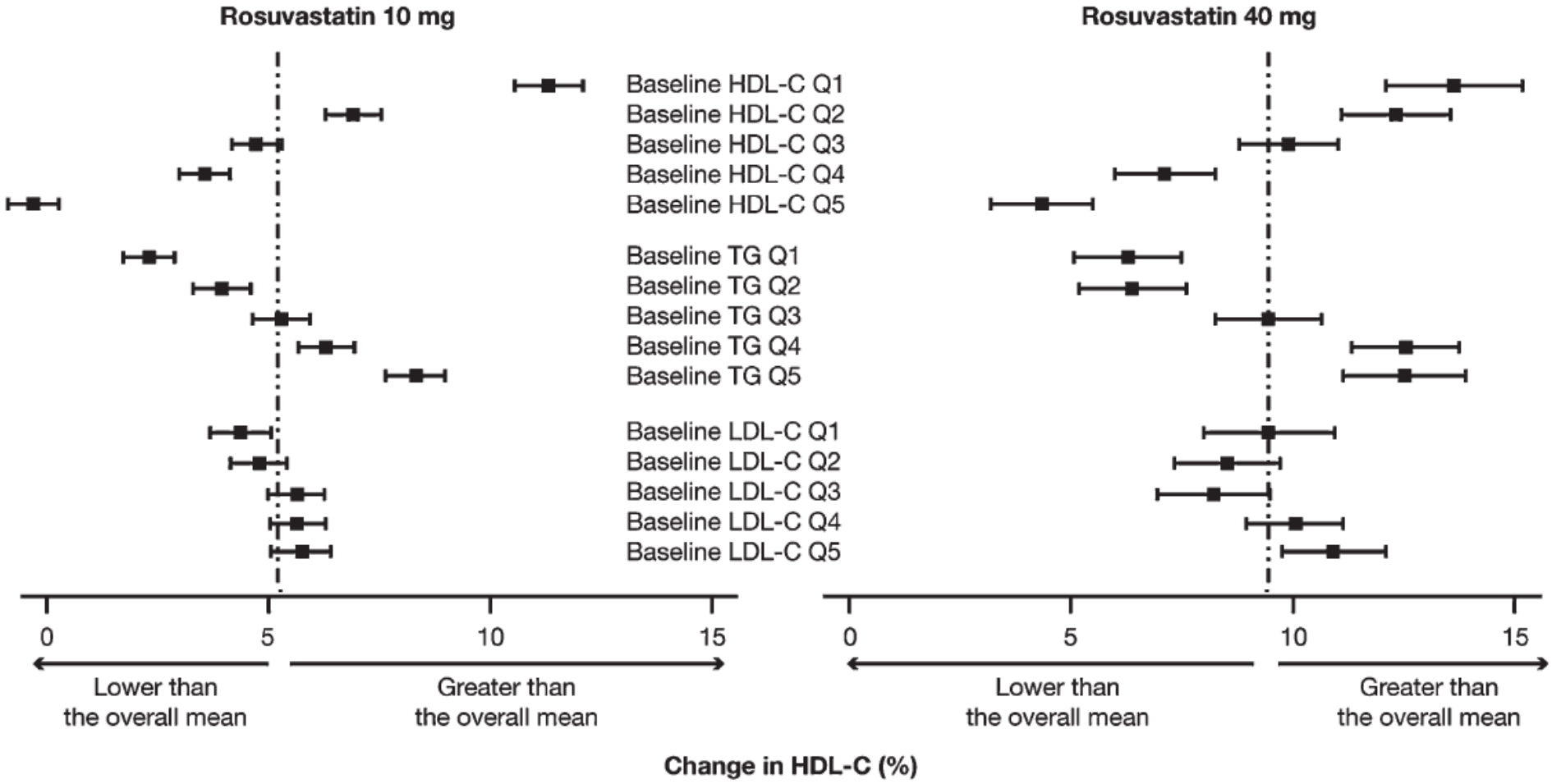
Barter PJ, et al. J Lipid Res 2010;51:1546-53

