Review of guidelines for management of dyslipidemia in diabetic patients

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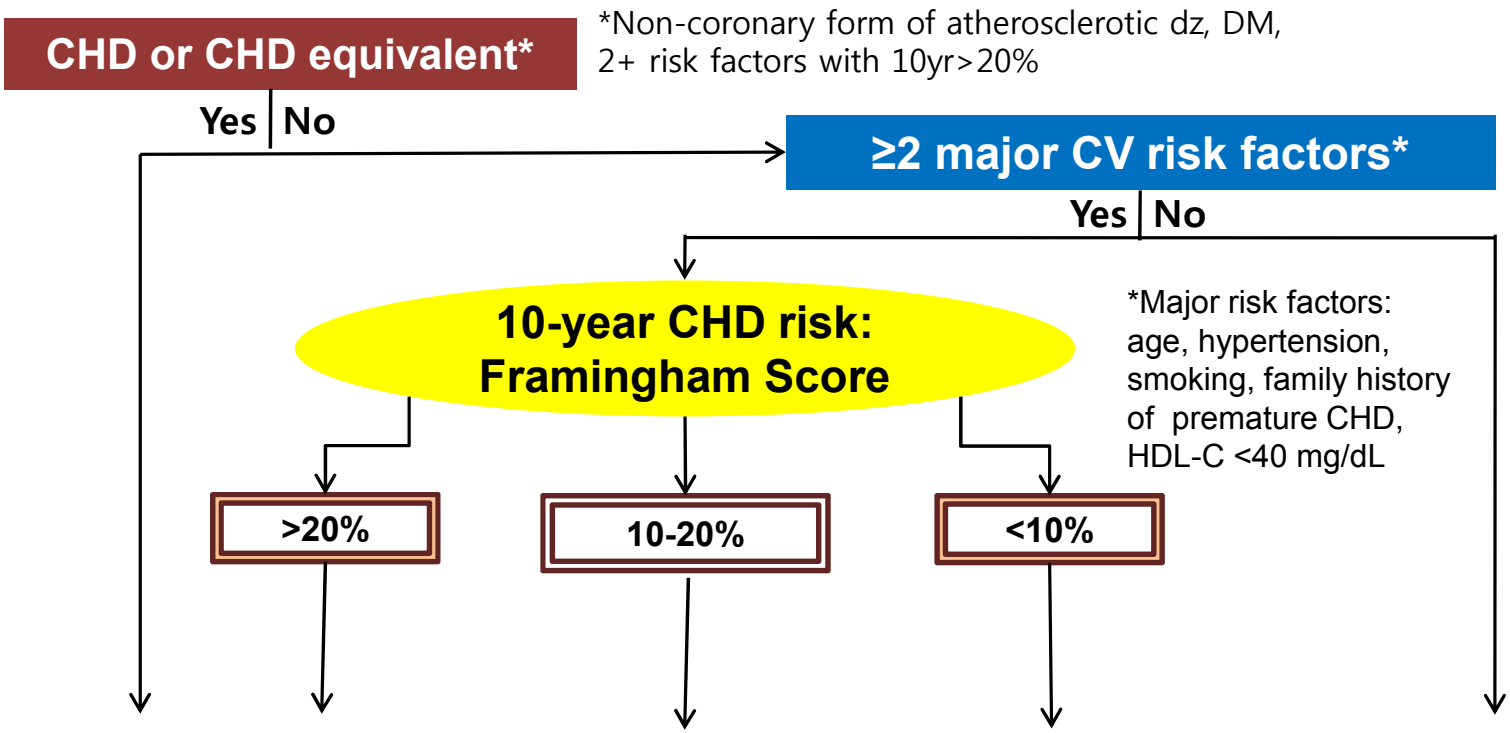
Contents

- Review of guidelines
  - 2001: National Cholesterol Education Program (NCEP) Adult treatment Panel III (ATP III)
  - 2004: NCEP ATP III Update
  - 2008: ADA/ACC (American College of Cardiology Foundation)
  - 2011: ESC/EAS (European Society of Cardiology/ European Atherosclerosis Society)

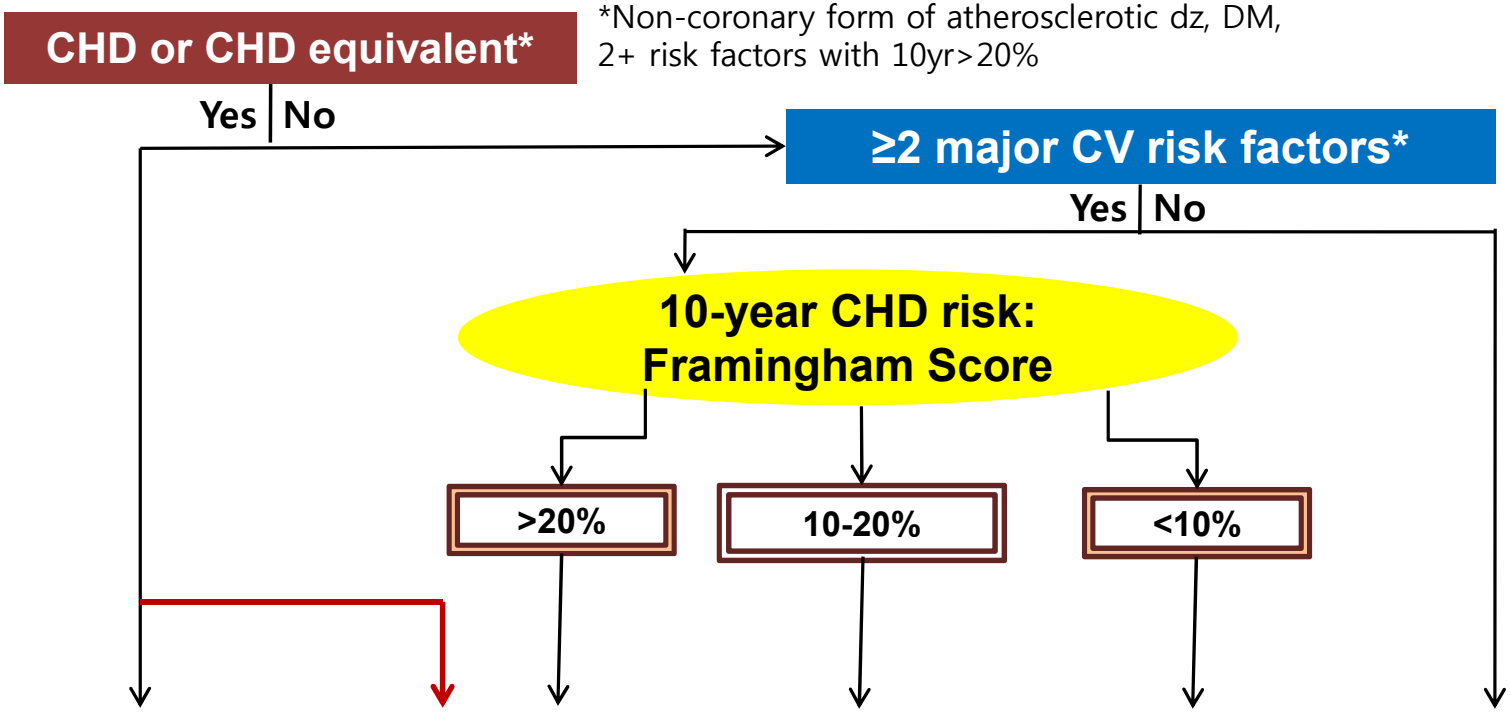
- Issue for NCEP ATP IV

2001 NCEP ATP III: LDL-C Goal Values



Risk	High	Moderately high	Moderate	Low
LDL goal	<100	<130	<130	<160
Medication start	≥130 (100-129: optional)	≥130	≥160	≥190 (160-189: optional)

2004 NCEP ATP III Update: LDL-C Goal Values



Risk	Very High	High	Moderately high	Moderate	Low
LDL goal	<70	<100	<130	<130	<160
Med start		≥100 (<100: optional)	≥130 (100-129: optional)	≥160	≥190 (160-189: optional)

Very High Risk in updated ATP III

- Established CVD plus
  - Multiple major risk factors (especially diabetes)
  - Severe and poorly controlled risk factors (especially continued smoking)
  - Multiple risk factors of MetS (especially Tg ≥200, non-HDL-C ≥130, and HDL-C <40)
  - Acute coronary syndrome

→ LDL-C goal <70 mg/dL

NCEP ATP III Update

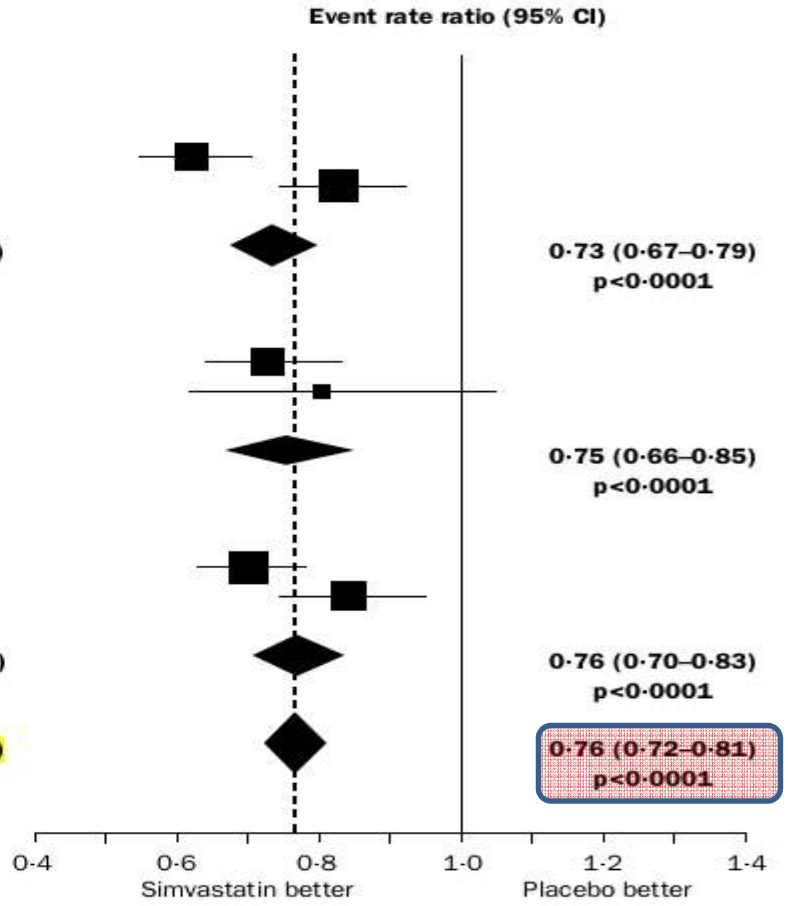
- In high risk persons (10yr CHD risk >20%), LDL-C goal <100 mg/dL
  - If LDL-C ≥100mg/dL, LDL-lowering drug is indicated
  - If LDL-C <100mg/dL, LDL-lowering drug is an option
  - If high Tg or low HDL-C, consider fibrate or nicotinic acid with LDL-lowering drug
  - When Tg ≥200mg/dL, non-HDL-C is secondary target of therapy, with a goal 30mg/dL higher than LDL-C goal

