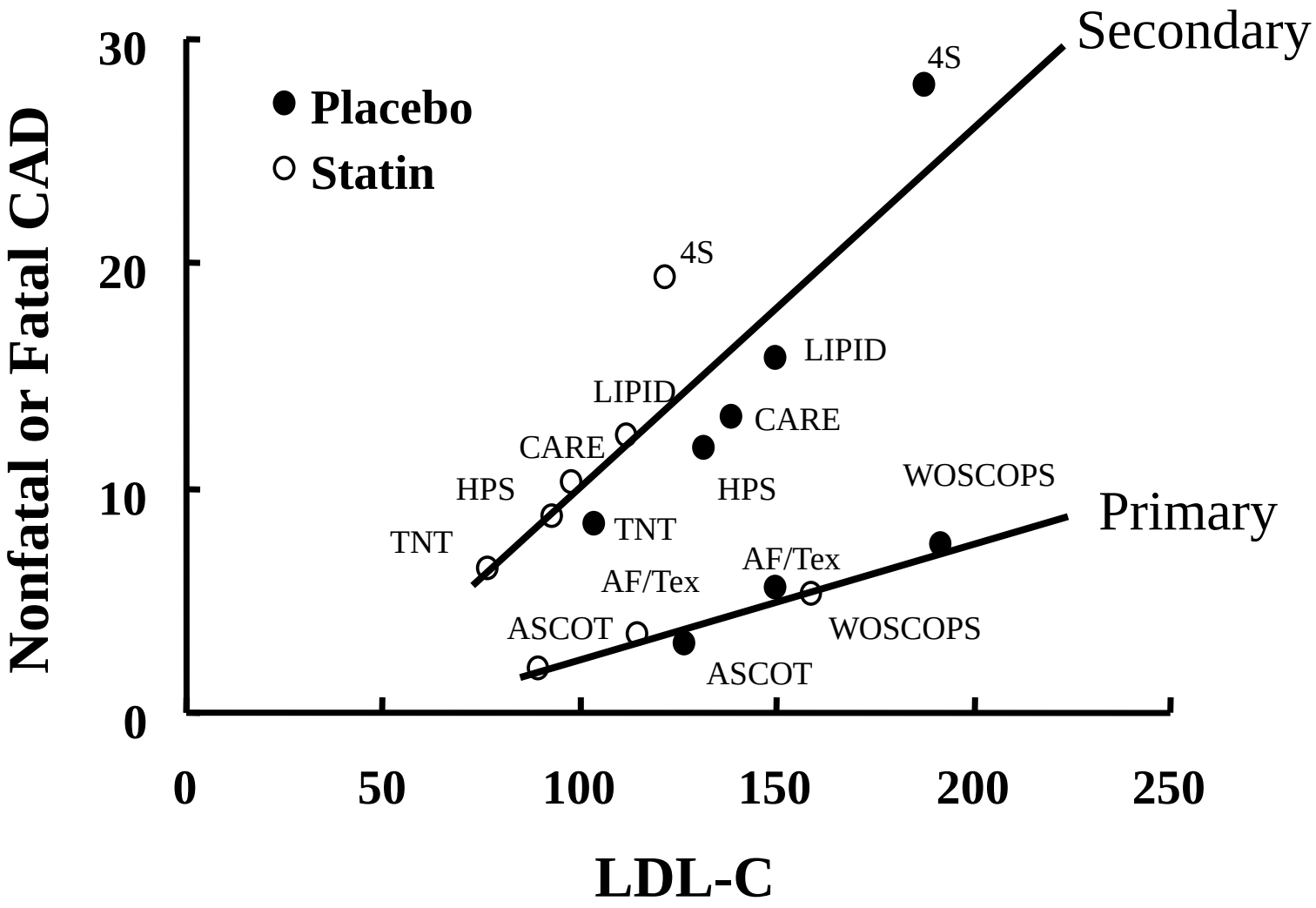
고지혈증
LDL, HDL and Triglyceride
Triple Crown 가능한가?

중앙대학교

김치정

LDL Cholesterol

LDL-C and Nonfatal or Fatal CAD



증례

55세 비흡연 남자

혈압이 160/95 mmHg

식이요법 후에

콜레스테롤 240 mg/dL

HDL 콜레스테롤이 50 mg/dL

중성지방이 150 mg/dL

계산된 LDL 콜레스테롤은 160 mg/dL

CHD Risk Factors Other Than LDL Cholesterol (ATP III)

Positive Risk Factors

- Age Male: ≥45 years, Female: ≥55 years
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)
- Current cigarette smoking
- Hypertension (≥140/90 mmHg, or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)

Negative (protective) Risk Factor

- High HDL cholesterol (≥60 mg/dL)

Framingham Point Score (Men)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	**8**
60-64	10
65-69	11
70-74	12
75-79	13

Chol	Age				
	20-39	40-49	50-59	60-69	70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	**4**	2	1
>279	11	8	5	3	1
Nonsmoker	0	0	**0**	0	0
Smoking	8	5	3	1	1

HDL (mg/dL)	Points
>59	-1
50-59	**0**
40-49	1
<40	2

Systolic BP	Tx(-)	Tx(+)
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
>159	**2**	3

Risk	
Total Risk Point	10-Y (%)
<0	<1
0-4	1
5-6	0
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	**16**
15	20
16	25
>16	>29

위험도에 따른 LDL-C의 치료목표 농도와 생활방식의 개선과 약물치료를 시작하는 농도 (ATP III+ , 2004)