DEFINE
Anacetrapib: Systolic and diastolic BP



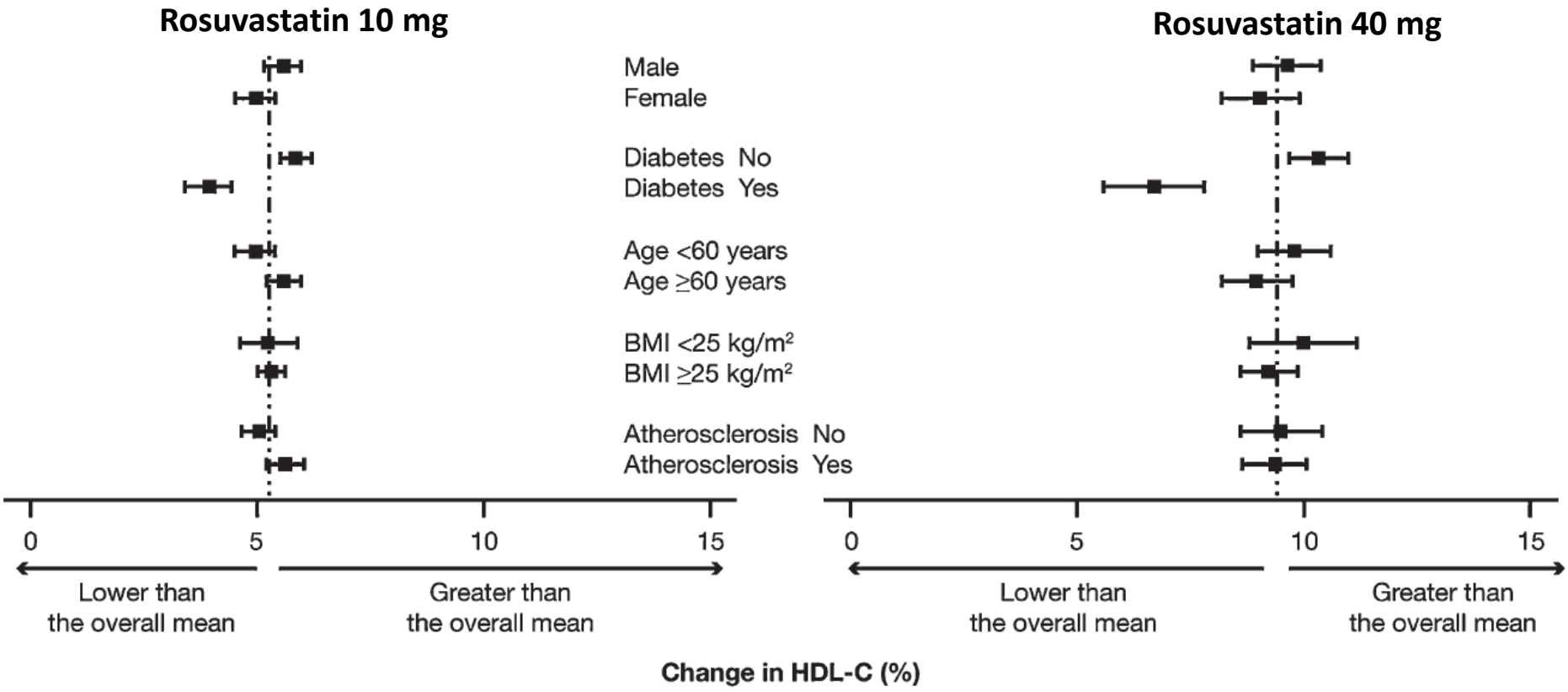
Cannon CP, et al. NEJM 2010;363:2406-15

HDL-C – raising effect of Rosuvastatin by baseline lipoprotein and triglyceride



Barter PJ, et al. J Lipid Res 2010;51:1546-53

HDL-C – raising effect of Rosuvastatin by baseline characteristics



Barter PJ, et al. J Lipid Res 2010;51:1546-53

Selected baseline data of HDL-C Quartiles Mean values

	Q1 31.3 – 50.2 mg/DL	Q2 50.3 – 58.3 mg/DL	Q3 58.4 – 66.0 mg/dl	Q4 66.1 – 127.4 mg/dl	P-value for trend
Age (yrs)	55.9	57.0	56.6	57.2	0.0126
BMI (kg/m^2)	25.3	26.0	24.4	23.9	<0.0001
HR (beats/min)	64.4	63.4	62.1	61.9	0.0007
Triglycerides (mg/dl)	161.3	125.8	106.3	104.5	<0.0001
LDL-C (mg/dl)	174.5	167.5	157.1	154.0	<0.0001
Fitness (kJ/kg)	1.26	1.34	1.45	1.47	<0.0001

Skretteberg PT, et al. Atherosclerosis 2011 doi:10.1016/j.atherosclerosis.

Effect of Recombinant ApoA-I Milano on Coronary Atherosclerosis in Patients With Acute Coronary Syndromes

A Randomized Controlled Trial

Steven E. Nissen, MD
Taro Tsunoda, MD
E. Murat Tuzcu, MD
Paul Schoenhagen, MD
Christopher J. Cooper, MD