- When LDL-lowering drugs are used, LDL-C levels should be reduced at least 30-40%

Rationale for LDL-C goal <70 mg/dL : Heart Protection Study

- CAD, other occlusive vascular disease, no vascular disease
- Simvastatin 40mg vs. placebo, N=20536

Type of major vascular event	Simvastatin-allocated (10 269)	Placebo-allocated (10 267)
Coronary events		
Non-fatal MI	357 (3·5%)	574 (5·6%)
Coronary death	587 (5·7%)	707 (6·9%)
Subtotal: major coronary event	**898 (8·7%)**	**1212 (11·8%)**
Strokes		
Non-fatal stroke	366 (3·6%)	499 (4·9%)
Fatal stroke	96 (0·9%)	119 (1·2%)
Subtotal: any stroke	**444 (4·3%)**	**585 (5·7%)**
Revascularisations		
Coronary	513 (5·0%)	725 (7·1%)
Non-coronary	450 (4·4%)	532 (5·2%)
Subtotal: any revascularisation	**939 (9·1%)**	**1205 (11·7%)**
ANY MAJOR VASCULAR EVENT	**2033 (19·8%)**	**2585 (25·2%)**

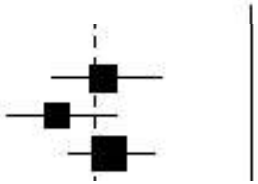


CV event: 24% reduction

Lancet 2002; 360:7-22

Effect of CV risk reduction in subjects with baseline LDL-C < 130mg/dL

Presenting feature	Simvastatin-allocated	Placebo-allocated	Event rate ratio (95% CI)	Heterogeneity or trend χ^2
LDL cholesterol (mmol/L)				
<116 mg/dl	598/3389(17·6%)	756/3404(22·2%)		0·10
117~135 mg/dl	484/2549(19·0%)	646/2514(25·7%)		
≥135 mg/dl	951/4331(22·0%)	1183/4349(27·2%)		



Even among 3,421 presenting with LDL <100 mg/dL, simvastatin Produced a reduction in risk about as great as that seen among those presenting with higher LDL-C concentrations (a quarter)

Lancet 2002; 360:7-22

PROVE IT - TIMI 22

The NEW ENGLAND JOURNAL of MEDICINE

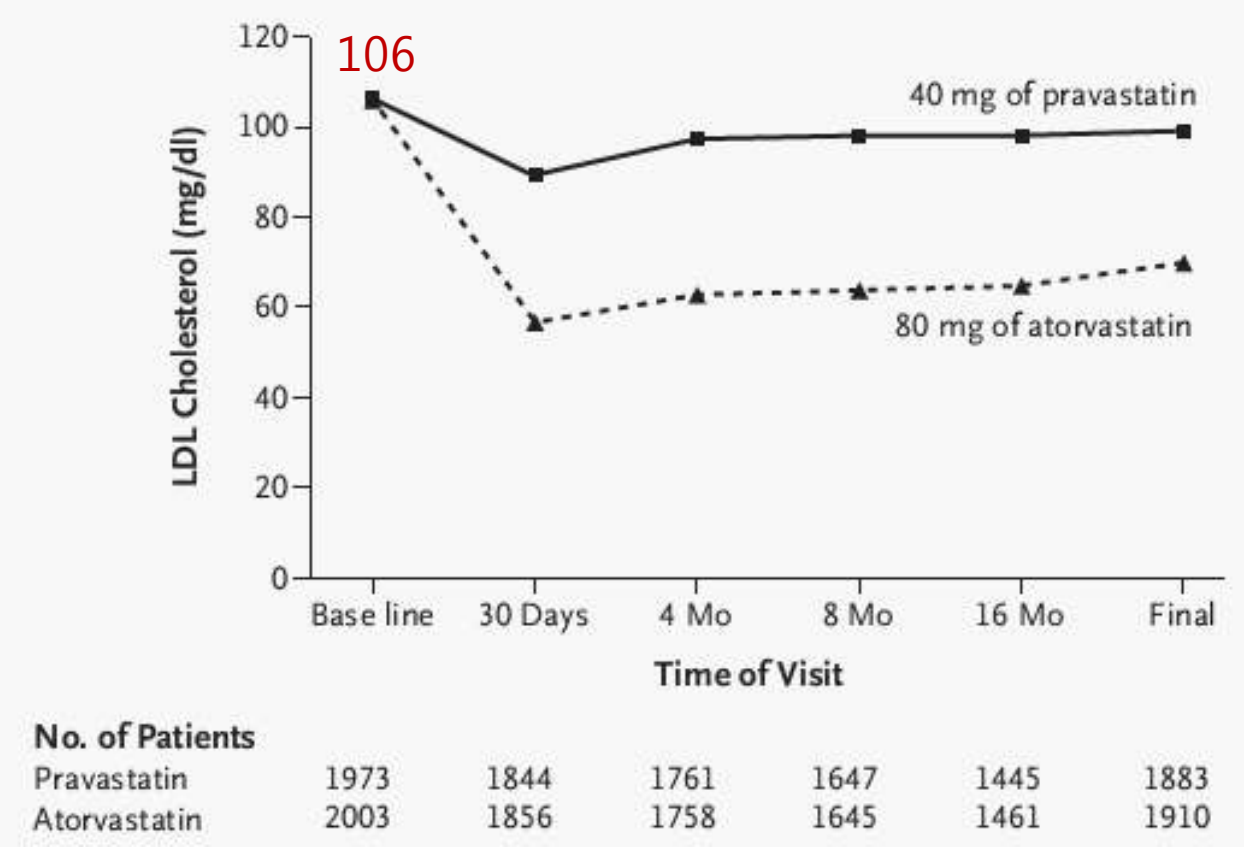
ESTABLISHED IN 1812 APRIL 8, 2004 VOL. 350 NO. 15

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Pravastatin 40mg vs. atorvastatin 80mg in acute coronary syndrome
N=4162

N Engl J Med 2004; 350:1495-1504

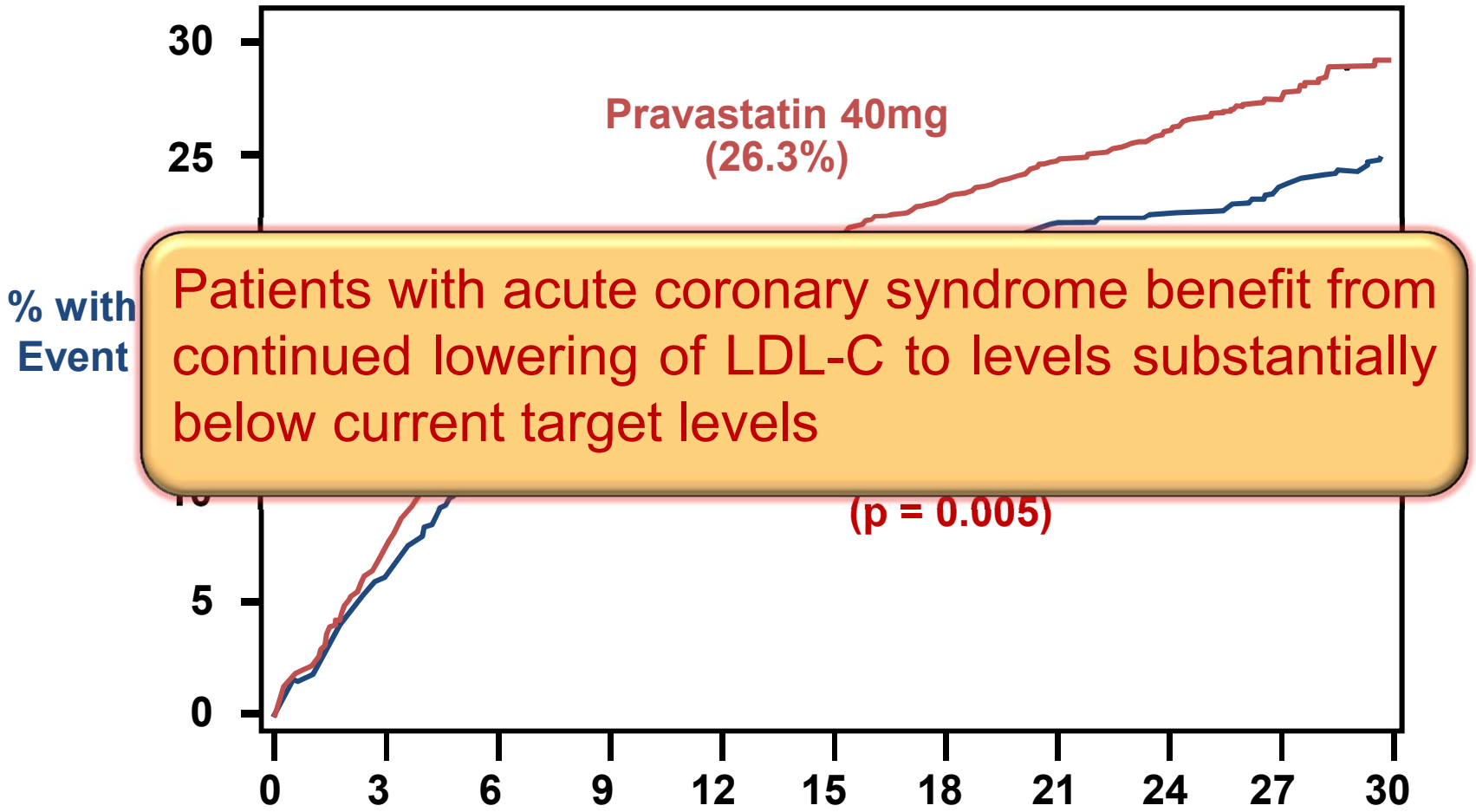
Median LDL-C levels during the study



No. of Patients						
Pravastatin	1973	1844	1761	1647	1445	1883
Atorvastatin	2003	1856	1758	1645	1461	1910