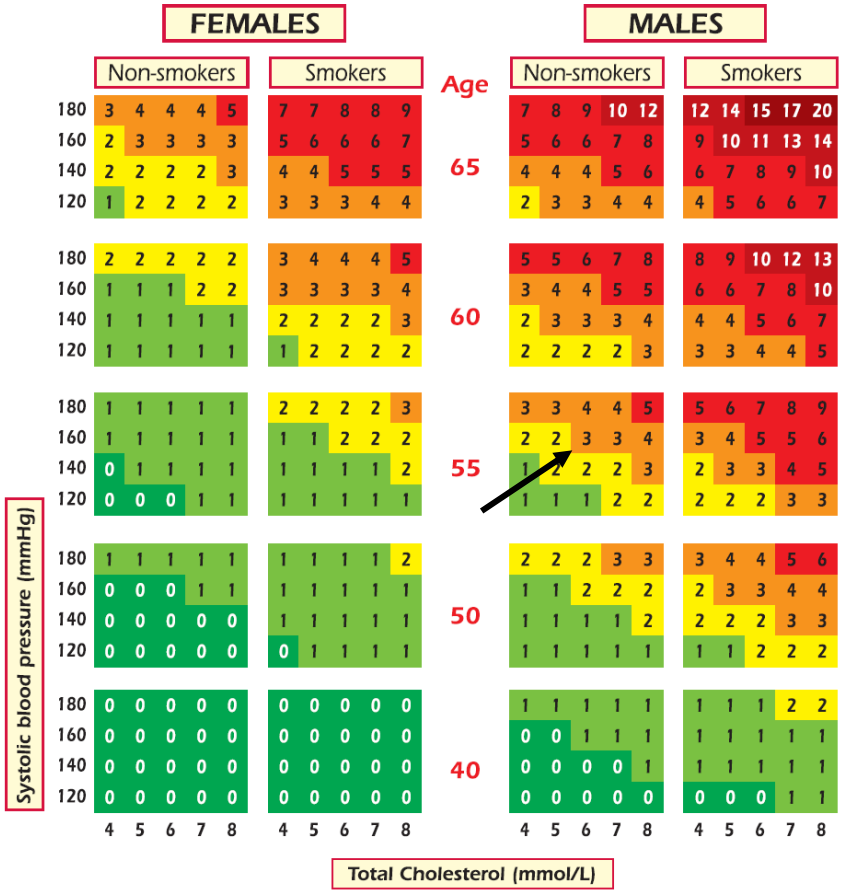
위험정도	목표 LDL-C 농도	생활방식의개선 시작 LDL-C 농도	약물치료 시작 LDL-C 농도
관상동맥질환 혹은 이에 상당하는 위험 (10년 위험>20%)*	<100 mg/dL (Optimal Goal <70 mg/dL)	≥100 mg/dL	≥130 mg/dL (≥100 mg/dL) (100-129 mg/dL 선택적) (<100 mg/dL 선택적)
2개이상의 위험인자 (10년 위험≤20%)	<130 mg/dL	>130 mg/dL	10년 위험 10-20% ≥130 mg/dL(100-129 선택적) 10년 위험<10% ≥160 mg/dL
1개 이하의 위험인자	<160 mg/dL	≥160 mg/dL	>190 mg/dL (160-189 mg/dL 선택적)

*; 관동맥질환에 준하는 조건; 1) 말초혈관질환, 복부대동맥류, 증상이 있는 경동맥질환, 2) 당뇨병, 3) 향후 10년 동안 관동맥질환이 발생할 가능성이 20%를 넘는 경우

Circulation. 2004;110:227

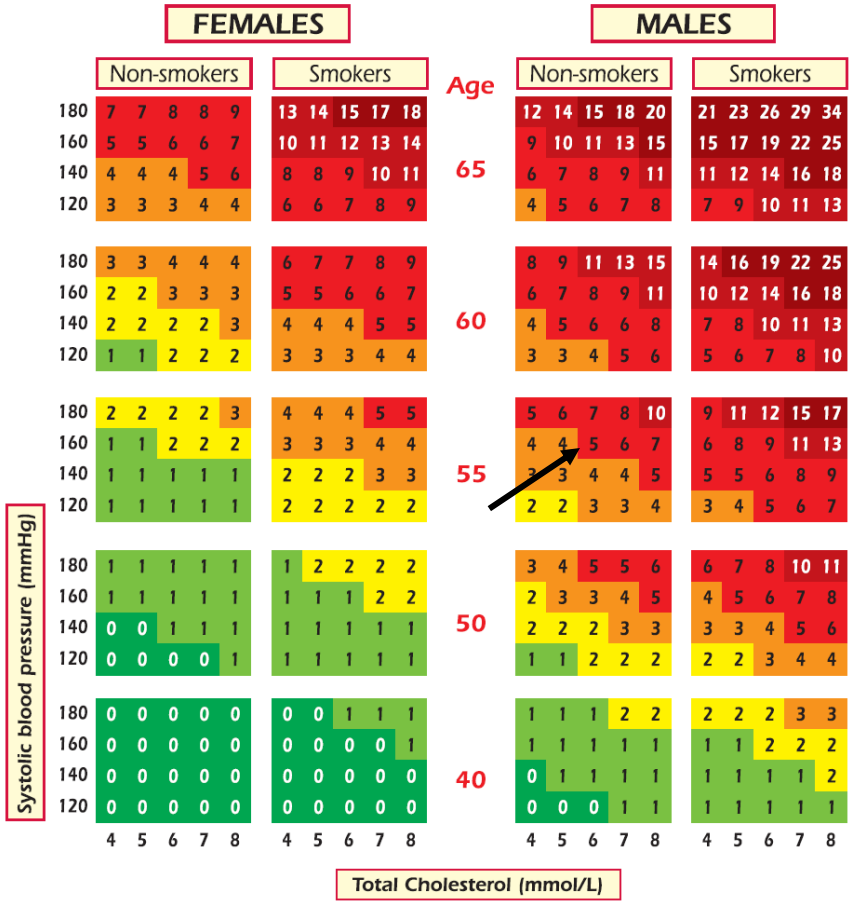
SCORE Charts
ESC/EAS Guidelines

Low Risk Regions



SCORE chart for use in low risk regions - HDL 1.4 mmol/L

High Risk Regions



SCORE chart for use in high risk regions - HDL 1.4 mmol/L

Atherosclerosis 217S (2011) S1

Intervention Strategies
ESC/EAS Guidelines.