Muhammad Yasin, MD
Gregory M. Eaton, MD
Michael A. Lauer, MD
W. Scott Sheldon, DO
Cindy L. Grines, MD
Stephen Halpern, MD
Tim Crowe, BS
James C. Blankenship, MD
Richard Kerensky, MD

Context Although low levels of high-density lipoprotein cholesterol (HDL-C) increase risk for coronary disease, no data exist regarding potential benefits of administration of HDL-C or an HDL mimetic. ApoA-I Milano is a variant of apolipoprotein A-I identified in individuals in rural Italy who exhibit very low levels of HDL. Infusion of recombinant ApoA-I Milano–phospholipid complexes produces rapid regression of atherosclerosis in animal models.

Objective We assessed the effect of intravenous recombinant ApoA-I Milano/phospholipid complexes (ETC-216) on atheroma burden in patients with acute coronary syndromes (ACS).

Design The study was a double-blind, randomized, placebo-controlled multicenter pilot trial comparing the effect of ETC-216 or placebo on coronary atheroma burden measured by intravascular ultrasound (IVUS).

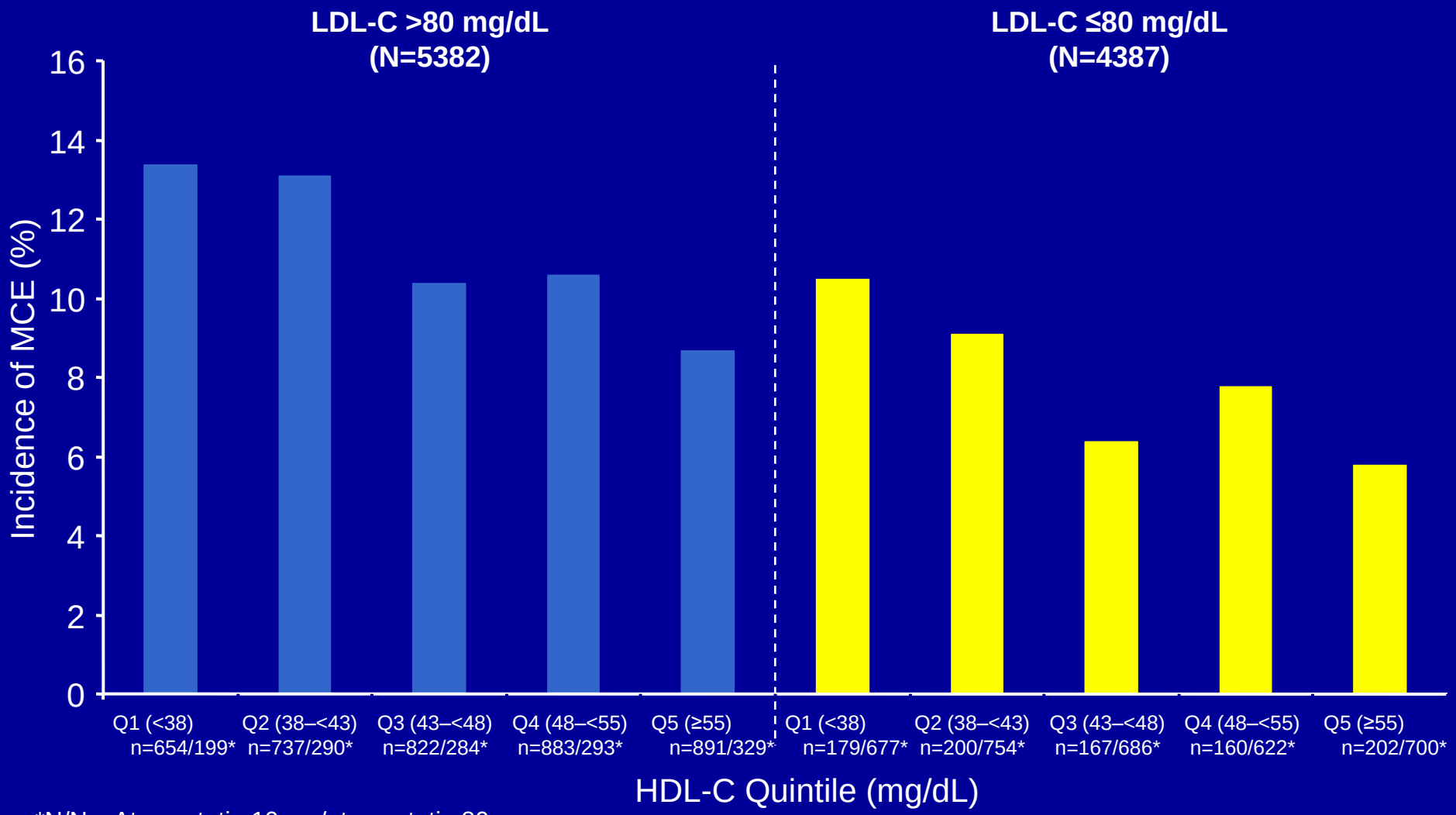
Setting Ten community and tertiary care hospitals in the United States.