N Engl J Med 2004; 350:1495-1504

All-Cause Death or Major CV Events



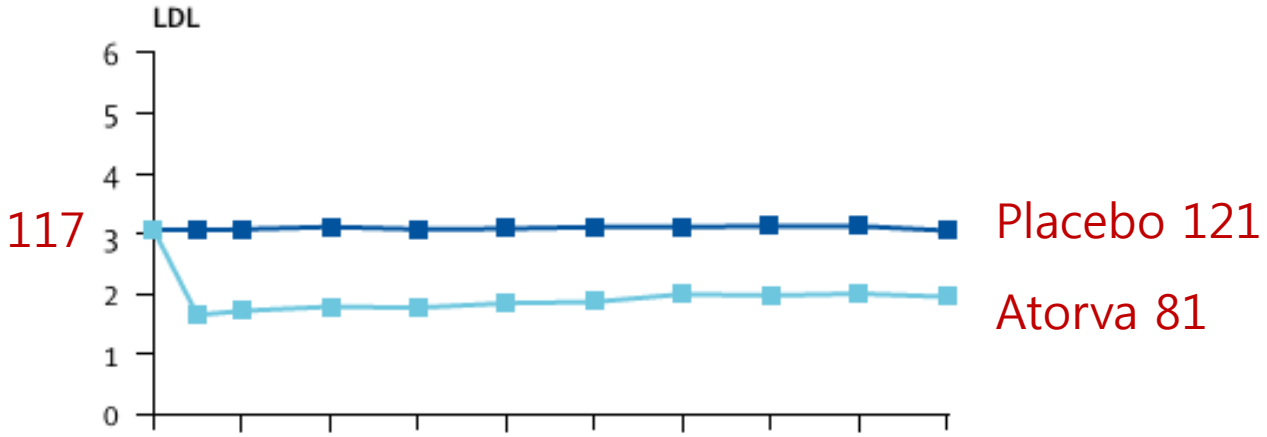
Patients with acute coronary syndrome benefit from continued lowering of LDL-C to levels substantially below current target levels

N Engl J Med 2004; 350:1495-1504

Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

*Helen M Colhoun, D John Betteridge, Paul N Durrington, Graham A Hitman, H Andrew W Neil, Shona J Livingstone, Margaret J Thomason, Michael I Mackness, Valentine Charlton-Menys, John H Fuller, on behalf of the CARDS investigators**

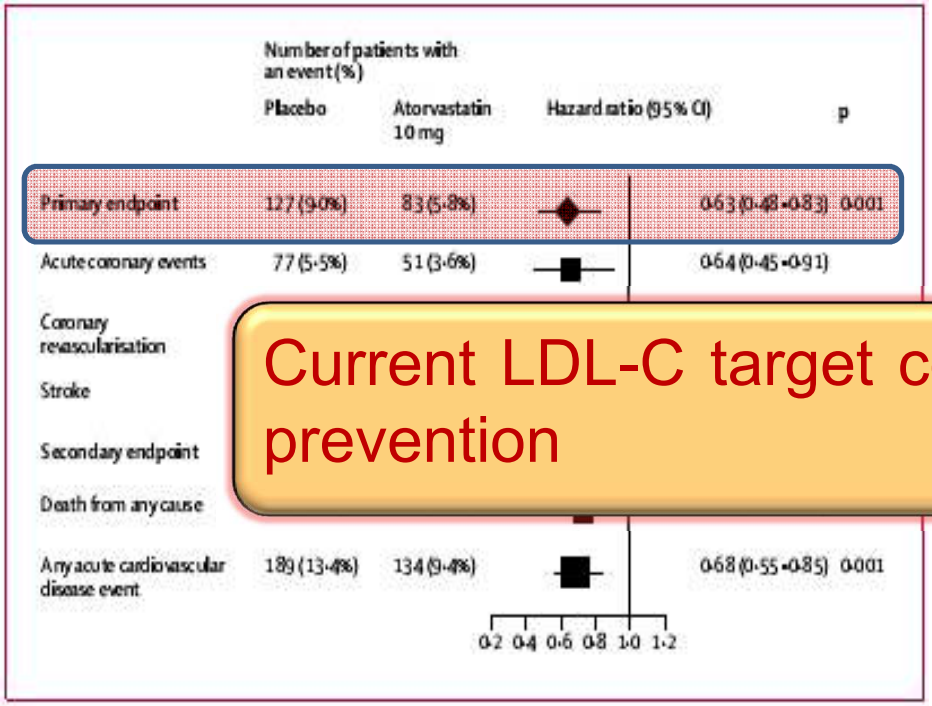
- T2DM without CVD and without high LDL-C, ≥1 risk factors
- N=2838
- Atorvastatin 10mg vs. placebo for primary prevention

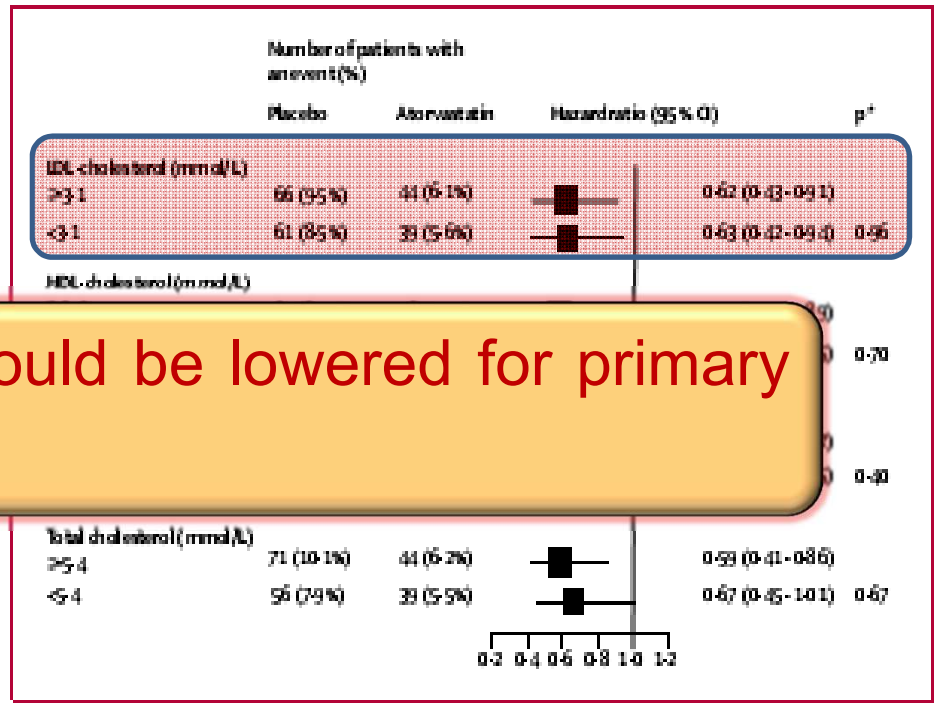


Lancet 2004; 364:685-96

CARDS trial

- 36% reduction in major CV event
- 743 patients with baseline LDL-C <100mg/dl, 26% reduction in major CV event





Current LDL-C target could be lowered for primary prevention

Lancet 2004; 364:685-96

2008 ADA and ACC Consensus Statement

	Goal Values (mg/dL)		
	LDL-C	Non-HDL-C	Apo B
Highest Risk: · CVD or · DM with ≥1 major risk factor*	<70	<100	<80
High Risk: · No CVD, no DM with ≥2 major risk factors · DM with no major risk factors	<100	<130	<90

*Risk factor: smoking, hypertension, family history of premature CAD

ESC/EAS 2011 Guidelines: Lipid Targets

More aggressive target for high-risk patients

		LDL-C	Non–HDL-C	Apo B
		Primary Target	Secondary Targets	
Very high risk	Documented CVD Type 2 diabetes Type 1 diabetes with target organ damage (such as microalbuminuria) ≥ CKD stage 3 A calculated 10-year risk SCORE ≥10%	~70 mg/dL And/or ≥50% reduction from baseline	~100 mg/dL	<80 mg/dL
High risk	Markedly elevated single-risk factors (eg, familial dyslipidemias or severe hypertension) A calculated 10-year risk SCORE ≥5% and <10% for fatal CVD	~100 mg/dL	~130 mg/dL	<100 mg/dL
Moderate risk	SCORE is ≥1% and <5% at 10 years	~115 mg/dL	~145 mg/dL	Not defined

ESC/EAS 2011 Guidelines: Recommendations for treatment of dyslipidemia in diabetes

		Class	Level
Type 1 DM	• Microalbuminuria and renal disease • LDL-C lowering (≥30%) with statins irrespective of the basal LDL-C concentration	I	C
Type 2 DM	• CVD or CKD • Without CVD - over the age of 40 years - ≥1 more CVD risk factors - markers of target organ damage : LDL-C <70 mg/dL non-HDL-C is <100 mg/dL, apo B is <80 mg/dL	I	B
Type 2 DM	• Primary target: LDL-C goal <100 mg/dL • Secondary targets: Non-HDL-C <130 mg/dL and apo B <100 mg/dL	I	B

Issues for ATP IV

- LDL-C goals for primary and secondary prevention
- CVD risk assessment
- Alternative treatment targets:
  - Apo B, non HDL-C,LDL particle number, Lp-PLA2, Lp(a), hsCRP
- Direct targeting of HDL-C and triglyceride
  - Role of fibrates, niacin, omega-3 fatty acid