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	>190 mg/dL >4.9 mmol/L
<1	No lipid intervention	No lipid intervention	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	저위험지역	IIa/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	고위험지역	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class[a]/Level[b]	IIa/A	IIa/A	I/A	I/A	I/A

Atherosclerosis 217S (2011) S1

증례

68세 여자

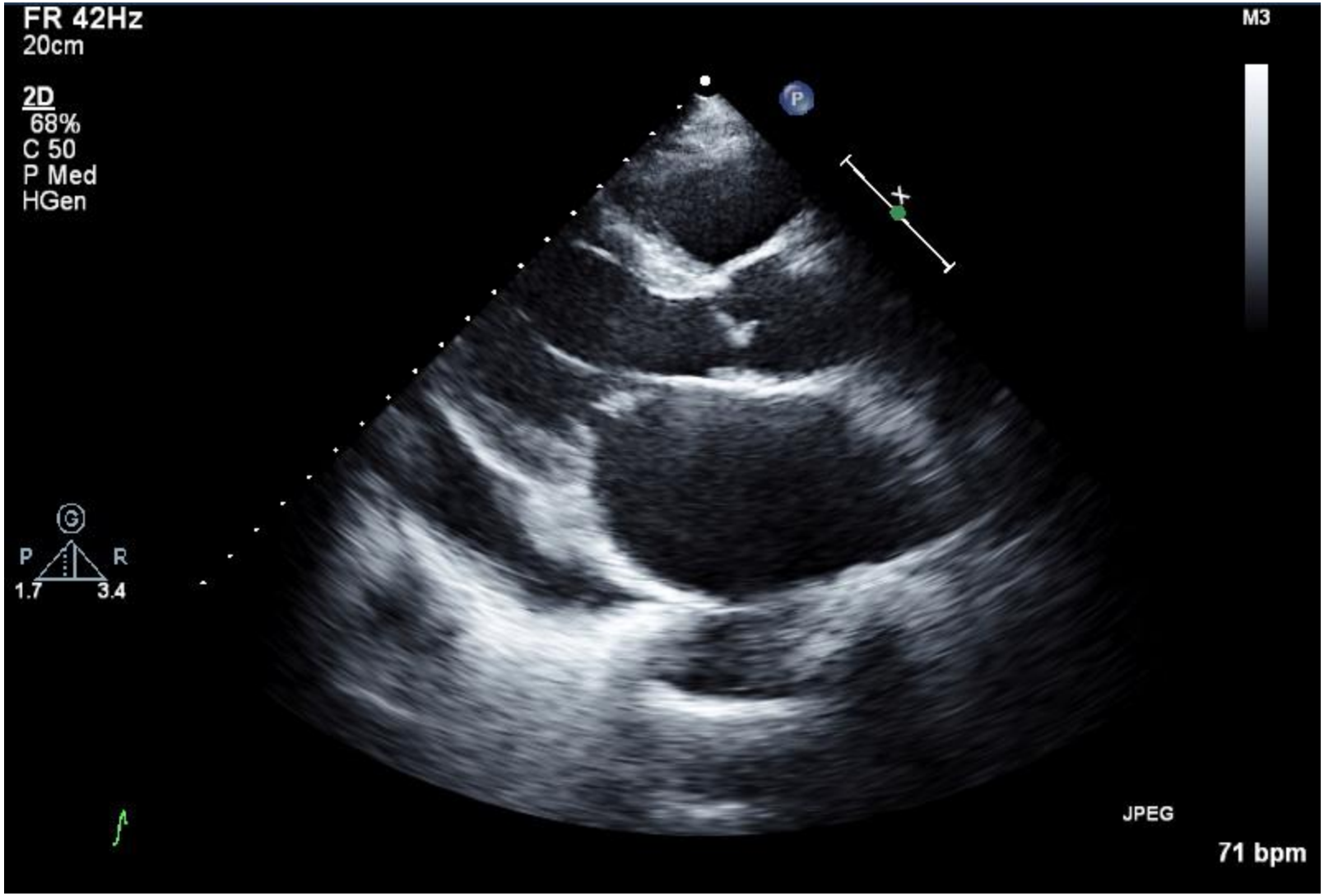
호흡곤란

콜레스테롤 309 mg/dL

HDL 콜레스테롤이 59 mg/dL

중성지방이 126 mg/dL

계산된 LDL 콜레스테롤은 225 mg/dL


FR 42Hz
20cm
2D
68%
C 50
P Med
HGen
M3
P
G
P
R
1.7
3.4
JPEG
71 bpm

갑상선기능검사

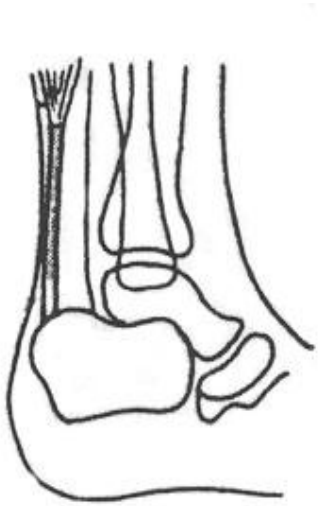
- TSH 51 uIU/mL (N; 0.35-5.5)
- T3 0.37 ng/mL(N; 0.60-1.81)
- Free T4 0.24 ng/dL(N; 0.89-1.76)