Patients Between November 2001 and March 2003, 123 patients aged 38 to 82 years consented, 57 were randomly assigned, and 47 completed the protocol.

Interventions In a ratio of 1:2:2, patients received 5 weekly infusions of placebo or ETC-216 at 15 mg/kg or 45 mg/kg. Intravascular ultrasound was performed within 2 weeks following ACS and repeated after 5 weekly treatments.

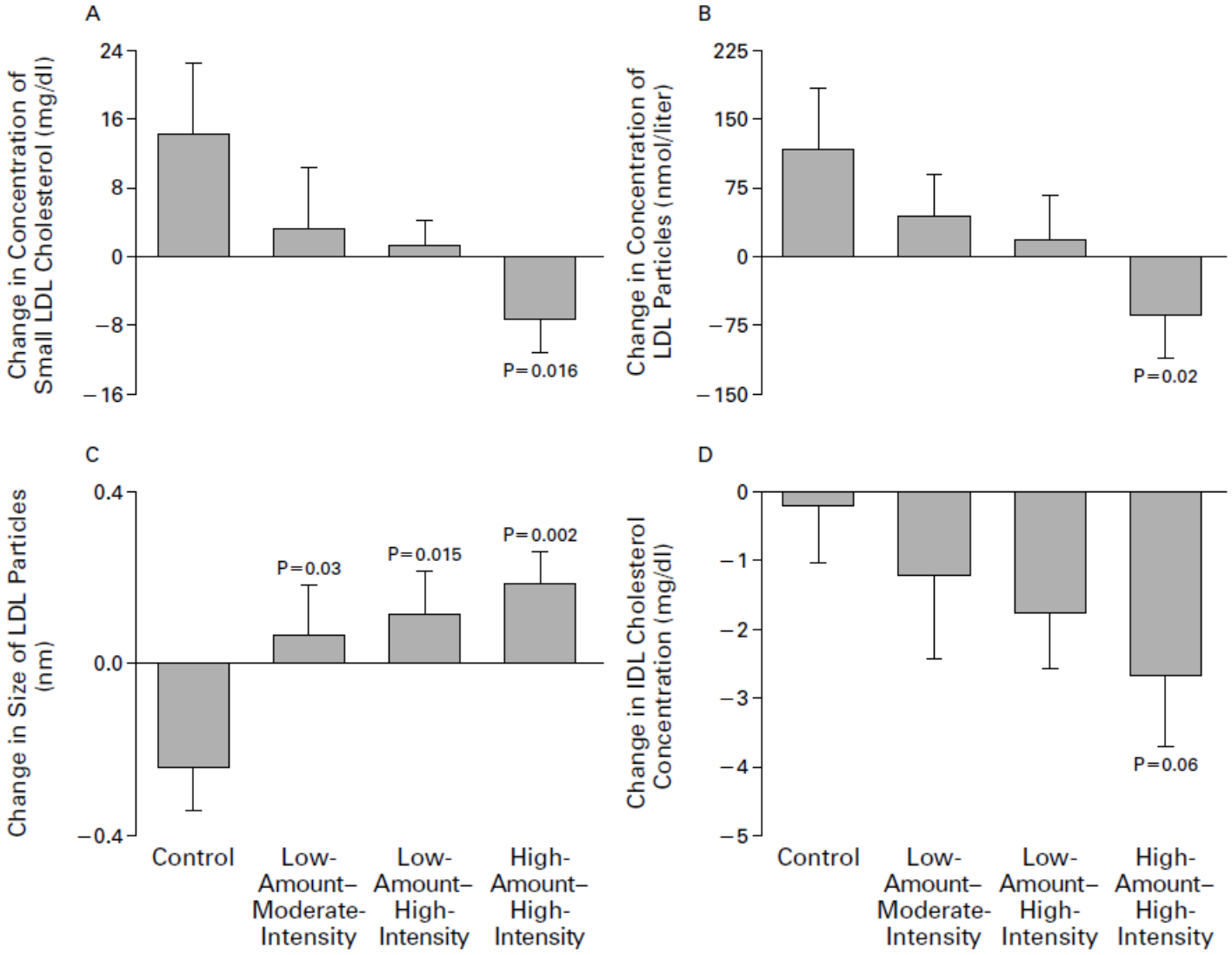
JAMA 2003

Incidence of Major CV Events Across HDL-C Quintiles at High and Low LDL-C



*N/N – Atorvastatin 10 mg/atorvastatin 80 mg

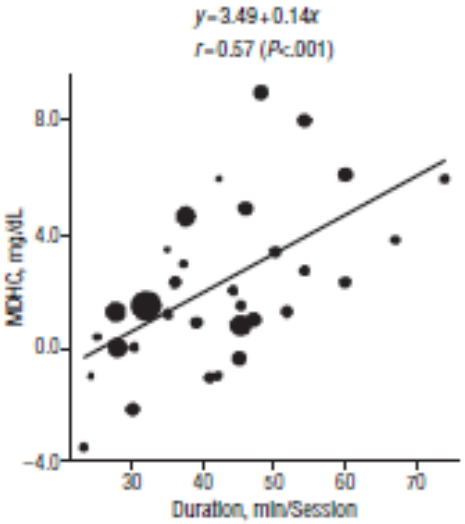
LDL and IDL according to exercise

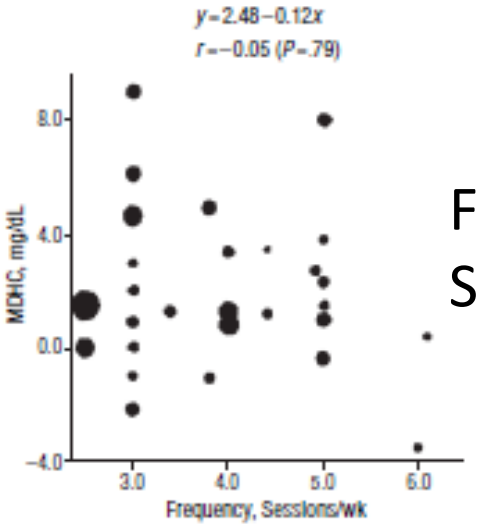


Kraus WE, et al. NEJM 2002;347:786-789

Meta-analysis: Exercise vs. Control
Mean Difference in HDL-C Change and Exercise

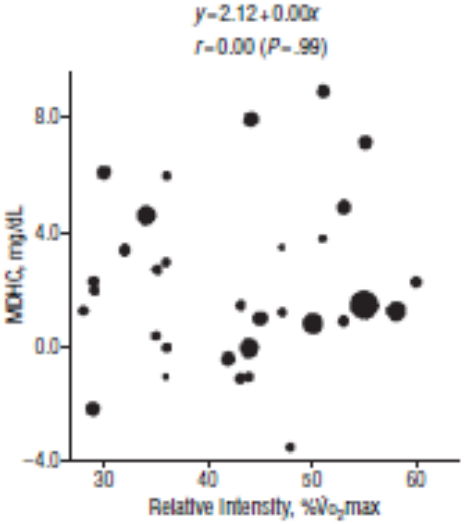
Duration (min.)

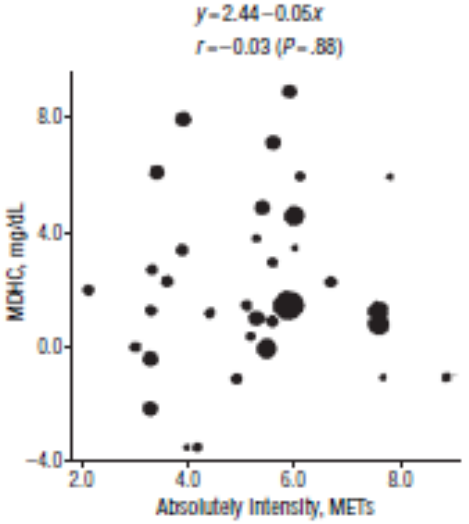




Frequency Sessions/Week

Relative intensity (% $\dot{V}o_2$max)