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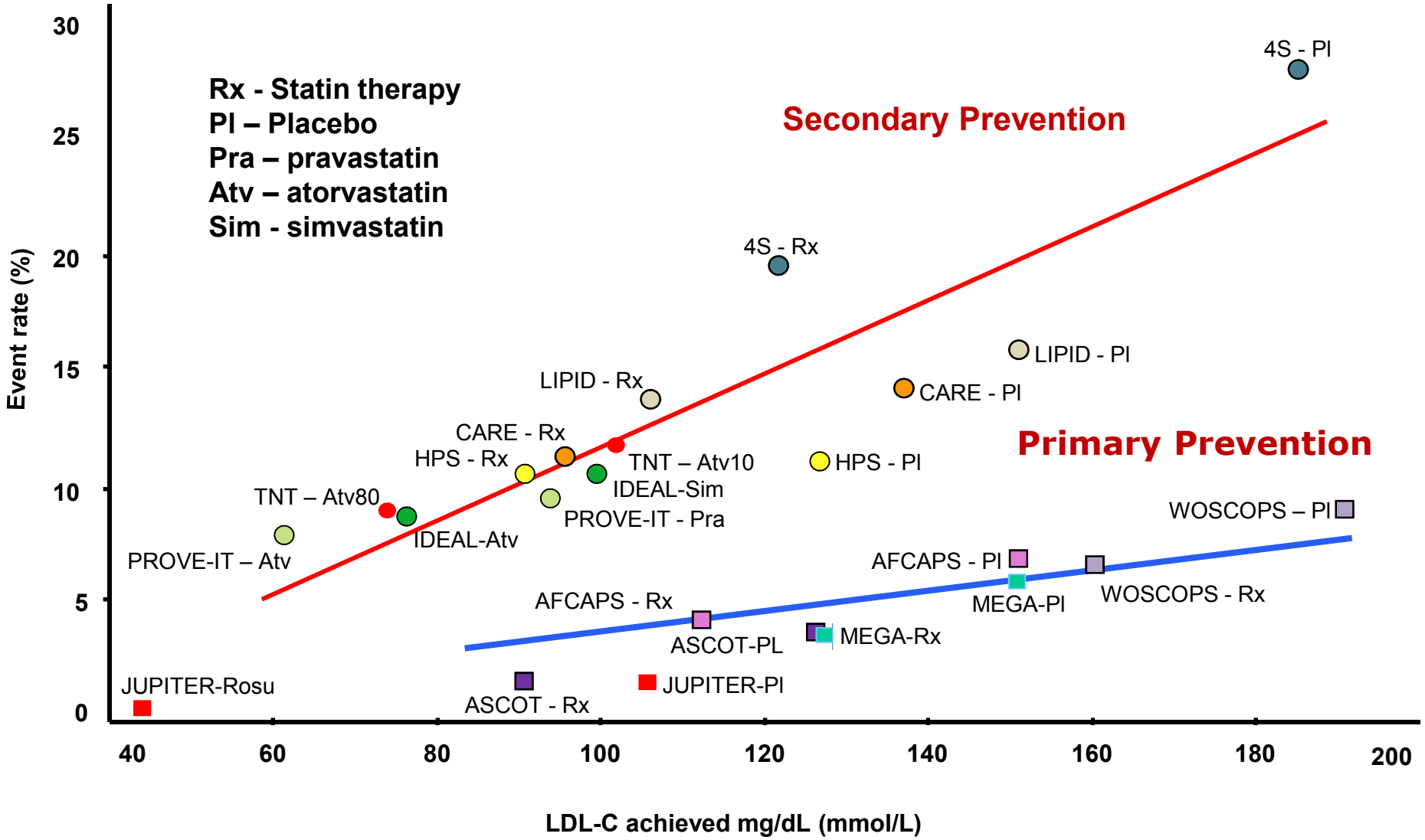
On-treatment LDL-C is closely related to CHD events in statin trials – lower is better



Effects of statin in people at low risk

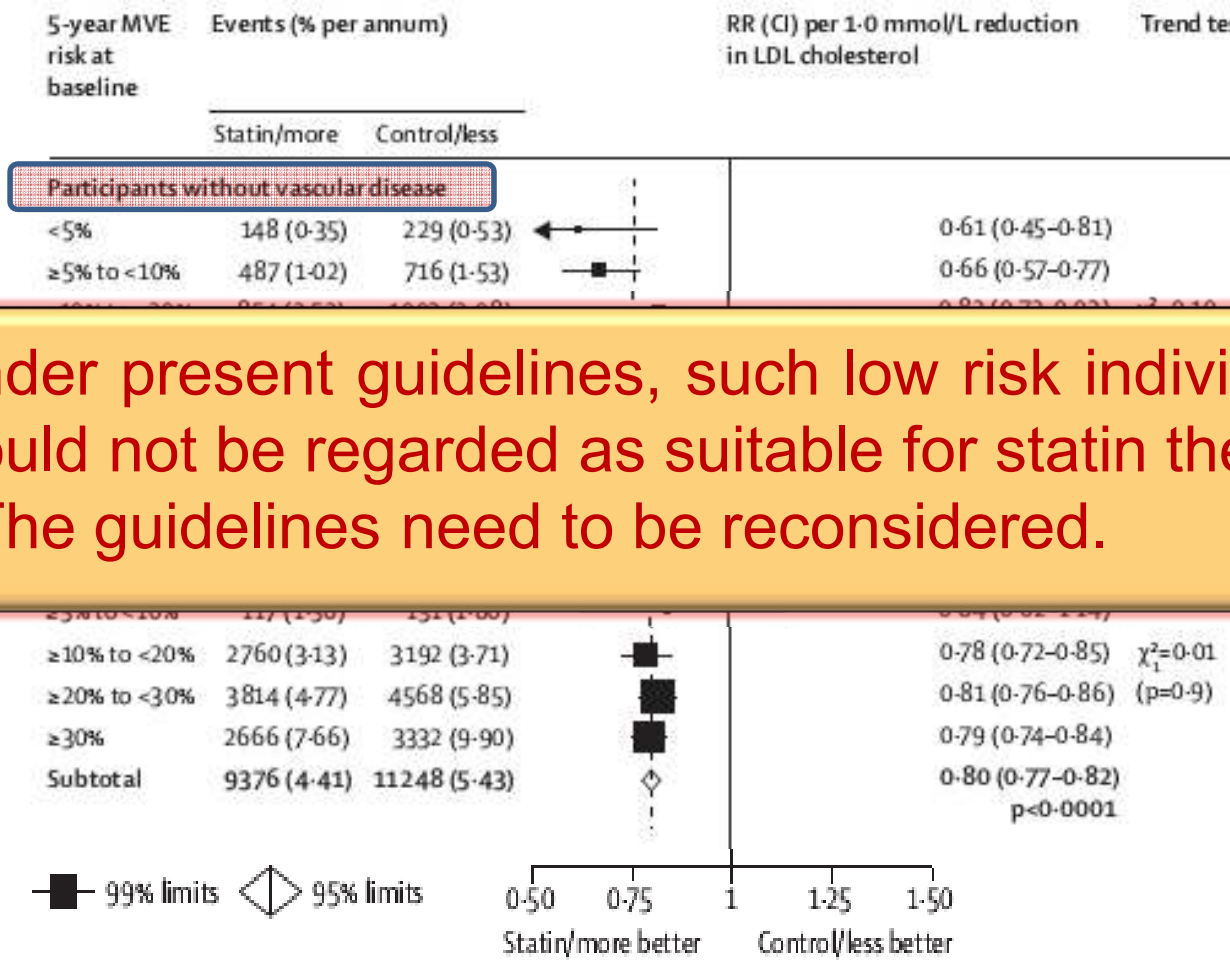
The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaborators**

- 22 trials of statin vs. control & 5 trials of more vs. less statin
- Subjects were separated into five categories of baseline 5-yr major vascular event risk (<5, 5~10, 10~20, 20~30, ≥30%)

Lancet 2012; 380: 581-90

Statin therapy reduces the major vascular events in low risk individuals



Under present guidelines, such low risk individuals would not be regarded as suitable for statin therapy --The guidelines need to be reconsidered.

Lancet 2012; 380: 581-90

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CVD risk assessment

- Example: 56yr old women, without CV sx, ex-smoker (4yrs ago), no f/hx of MI or sudden cardiac death, BP 138/76 mmHg, FPG 109 mg/dl, TC 210mg/dl, HDL 42 mg/dl, Tg 201 mg/dl, has never taken any medication
- What is her risk for future CVD event?

Risk Score	Estimated Risk
Framingham	
10-yr CHD risk score	2%
Global CVD score	10%*
Heart age/vascular age	73
Reynolds	6%
SCORE (fatal CVD)	1%–2%†
QRISK	11%
ASSIGN	14%
Lifetime risk for CVD	39%

J Am Coll Cardiol 2010; 55: 1169-77

Risk Score	Estimated Risk
Framingham	
10-yr CHD risk score	2%
Reynolds	
Negative FH, hsCRP 0.5 mg/l	2%
Negative FH, hsCRP 3.0 mg/l	3%
Negative FH, hsCRP 8.0 mg/l	4%
Positive FH, hsCRP 0.5 mg/l	3%
Positive FH, hsCRP 3.0 mg/l	5%
Positive FH, hsCRP 8.0 mg/l	6%
SCORE (fatal CVD)	
Country of low cardiovascular risk	1%
Country of high cardiovascular risk	2%
QRISK	
Negative FH, BMI <23 kg/m^2	6%
Negative FH, BMI 23–32 kg/m^2	6%
Negative FH, BMI ≥33 kg/m^2	7%
Positive FH, BMI <23 kg/m^2	10%
Positive FH, BMI 23–32 kg/m^2	11%
Positive FH, BMI ≥33 kg/m^2	12%
ASSIGN*	
Negative FH, SIMD <10	7%–8%
Negative FH, SIMD 10–29	8%–10%
Negative FH, SIMD ≥30	10%–15%
Positive HH, SIMD <10	12%–13%
Positive FH, SIMD 10–29	13%–15%
Positive FH, SIMD ≥30	15%–23%
Lifetime risk for CVD	39%

SIMD
:Scottish Index of Multiple Deprivation

J Am Coll Cardiol 2010; 55: 1169-77

Newer CVD prediction algorithms

- Lifetime risk
- Composite endpoints (all CVD, PAD, stokes, heart failure, angina, revascularization..)
- Inclusion of family history, hs-CRP, HbA1c, social deprivation, BMI
- Vascular imaging
- Validation/calibration in other populations