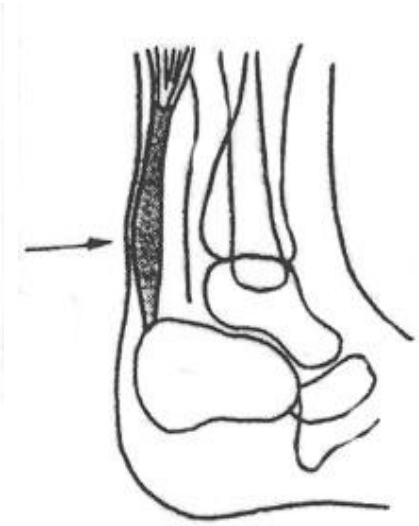
고콜레스테롤혈증의 이차적 원인

- 갑상선 기능저하
- Obstructive liver disease
- 만성신부전, 신증후군
- 당뇨병
- 약제 (progestins, anabolic steroids, corticosteroids)

Tendon Xanthoma

Tendon Xanthoma





가족성 고콜레스테롤혈증
Familial Hypercholesterolemia

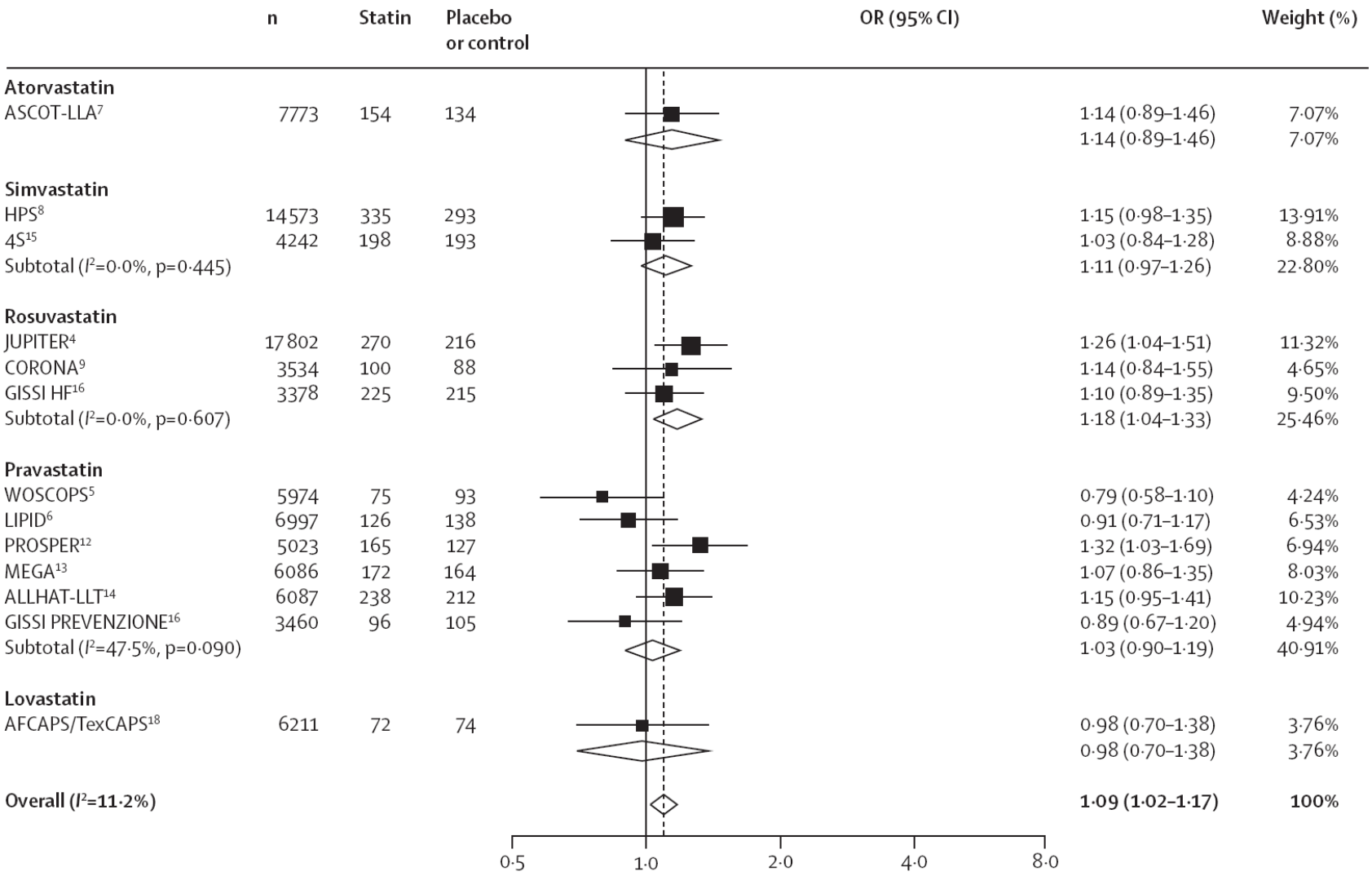
- LDL 수용체의 돌연변이
- 이형접합체(heterozygote)는 500명당 1명

  - LDL 콜레스테롤 농도가 많이 높고 (>190 mg/dL)
  - 고콜레스테롤혈증의 가족력
  - 인대 특히 손등, 팔꿈치, 무릎, 그리고 아킬레스 힘줄에 황색종(xanthoma)
  - 조기의 심혈관계질환의 가족력