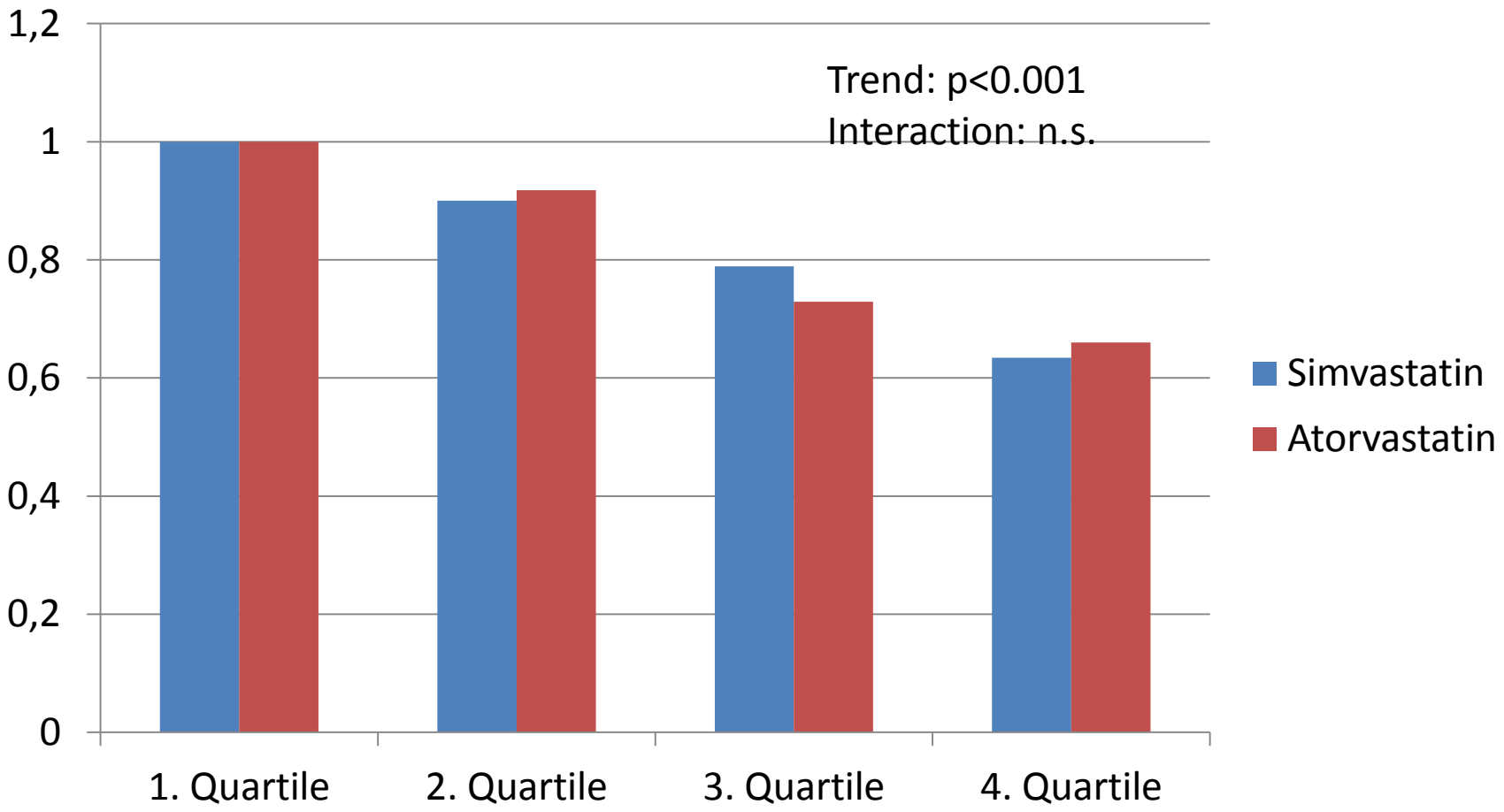




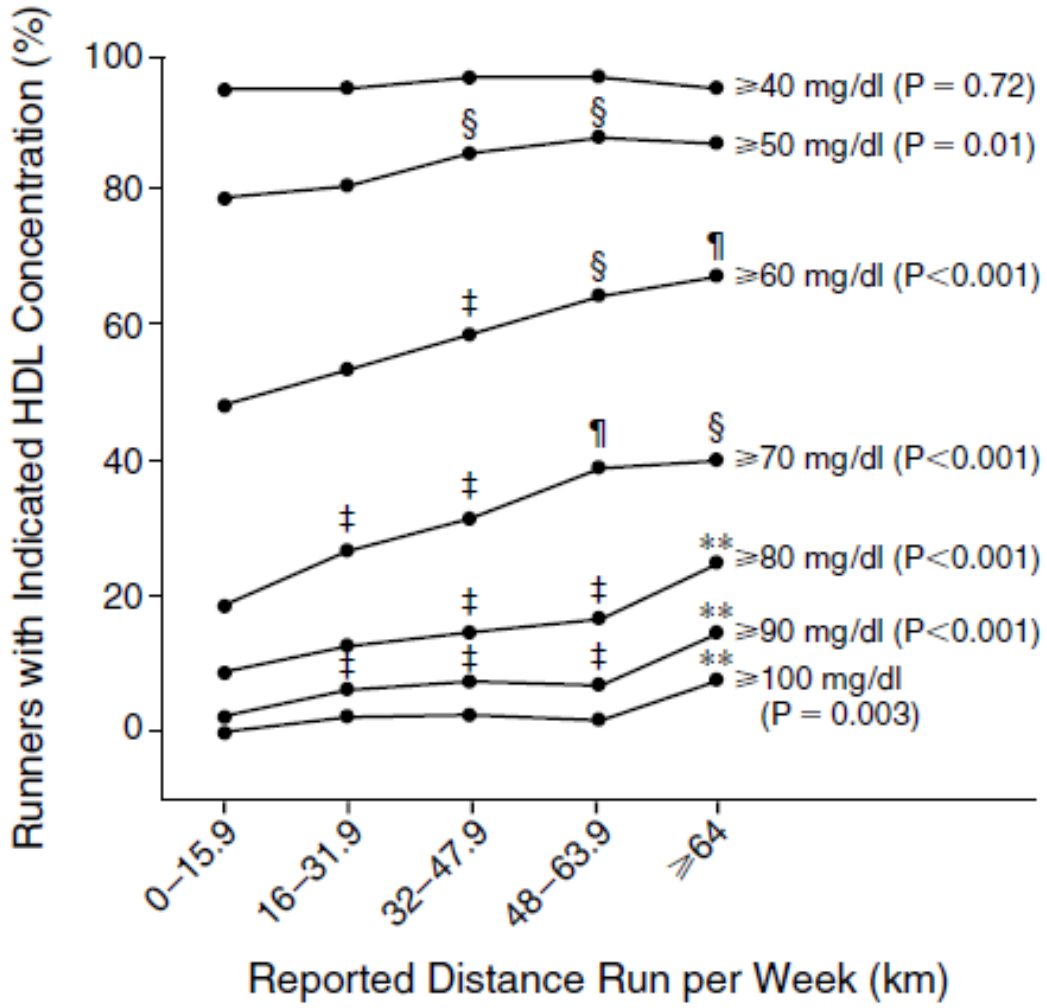
Absolute intensity (METs)

Kodama S, et al. Arch Intern Med 2007;167:999-1008

IDEAL: Relative Risk of CHD by on-treatment Apo A1



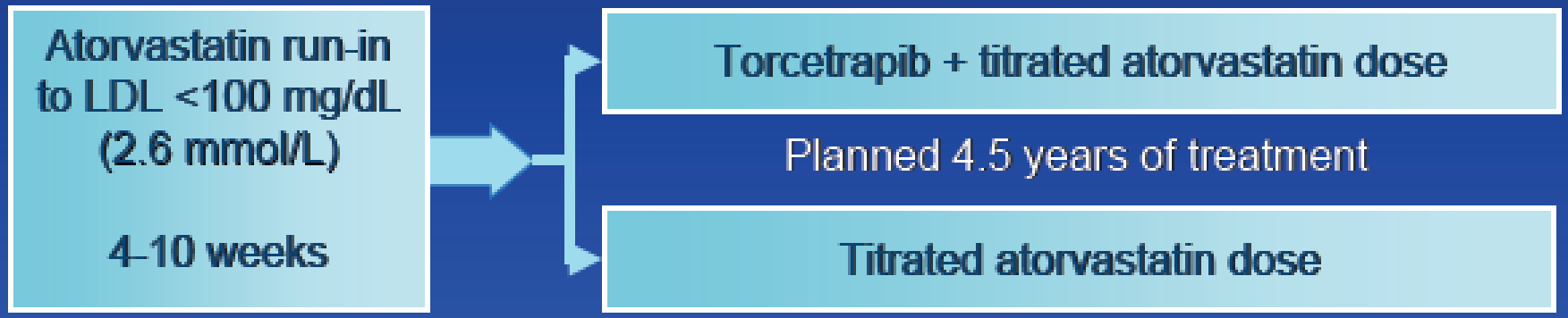
Percentage of Women with HDL-C Exceeding Specified Levels