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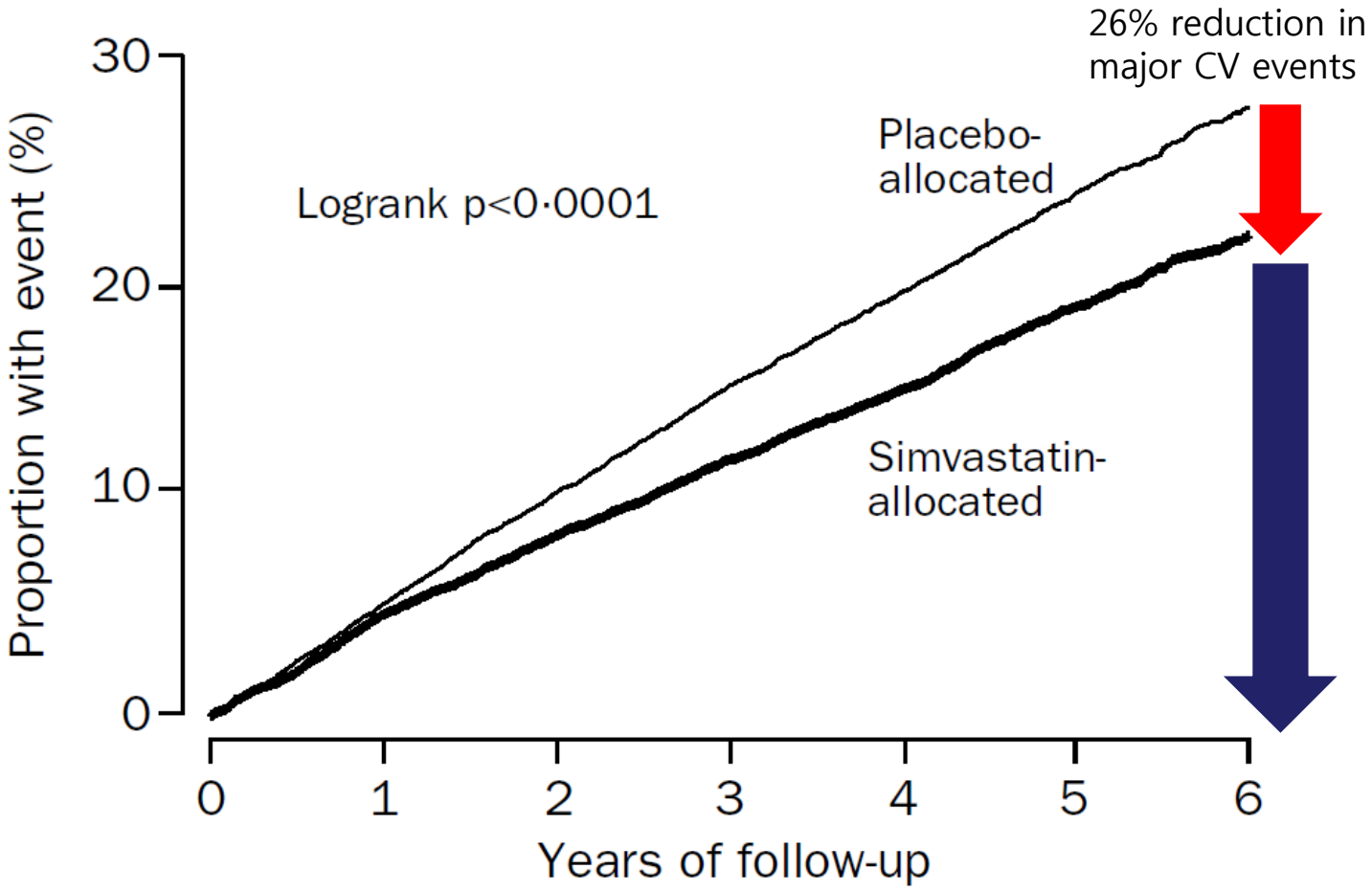
- Direct targeting of HDL-C and triglyceride
  - Role of fibrates, niacin, omega-3 fatty acid

There is a still residual risk



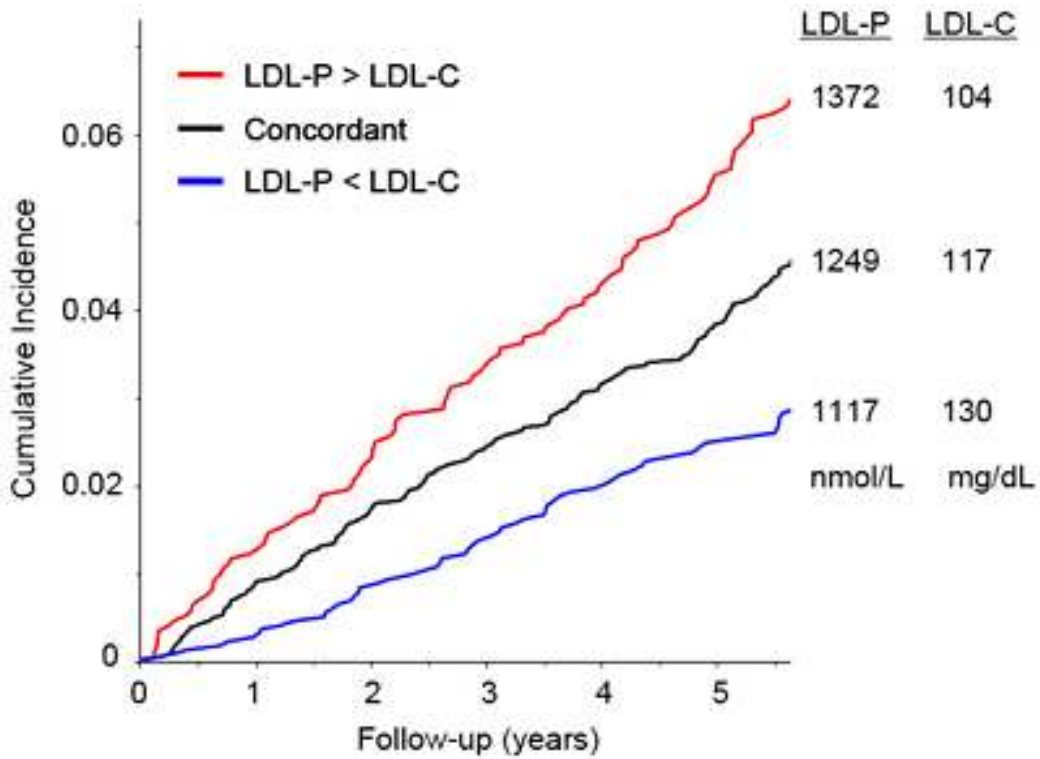
Ann Intern Med, 2006;144;4;229-238

HPS Collaborative Group, Lancet 2002;360:7–22

Non-HDL-C and apoB

- Non-HDL-C: sum of LDL-C, VLDL, IDL
- ApoB: direct indication of total number of apoB containing lipoprotein particles (atherogenic particles)
- Stronger predictors of CVD mortality than LDL-C
- Independent predictor of CHD regardless of Tg level
- Performance to predict CVD for non-HDL-C and apoB, has been a point of ongoing debate

LDL particle number (LDL-P)



Individuals with elevated triglycerides or low HDL-C manifest greater elevations of LDL-P concentrations at a given level of LDL-C

Journal of Clinical Lipidology 2011; 5:338-367

Lipoprotein-associated phospholipase A2 ($Lp\text{-}PLA_2$) and lipoprotein (a)

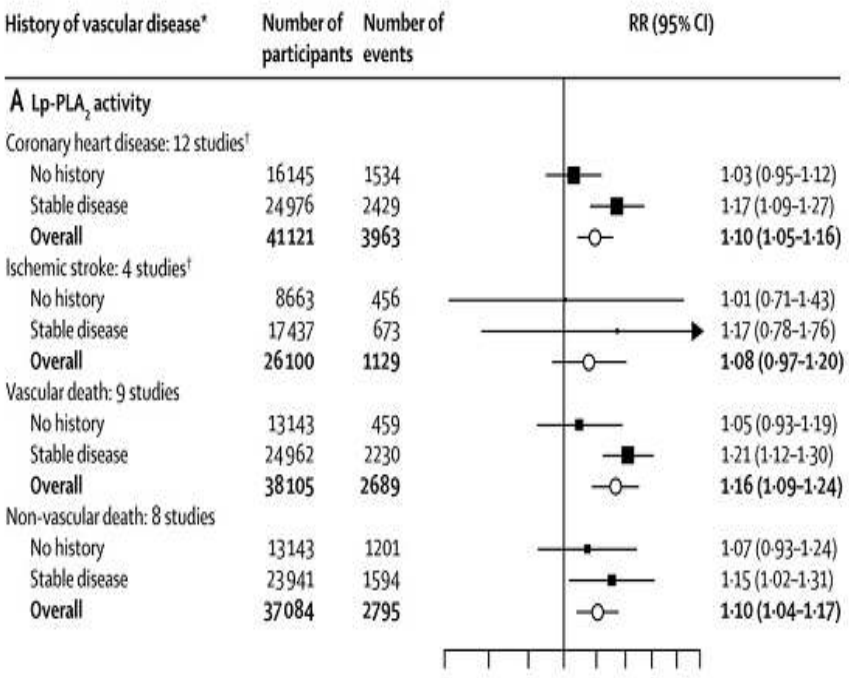
고려대학교 KOREA UNIVERSITY

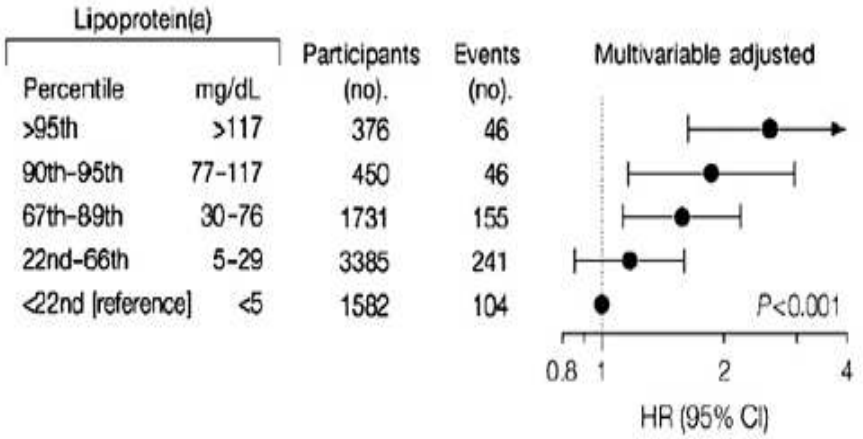
$Lp\text{-}LPA_2$

- Inflammatory biomarker linked to plaque inflammation and rupture

Lp(a)