Inhibitors and inducers of enzymatic pathways involved in statin metabolism

CYP substrates	Inhibitors	Inducers
CYP3A4 **Atorvastatin, Lovastatin, Simvastatin Pravastatin(m)**	ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, tricyclic antidepressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, sertraline, cyclosporin A, tacrolimus, mibefradil, amiodarone, danazol, diltiazem, verapamil, protease inhibitors, midazolam, corticosteroids, grapefruit juice, Tamoxifen	phenytoin, phenobarbital, barbiturates, rifampin, dexamethasone, cyclophosphamide, carbamazepine, omeprazole, St John's Wort
CYP2C9 **Fluvastatin, Rosuvastatin(m) Pitavastatin(m)**	ketoconazole, fluconazole, amiodarone, sulfaphenazole, oxandrolone, dronedarone, warfarin	rifampicin, phenobarbital, phenytoin

Statins And DM Risk



HDL Cholesterol

HDL-C0이 낮은 원인

- Elevated triglycerides
- Overweight and obesity
- Physical inactivity
- Type 2 diabetes
- Cigarette smoking
- Very high carbohydrate intakes (>60% energy)
- Drugs (beta-blockers, anabolic steroids, progestational agents)

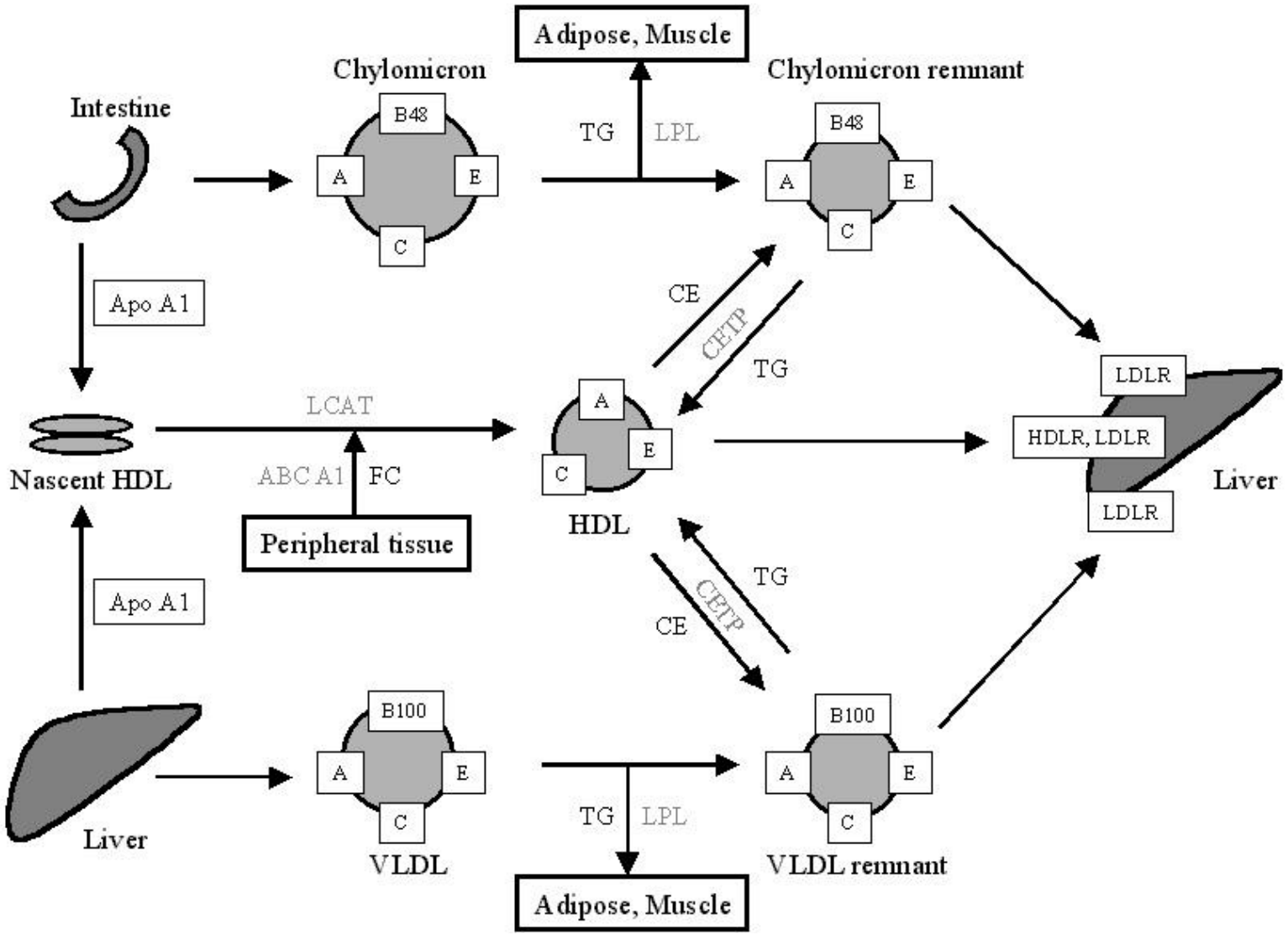
Veterans Affairs HDL-C Intervention Trial (VA-HIT)

Double-blind, randomized, multicenter
2531 men with coronary heart disease, HDL-C<40 mg/dL, LDL-C≤ 140 mg/dL
Placebo vs gemfibrozil 1200mg
Median 5.1 year follow-up
Primary end point: nonfatal MI or CAD death