Williams PT. NEJM 1996;334:1298-1303

ILLUMINATE: Long-term Outcomes in Patients With CHD or CHD Risk Equivalence

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events



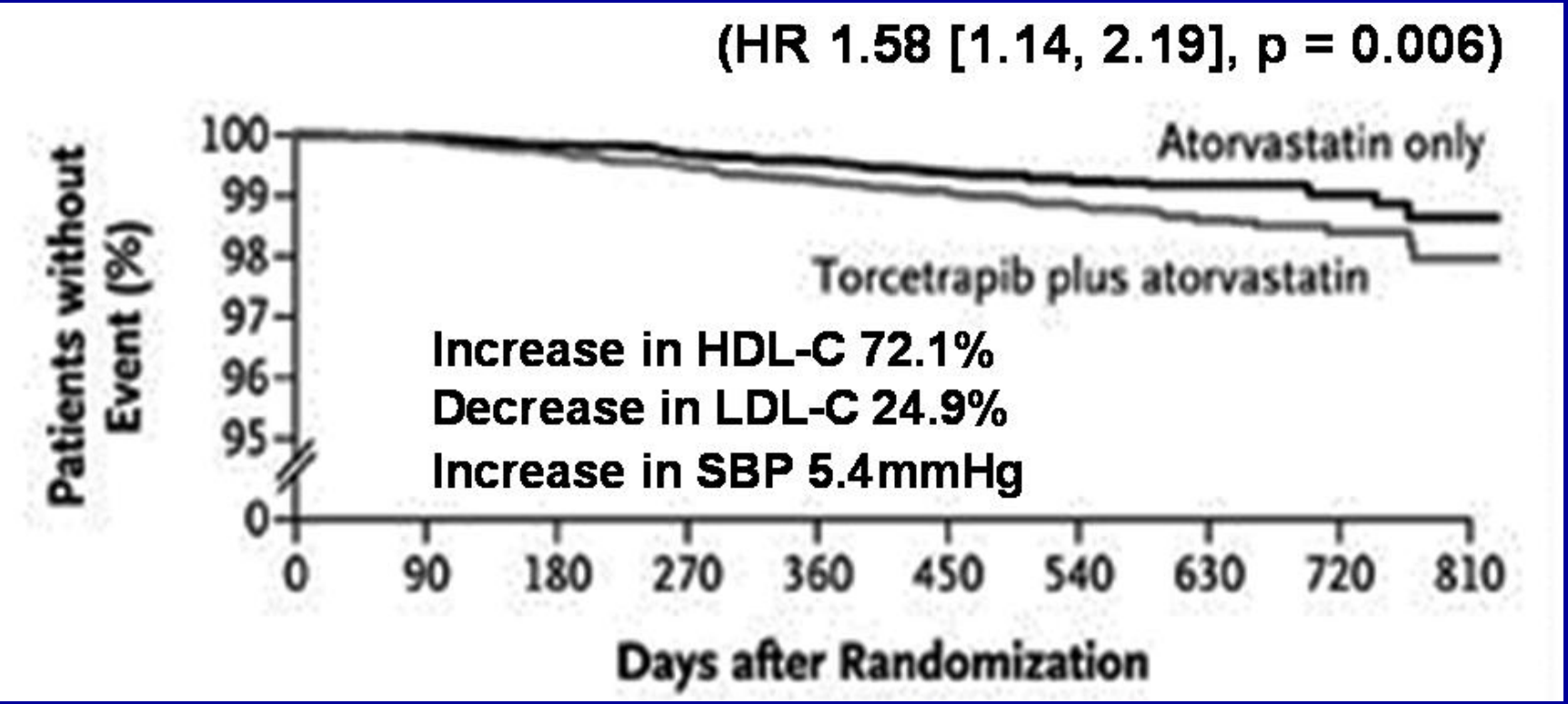
Patient Population	Subjects	Primary End Point
• Men or postmenopausal women • Statin eligible • Any HDL-C level • CHD or risk equivalent (type 2 DM)	• 15,000 • 7 countries	• Major cardiovascular events • Power=0.9 for 21% reduction

Cardiovascular events and mortality in the ILLUMINATE trial at termination of the trial on Dec 02, 2006

Atorvastatin Group=A (n=7534)
Torcetrapib/Atorvastatin Group=T/A (n=7533)

	A	T/A	
Major cardiovascular events	373	464	(p=0.001)
Deaths	59	93	(p=0.006)

ILLUMINATE: Death from Any Cause



P Barter et al. 2007; 357: 2109-22

HPS2-THRIVE: Randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease.

Jane Armitage on behalf of the
HPS2-THRIVE Collaborative Group

Financial Disclosure: Grant to Oxford University. Designed, conducted and analysed independently of the grant source (Merck & Co). No honoraria or consultancy fees accepted.

UNIVERSITY OF OXFORD

hps2 THRIVE

HPS2-THRIVE: Eligibility

Men and women

Aged 50-80 years

Prior history of: myocardial infarction;
ischaemic stroke or TIA;
peripheral arterial disease; or
diabetes with other CHD

No contra-indication to study treatments

No significant liver, kidney or muscle disease

UNIVERSITY OF OXFORD

hps2 THRIVE

HPS2-THRIVE: Active pre-randomization run-in

Screened (51,698)

High cardiovascular risk patients screened in 245 sites within 6 countries

LDL lowering phase (36,059)

Standardise background LDL-lowering therapy with simvastatin 40 mg (+/- ezetimibe) daily (to total cholesterol target of 135 mg/dL)

Active ER niacin plus laropiprant (38,369)

Test compliance with ER niacin 2 grams plus laropiprant 40 mg (ERN/LRPT) daily for 1 month

Randomization (25,673)

ER niacin 2g plus laropiprant 40 mg daily vs. matching placebo tablets

UNIVERSITY OF OXFORD

hps2 THRIVE

Reasons for stopping study treatment

	ERN/LRPT (12,838)	Placebo (12,835)	Excess
Any medical	16.4%	7.9%	8.5%
Skin	5.4%	1.2%	4.2%
Gastrointestinal	3.9%	1.7%	2.1%
Musculoskeletal	1.8%	1.0%	0.8%
Diabetes-related	0.9%	0.4%	0.5%
Liver	0.4%	0.3%	0.1%
Other	4.1%	3.3%	0.8%
Any non-medical	8.9%	8.7%	0.3%
Any reason	**25.4%**	**16.6%**	**8.7%**

78% average compliance with active ERN/LRPT

UNIVERSITY OF OXFORD

hps2 THRIVE

Effect of ERN/LRPT on glucose related SAEs

Serious adverse event	ERN/LRPT	Placebo	Risk ratio (95% CI)
Participants with diabetes at randomization (n= 8299)			
Minor hyperglycaemic problem	8.7%	5.8%	1.55 (1.32-1.82)
Major hyperglycaemic problem	1.0%	0.3%	3.09 (1.81-5.27)
Hypoglycaemia	1.1%	0.7%	1.50 (0.96-2.35)
Other diabetic complication	1.1%	1.2%	0.93 (0.62-1.40)
Any diabetic complication	**460 (11.1%)**	**311 (7.5%)**	**1.55 (1.34-1.78)**
Participants without diabetes at randomization (n= 17,374)			
New-onset diabetes mellitus	**792 (9.1%)**	**632 (7.3%)**	**1.27 (1.14-1.41)**