- Interfere with conversion of plasminogen to plasmin





Journal of Clinical Lipidology 2011; 5:338-367

CRP: JUPITER Study

The NEW ENGLAND JOURNAL of MEDICINE

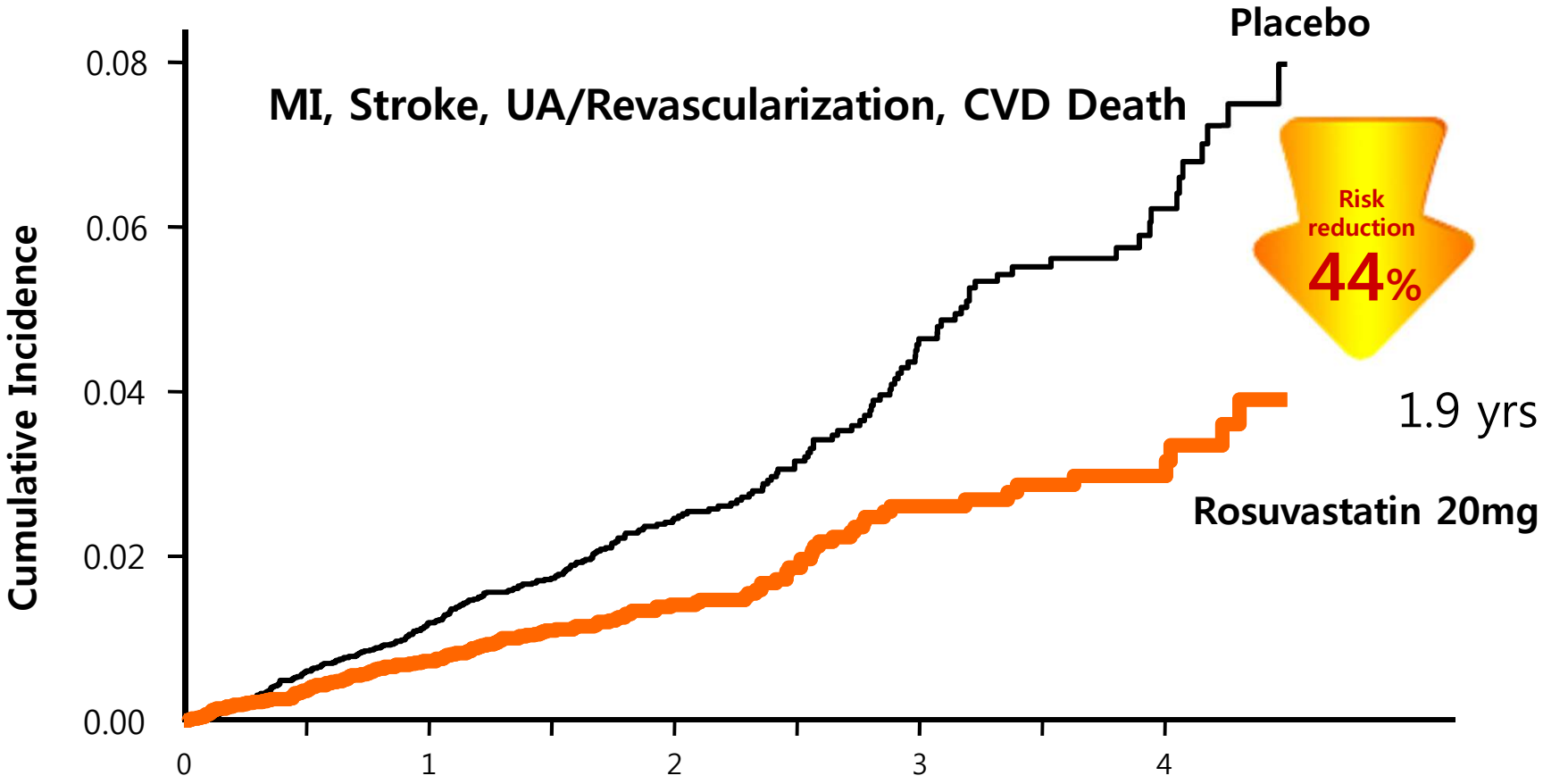
ESTABLISHED IN 1812 NOVEMBER 20, 2008 VOL. 359 NO. 21

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

- Patients with low to normal levels of LDL-C <130 mg/dL
- At increased CV risk: CRP ≥2.0 mg/L
- either rosuvastatin 20 mg or placebo
- Outcome: major cardiovascular event
- N= 17,802

N Engl J Med 2009; 361:2113-22

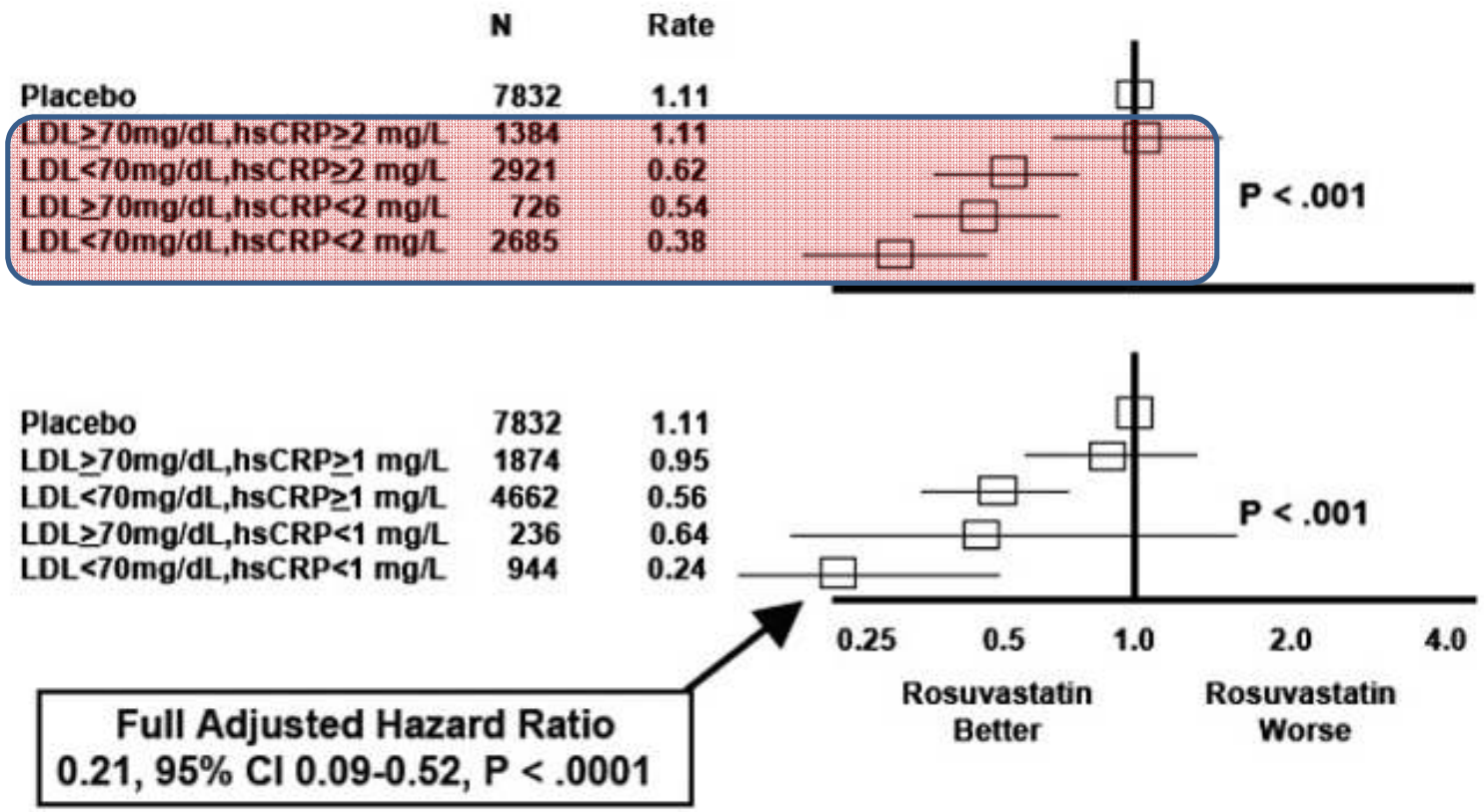
Jupiter Study: primary endpoint



Number at Risk										
Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958	1,353	983	544	157
Placebo	8,901	8,621	8,353	6,508	3,872	1,963	1,333	955	534	174

N Engl J Med 2009; 361:2113-22

CV events by on-treatment levels of LDL-C and hsCRP



Lancet 2009; 373:1175-1182

Key questions about these non-traditional risk markers?

- Should these markers be included in the risk prediction model?
- Should these markers be targets for therapy?

	Initial Clinical Assessment					
	CRP	**Lp-PLA$_2$**	**Apo B**	**LDL-P**	**Lp(a)**	**HDL or LDL Subfractions**
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Recommended for routine measurement	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
CHD or CHD Equivalent	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Family History	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended
Recurrent Events	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended

	On-Treatment Management Decisions					
	CRP	**Lp-PLA$_2$**	**Apo B**	**LDL-P**	**Lp(a)**	**HDL or LDL Subfractions**
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Not recommended	Not recommended
CHD or CHD Equivalent	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
Family History	Consider for selected patients	Not recommended	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Recurrent Events	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended

Journal of Clinical Lipidology 2011; 5:338-367

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- Direct targeting of HDL-C and triglyceride
  - Role of fibrates, niacin, omega-3 fatty acid

Effect of fibrate

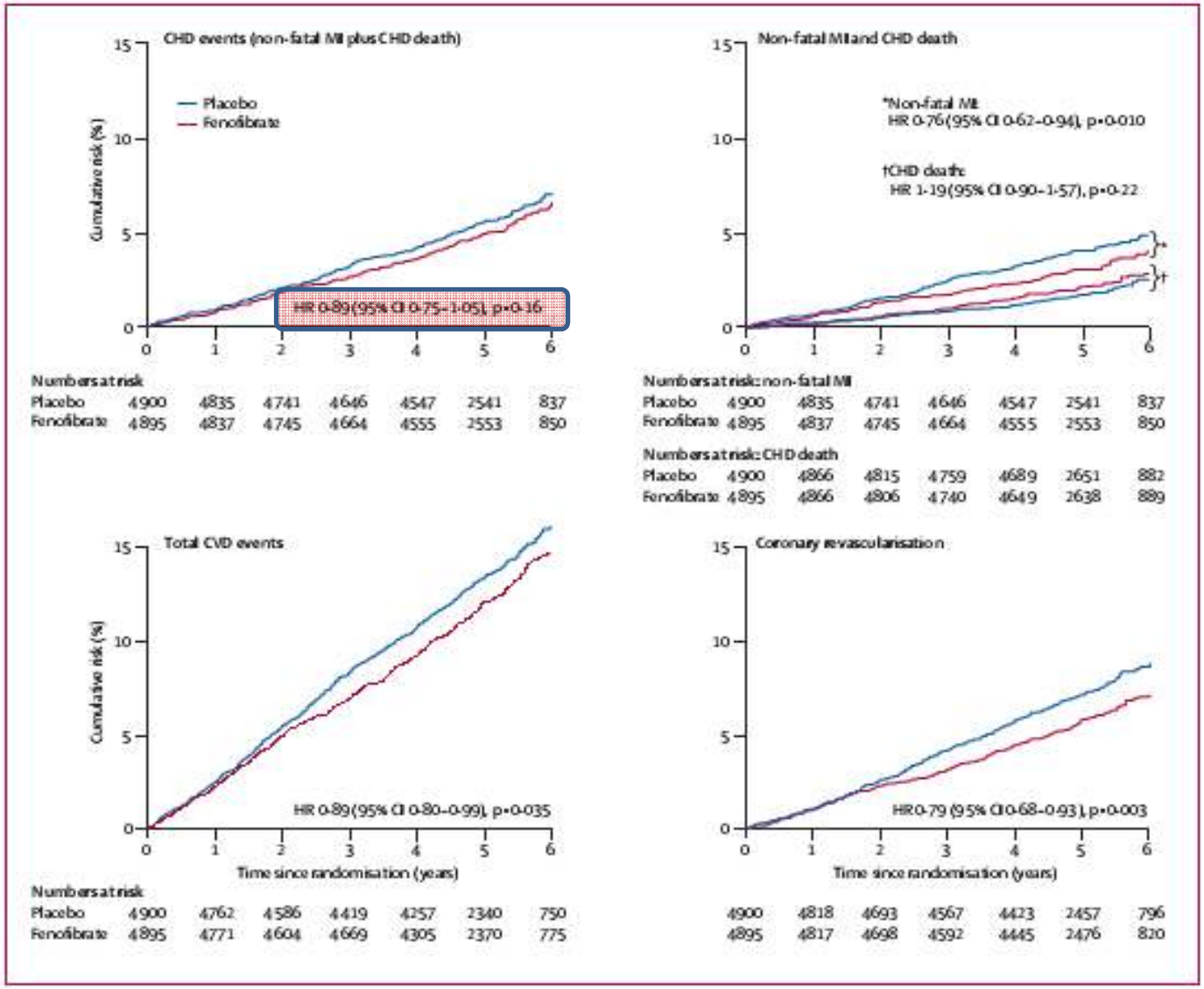
Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial