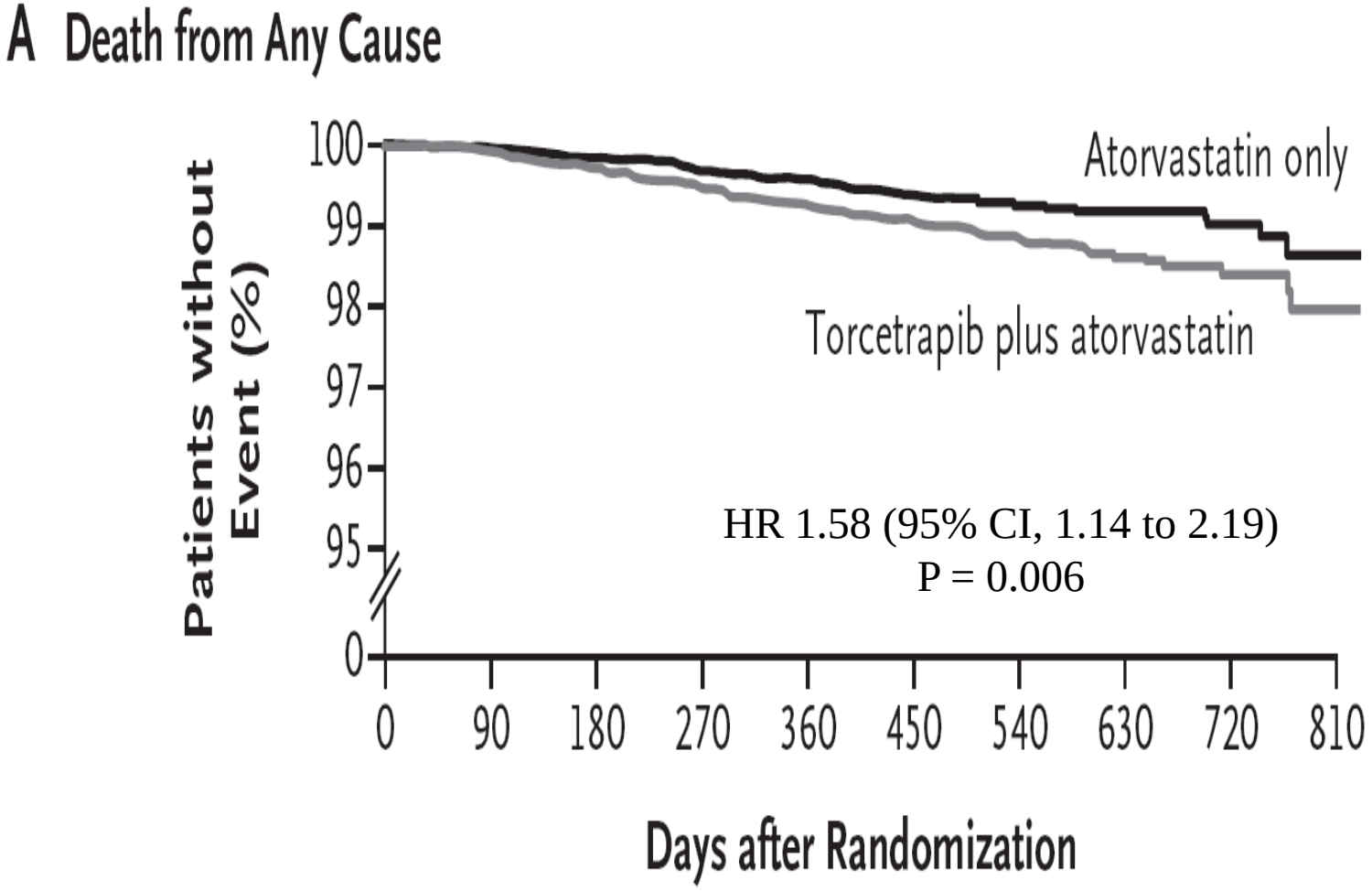
	No	HDL-C (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)	Major C Event(%)	CHD Death(%)	Total Death(%)
Gemfibrozil	**1264**	**34**	**113**	**115**	**219(17)**	**93(7.4)**	**198(16)**
Control	**1267**	**32**	**113**	**166**	**275(22)**	**118(9.3)**	**220(17)**
Relative Reduction		**-6%**	**0%**	**31%**	**22%**	**22%**	**11%**
(95% CI)					**(7-35%)**	**(-2-41%)**	**(-8-27%)**

Rubins. NEJM 1999;341:410

지질 대사


Adipose, Muscle
Chylomicron
Chylomicron remnant
Intestine
B48
A
E
C
TG
LPL
Apo A1
CE
CETP
TG
LDLR
LCAT
A
E
C
HDLR, LDLR
Nascent HDL
ABC A1
FC
Peripheral tissue
HDL
Liver
LDLR
Apo A1
TG
CE
CETP
B100
A
E
C
Liver
VLDL
TG
LPL
VLDL remnant
Adipose, Muscle

Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events Trial (ILLUMINATE)