UNIVERSITY OF OXFORD

hps2 THRIVE

Effect of ERN/LRPT on GI, muscle and skin SAEs

Serious Adverse Event	ERN/LRPT (12,838)	Placebo (12,835)	Risk ratio (95% CI)
Gastrointestinal			
GI bleeding	0.8%	0.6%	1.53 (1.14-2.05)
Peptic ulcer/upper GI	1.9%	1.4%	1.37 (1.13-1.65)
Lower GI	0.9%	0.7%	1.39 (1.06-1.83)
Other GI	1.0%	1.0%	0.99 (0.77-1.27)
Any gastrointestinal SAE	**620 (4.8%)**	**491 (3.8%)**	**1.28 (1.13-1.44)**
Musculoskeletal			
Myopathy	0.6%	0.1%	4.43 (2.62-7.50)
Gout	0.3%	0.2%	1.91 (1.16-3.15)
Other	2.9%	2.7%	1.08 (0.93-1.25)
Any musculoskeletal SAE	**481 (3.7%)**	**385 (3.0%)**	**1.26 (1.10-1.44)**
Skin			
Rash	0.4%	0.3%	1.63 (1.07-2.48)
Ulcer	0.2%	0.1%	1.61 (0.82-3.14)
Other	0.1%	0.0%	2.59 (1.05-6.37)
Any skin SAE	**86 (0.7%)**	**51 (0.4%)**	**1.67 (1.20-2.34)**

UNIVERSITY OF OXFORD

THRIVE

Effect of ERN/LRPT on infection and bleeding

Serious Adverse Event	ERN/LRPT (12,838)	Placebo (12,835)	Risk ratio (95% CI)
Infection			
Lower respiratory	4.3%	3.7%	1.17 (1.03-1.32)
Urinary tract	0.9%	0.8%	1.07 (0.82-1.39)
Abdominal/gastrointestinal	0.6%	0.5%	1.26 (0.91-1.75)
Skin	0.5%	0.3%	1.66 (1.14-2.43)
Other	2.4%	1.7%	1.38 (1.16-1.63)
Any infection SAE	**1031 (8.0%)**	**853 (6.6%)**	**1.22 (1.12-1.34)**
Bleeding			
Gastrointestinal	0.8%	0.6%	1.53 (1.14-2.05)
Intracranial	1.1%	0.9%	1.17 (0.92-1.50)
Other	0.6%	0.4%	1.66 (1.18-2.34)
Any bleeding SAE	**326 (2.5%)**	**238 (1.9%)**	**1.38 (1.17-1.62)**

UNIVERSITY OF OXFORD

hps2 THRIVE

Prespecified efficacy outcomes

Primary outcome: MAJOR VASCULAR EVENTS (MVE)

Defined as the first occurrence of either:

- MAJOR CORONARY EVENT = Non-fatal MI or coronary death;
- STROKE = Any non-fatal or fatal stroke (including subarachnoid haemorrhage); or
- REVASCULARIZATION = Coronary or non-coronary artery surgery or angioplasty (including amputation)

Secondary outcomes:

- Separate components of the primary outcome
- MVE in patients with or without coronary heart disease, cerebrovascular disease, peripheral artery disease and diabetes
- Mortality, overall and by specific causes of death

UNIVERSITY OF OXFORD

hps2 THRIVE

Statistical power after about 4 years

Based on estimated 3200 MVEs during median follow-up of 4 years

Proportional reduction in risk	Statistical power at 2p:	
	<0.05	<0.01
8%	67%	43%
9%	78%	56%
10%	86%	68%
12%	96%	87%

UNIVERSITY OF OXFORD

hps2 THRIVE

Lipid differences (mg/dL) by age, sex, region and statin-based therapy

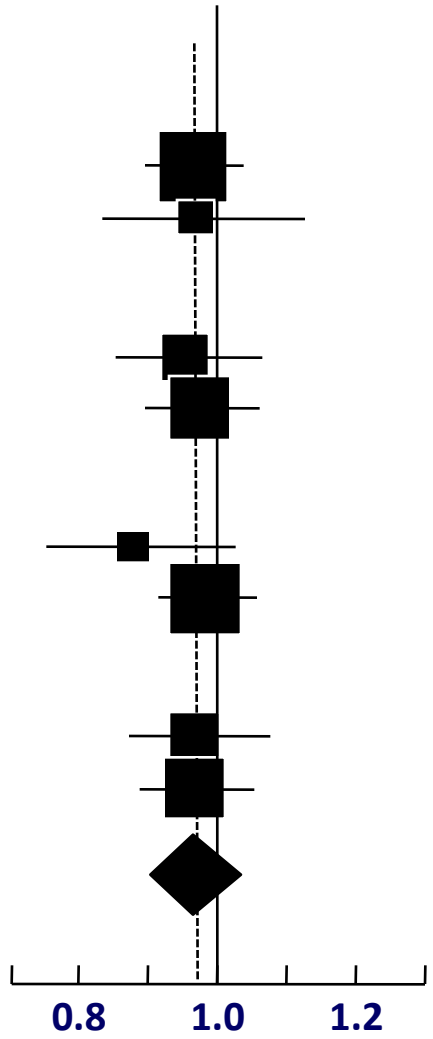
	Patients	LDL-C	HDL-C
Age (years)			
<65	12,932	-10	5
≥65 <70	5624	-11	7
≥70	7117	-8	7
Sex			
Male	21,229	-10	6
Female	4444	-8	7
Region			
Europe	14,741	-12	7
China	10,932	-7	5
Statin-based therapy			
Simvastatin 40mg	13,542	-8	6
Ezetimibe/simvastatin	12,131	-12	7
All	**25,673**	**-10**	**6**

UNIVERSITY OF OXFORD

THRIVE

MAJOR VASCULAR EVENTS by prior disease

	Randomized allocation ERN/LRPT (12,838)	Randomized allocation Placebo (12,835)	Risk ratio & 95% CI	Het or trend χ^2 (uncorrected p value)
Coronary heart disease				
Yes	1361 (13.5%)	1413 (14.0%)		0.00 (p=0.96)
No	335 (12.1%)	345 (12.5%)		
Cerebrovascular disease				
Yes	616 (15.2%)	656 (16.0%)		0.10 (p=0.75)
No	1080 (12.3%)	1102 (12.6%)		
Peripheral arterial disease				
Yes	302 (18.6%)	332 (20.9%)		1.66 (p=0.20)
No	1394 (12.4%)	1426 (12.7%)		
Diabetes mellitus				
Yes	678 (16.4%)	708 (17.0%)		0.00 (p=0.98)
No	1018 (11.7%)	1050 (12.1%)		
All	**1696 (13.2%)**	**1758 (13.7%)**		**3.5% SE 3.3 reduction**