*The FIELD study investigators**

- Type 2 DM, who are not taking statin therapy (N=9795)
- Micronized fenofibrate 200mg/d vs. placebo
- Primary outcome: coronary events

Lancet 2005; 366: 1849-61

Fenofibrate did not reduce the risk of the coronary events



Lancet 2005; 366: 1849-61

ACCORD Study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 29, 2010 VOL. 362 NO. 17

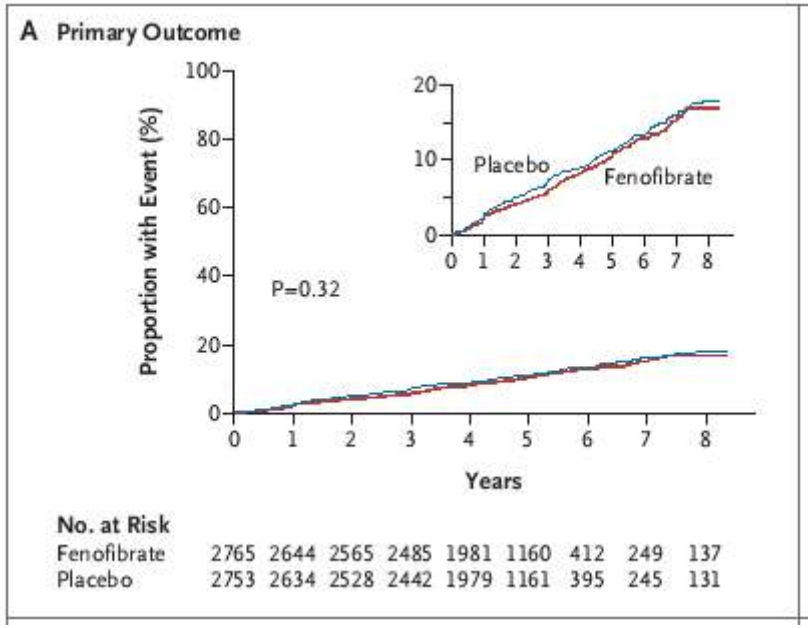
Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

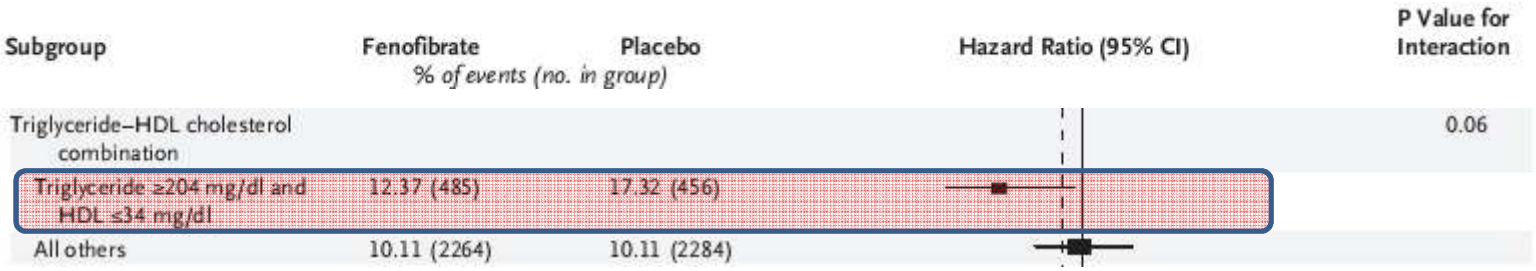
The ACCORD Study Group*

- Type 2 DM, who are being treated with simvastatin (N=5518)
- Fenofibrate 160 mg/d vs. placebo
- Primary outcome: major CV events

N Engl J Med 2010; 362: 1563-74

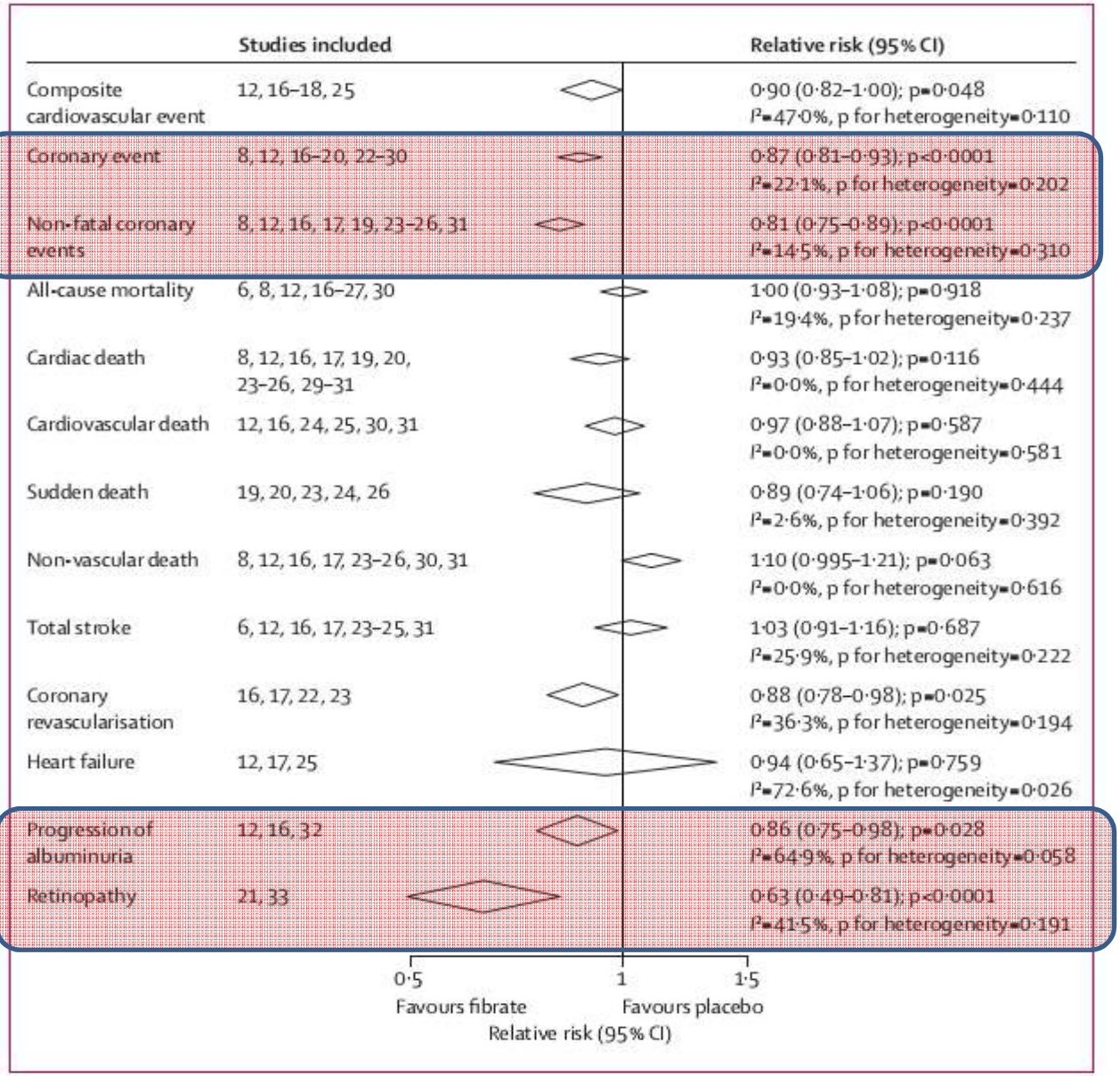
The combination of fenofibrate and simvastatin did not reduce the rate of CVD





N Engl J Med 2010; 362: 1563-74

Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis



Lancet 2010; 375: 1875-84

Comparison of ACCORD subgroup results with those from prior fibrate studies

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS ***(Gemfibrozil)***	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71%
BIP ***(Bezafibrate)***	-7.3% (0.24)	TG ≥ 200 mg/dl	-39.5%
FIELD ***(Fenofibrate)***	-11% (0.16)	TG ≥ 204 mg/dl HDL-C < 42 mg/dl	-27%
ACCORD ***(Fenofibrate)***	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31%