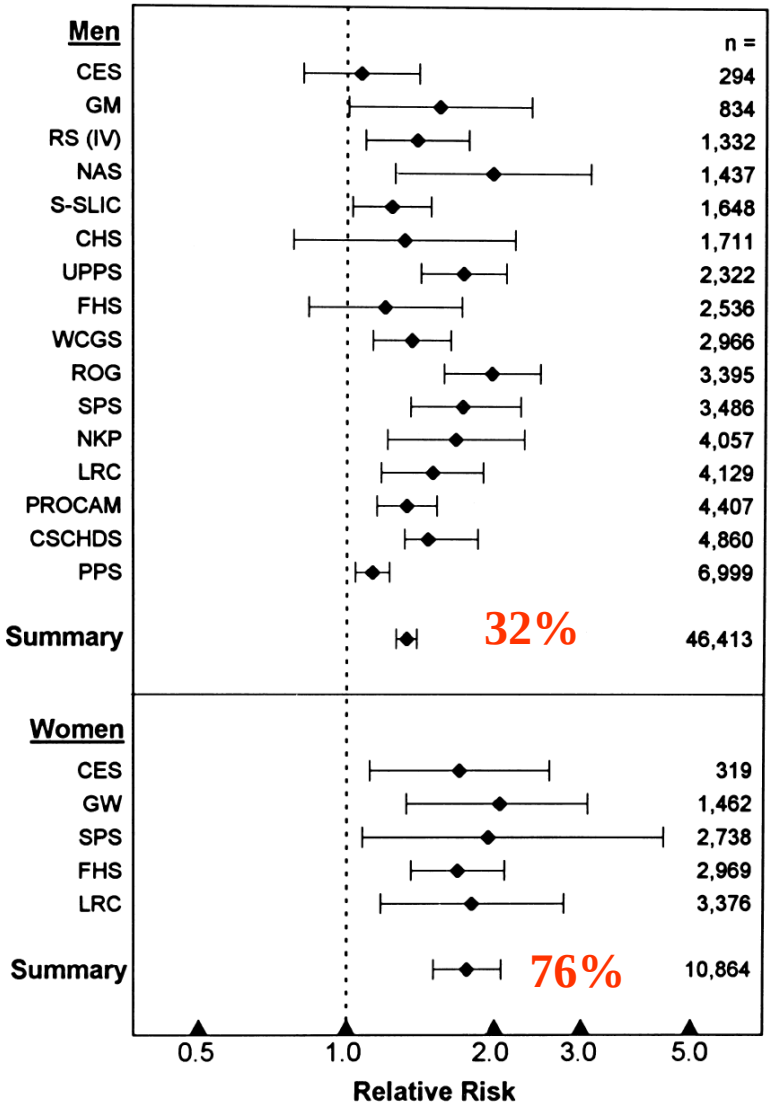


Circulation. 2008;118:2506

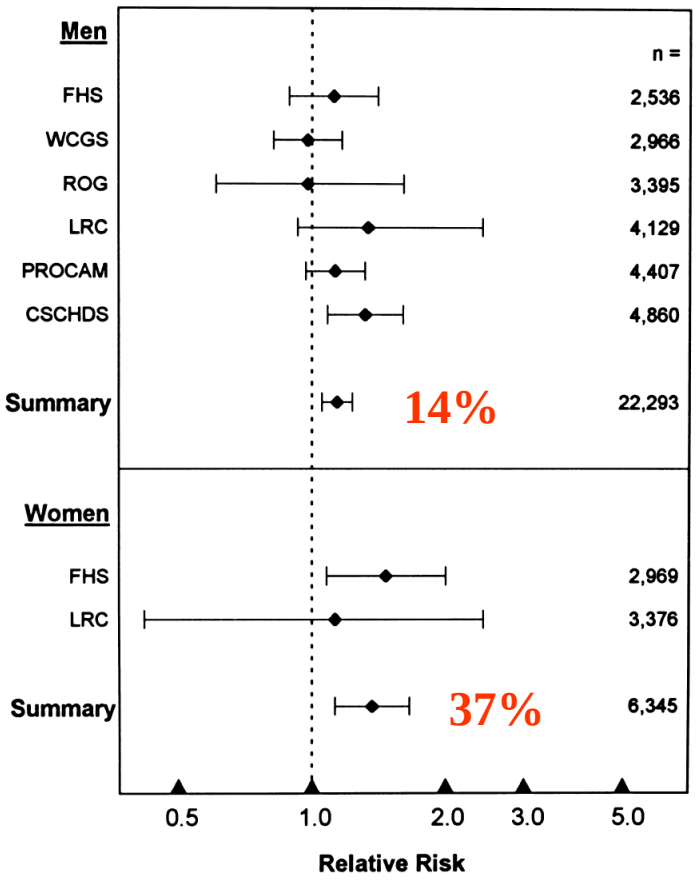
Triglyceride

Hypertriglyceridemia and CVD

Univariate Analysis



Multivariate Analysis



Am J Cardiol 1998;81(4A):7B

중성지방이 높은 이차적 원인

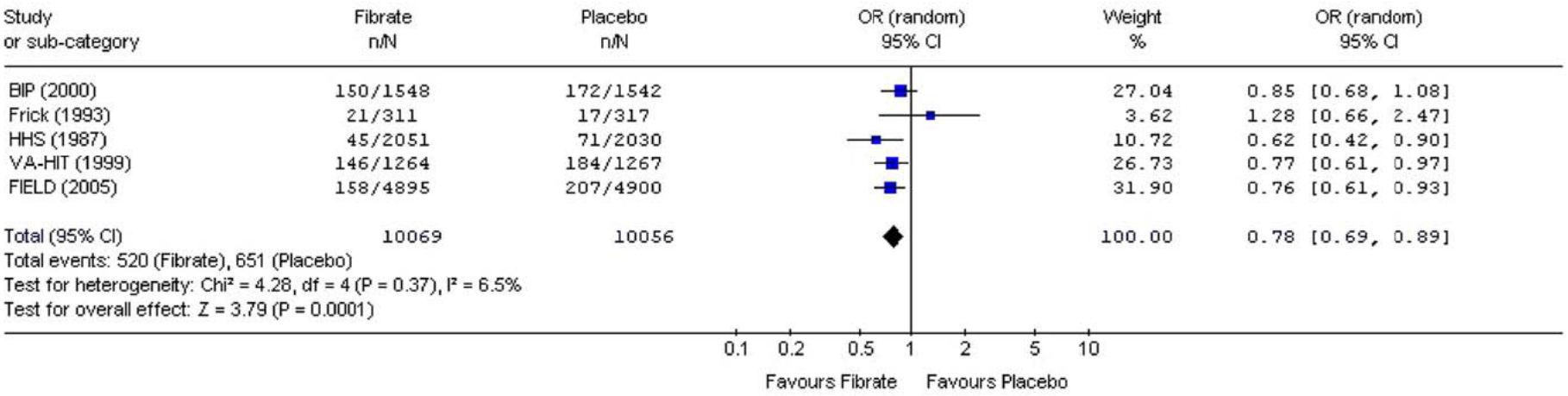
- 비만
- 운동부족
- 흡연
- 과량의 음주
- 탄수화물의 다량 섭취
- 당뇨, 만성신부전, 신증후군
- 베타 차단제, steroid, 에스트로젠 등의 약제