UNIVERSITY OF OXFORD

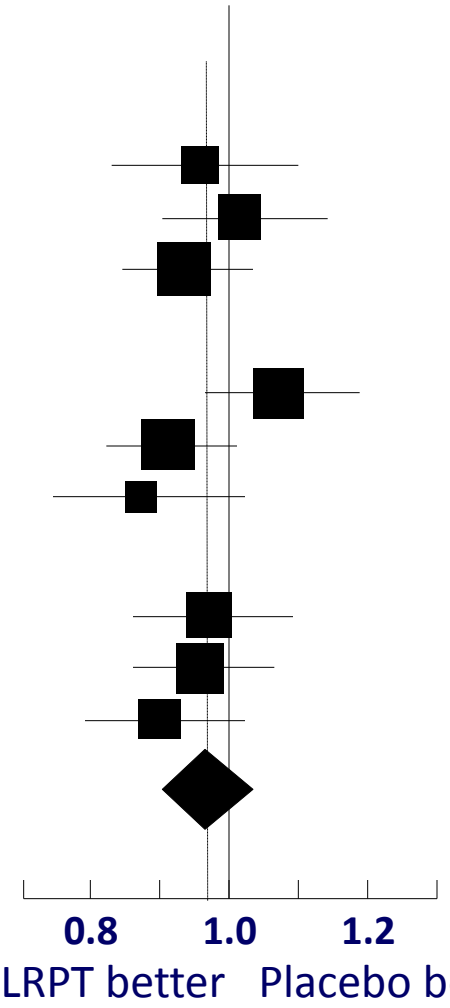
THRIVE

Lipid differences (mg/dL) by prior disease

	Patients	LDL-C	HDL-C
Coronary heart disease			
Yes	20,137	-10	6
No	5536	-10	7
Cerebrovascular disease			
Yes	8170	-9	6
No	17,503	-10	7
Peripheral arterial disease			
Yes	3214	-11	7
No	22,459	-9	6
Diabetes mellitus			
Yes	8299	-8	7
No	17,374	-10	6
All	**25,673**	**-10**	**6**

MAJOR VASCULAR EVENTS by baseline lipids

mg/dL (mmol/L)	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	Het or trend X^2 (uncorrected p value)
HDL cholesterol				
<35 (0.9)	388 (15.8%)	399 (16.3%)		0.20 (p=0.66)
≥35 <43	560 (13.7%)	546 (13.5%)		
≥43 (1.1)	748 (11.9%)	813 (12.8%)		
LDL cholesterol				
<58 (1.5)	724 (14.7%)	679 (13.8%)		5.91 (p=0.02)
≥58 <77	685 (12.4%)	761 (13.7%)		
≥77 (2.0)	287 (12.0%)	318 (13.5%)		
Triglycerides				
<89 (1.0)	541 (13.2%)	563 (13.4%)		0.66 (p=0.42)
≥89 <151	694 (12.8%)	712 (13.2%)		
≥151 (1.7)	461 (13.9%)	483 (14.8%)		
All	**1696 (13.2%)**	**1758 (13.7%)**		**3.5% SE 3.3 reduction**



UNIVERSITY OF OXFORD

HPS2 THRIVE

Lipid differences (mg/dL) by baseline lipids

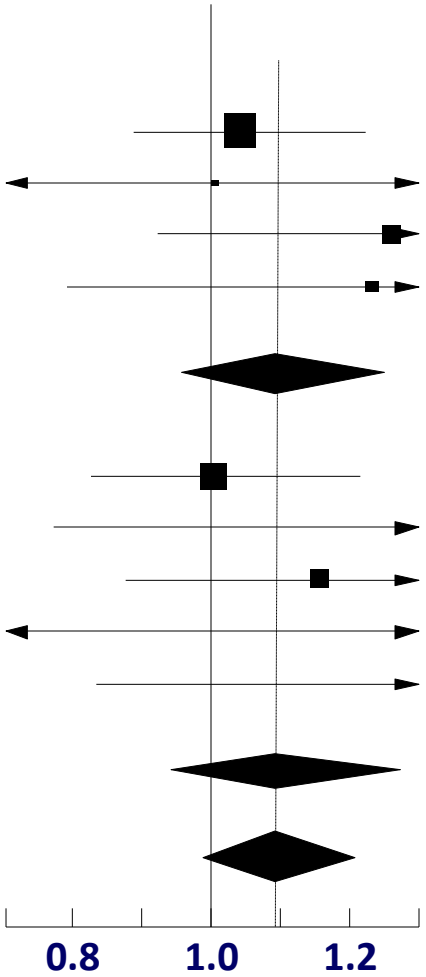
mg/dL (mmol/L)	Patients	LDL-C	HDL-C
HDL cholesterol			
<35 (0.9)	4900	-7	5
≥35 <43	8135	-9	6
≥43 (1.1)	12,638	-11	7
LDL cholesterol			
<58 (1.5)	9860	-7	6
≥58 <77	11,054	-10	6
≥77 (2.0)	4759	-15	7
Triglycerides			
<89 (1.0)	8297	-9	6
≥89 <151	10,801	-10	6
≥151 (1.7)	6575	-10	6
All	**25,673**	**-10**	**6**

UNIVERSITY OF OXFORD

hps2 THRIVE

Effect of ERN/LRPT on CAUSE-SPECIFIC MORTALITY

	Randomized allocation ERN/LRPT (12838)	Placebo (12835)	Risk ratio & 95% CI	p
Coronary	302 (2.4%)	291 (2.3%)		
Other cardiac	15 (0.1%)	15 (0.1%)		
Stroke	88 (0.7%)	70 (0.5%)		
Other vascular	43 (0.3%)	35 (0.3%)		
Vascular	**448 (3.5%)**	**411 (3.2%)**	**1.09 (0.96-1.25)**	**0.19**
Neoplastic	206 (1.6%)	206 (1.6%)		
Hepatic	3 (0.0%)	0 (0.0%)		
Other medical	106 (0.8%)	92 (0.7%)		
Non-medical	16 (0.1%)	12 (0.1%)		
Unknown	19 (0.1%)	11 (0.1%)		
Non-vascular	**350 (2.7%)**	**321 (2.5%)**	**1.09 (0.94-1.27)**	**0.25**
Any cause	**798 (6.2%)**	**732 (5.7%)**	**1.09 (0.99-1.21)**	**0.08**



UNIVERSITY OF OXFORD

THRIVE

HPS2-THRIVE: SUMMARY

- No significant benefit of ER niacin/laropiprant on the primary outcome of major vascular events when added to effective statin-based LDL-lowering therapy
- Significant excesses of serious adverse events (SAEs) due to known and unrecognised side-effects of niacin. Over 4 years, ER niacin/laropiprant caused SAEs in ~30 patients per 1000
- No clear evidence of differences in efficacy or safety in different types of patient (except for an excess of statin-related myopathy in Chinese patients)
- Findings are consistent with previous niacin trials. The role of ER niacin for the treatment and prevention of cardiovascular disease needs to be reconsidered