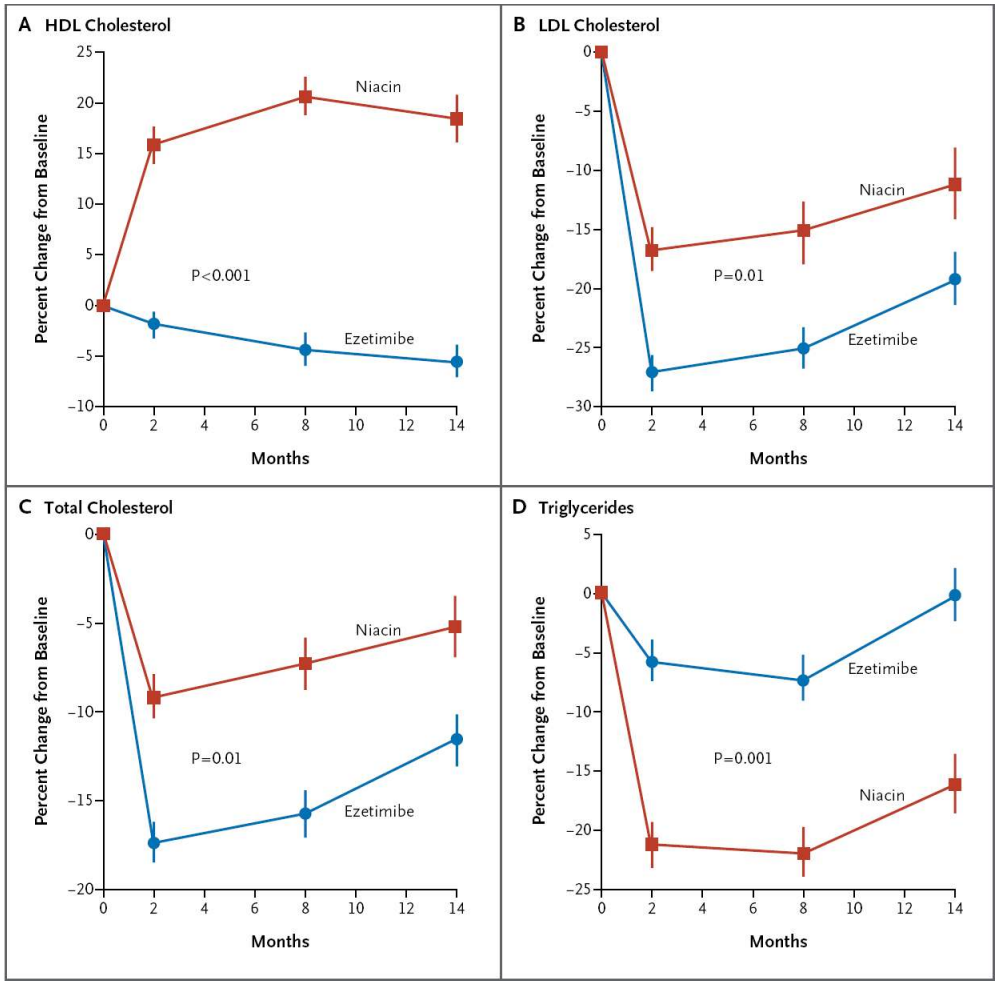
Niacin: ARBITER 6-HALTS

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness

- CHD or CHD equivalent who were receiving long-term statin therapy
- LDL<100 mg/dl, HDL <50 mg/dl (men), <55 mg/dl (women)
- ER niacin (2000 mg/d) vs. ezetimibe (10 mg/d)
- Outcome: change in carotid intima-media thickness
- N=208

N Engl J Med 2009; 361:2113-22

Niacin casues a significant regression of carotid IMT



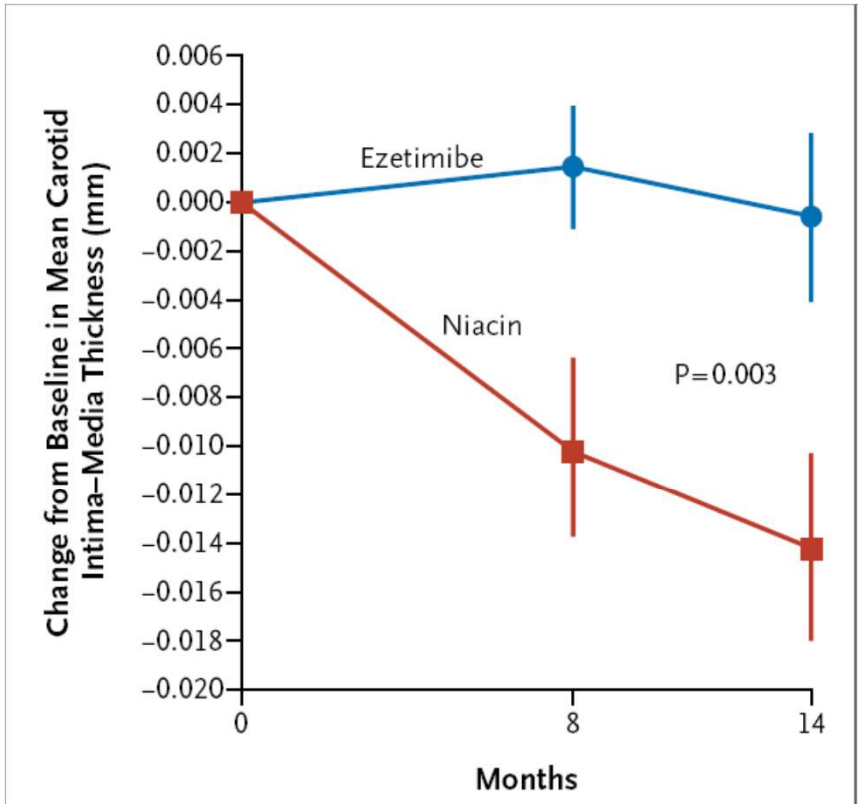


Figure 2. Changes in the Mean Carotid Intima–Media Thickness over the 14-Month Study Period, According to Treatment Group.

N Engl J Med 2009; 361:2113-22

Naicin: AIM-HIGH Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 15, 2011 VOL. 365 NO. 24

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators*

- Established CVD
- All patients received simvastatin to maintain LDL-C 40~80 mg/dl
- ER niacin 1500~2000 mg vs. placebo
- HDL:35->42, Tg 164->122, LDL: 74->62 mg/dl

N Engl J Med 2011; 365:2255-67

No incremental benefit from the addition of niacin to statin therapy

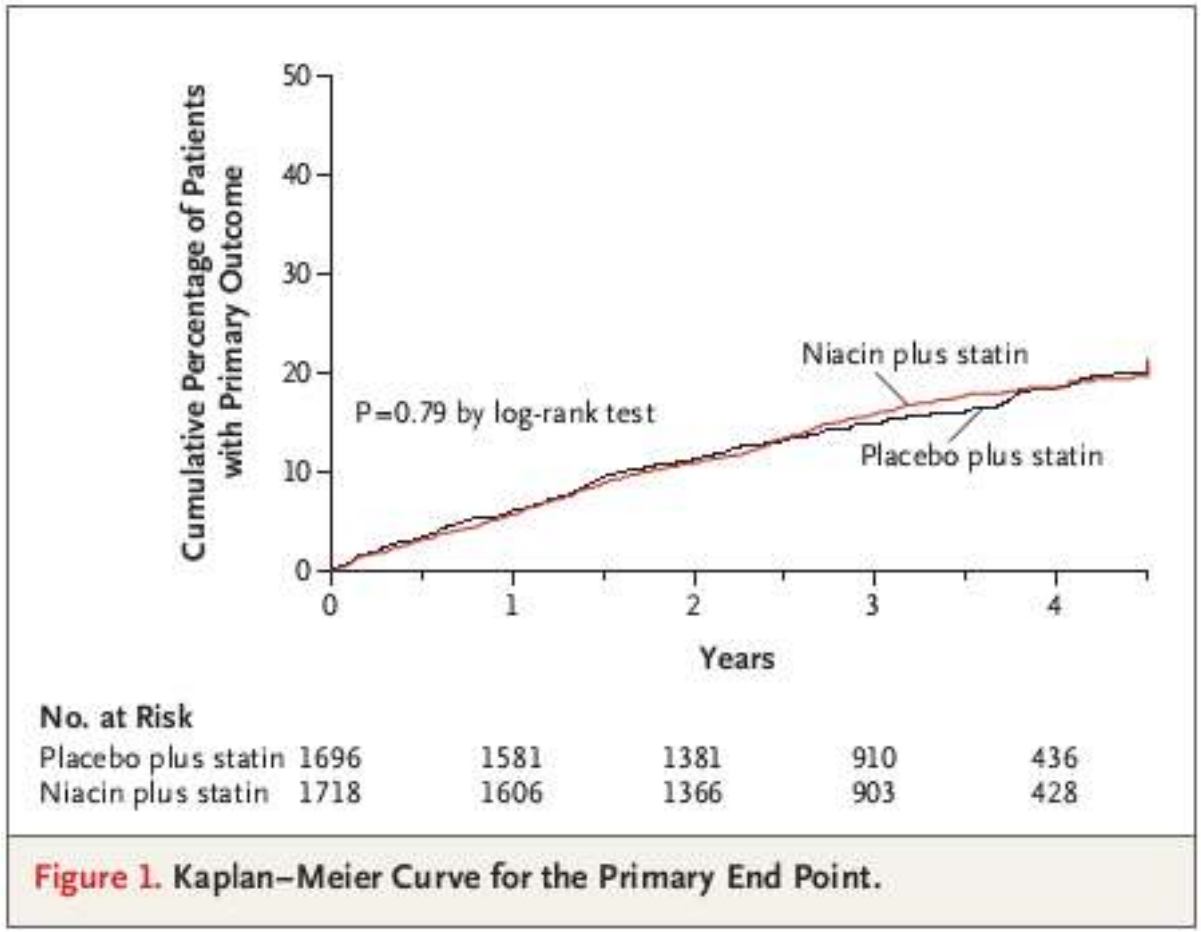


Figure 1. Kaplan–Meier Curve for the Primary End Point.

N Engl J Med 2011; 365:2255-67

On-going Non-statin based Lipid Trials

- Ezetimibe –IMPROVE-IT
- Niacin –HPS2-THRIVE
- Omega 3 F.A. – ASCEND, SU.FOL.OM3
- CETP inhibitor – Dal-OUTCOME (Dalceptrapib), REVEAL (anacetrapib) trial

The evidence base for drugs that target other lipid fractions is significantly less robust than that for statin therapy

Current status of new ATP IV guideline

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Thursday, November 08, 2012

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Clinical Practice Guidelines and Reports In Development

Cardiovascular Disease Risk Reduction in Adults

The NHLBI is currently sponsoring the development of reports with recommendations for clinical practice on reducing cardiovascular risk in adults. Three expert panels and two work groups are writing the following reports:

- Managing Blood Cholesterol in Adults: Report from the Adult Treatment Panel (ATP)
- Managing Blood Pressure in Adults: Report from the Joint National Committee (JNC)
- Managing Overweight and Obesity in Adults: Report from the Obesity Expert Panel
- Assessing Cardiovascular Risk: Report from the Risk Assessment Work Group
- Lifestyle Recommendations to Reduce Cardiovascular Risk: Report from the Lifestyle Work Group

The following table reflects the status of each report and progress through the remaining stages of the review process before the guidelines are released.

	Draft Finished	Federal Review	Expert Review	Advisory Council	Public Comment	HHS Clearance	Release
Lifestyle	Completed	Completed	Completed	In Progress			
Risk Assessment	Completed	Completed	Completed				
Cholesterol	Completed	Completed	Completed	In Progress			
Blood Pressure	In Progress						
Obesity	In Progress						

- **Draft Completed**: Expert panelists have completed a full draft of the systematic review and recommendations.
- **Federal Review**: Federal agency representatives of the NHLBI's National Program to Reduce Cardiovascular Risk (NPRCR) coordinating committee provide review and comment.
- **Expert Review**: External peer reviewers with expertise in the relevant risk factors provide review and

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Predictions for ATP IV

- LDL –C goal for primary and secondary prevention may be intensified
- CVD risk assessment may be updated
- Support for LDL-C targeted therapy, but further emphasis on non-HDL and apoB
- Role of novel risk markers
- Tempered recommendations for combination lipid-lowering medications
- Specific recommendations on certain sub-populations (diabetes, kidney disease, elderly)

Thank you for your attention!

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Some day in 2012…