Triglyceride Lowering Drugs

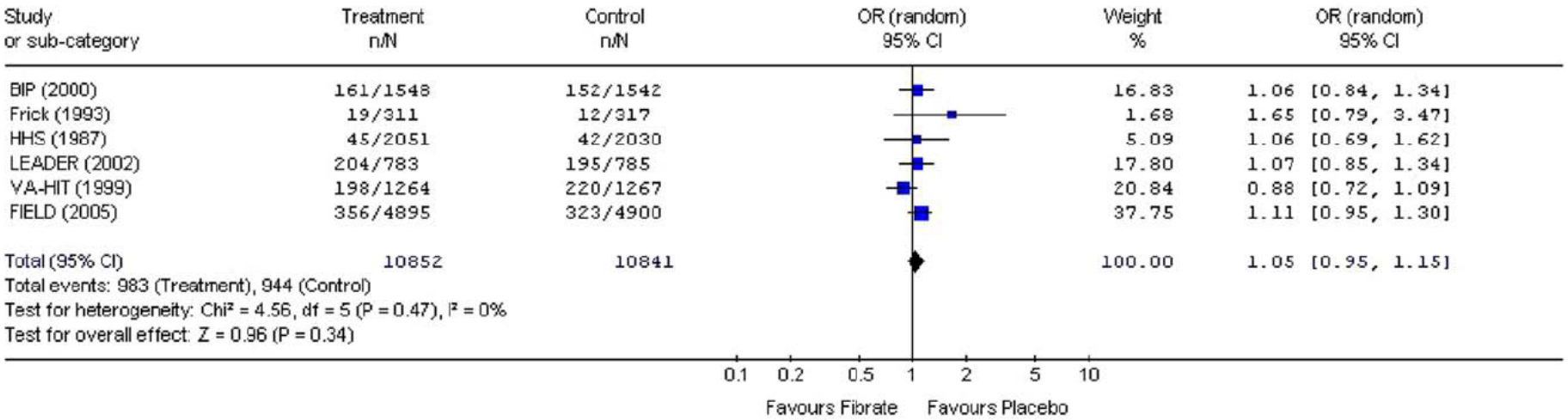
- **Nicotinic acid**
- **Fibrate**
- **Omega-3 fatty acid**

Effect of Fibrate on Nonfatal Myocardial Infarction and Mortality

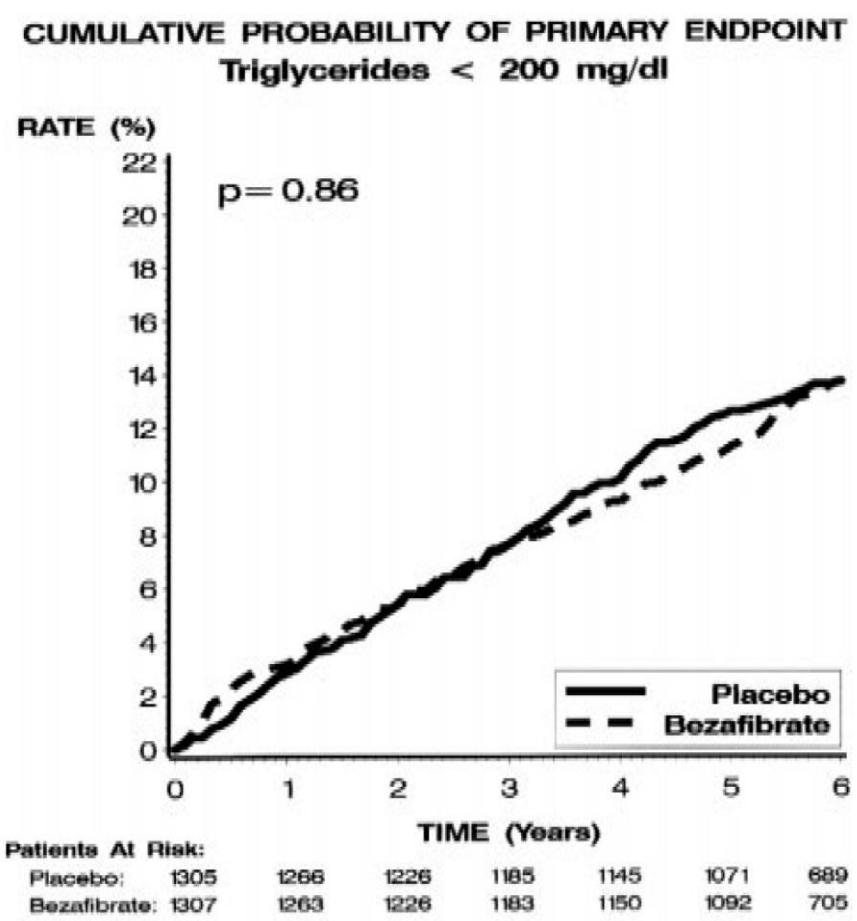
Nonfatal Myocardial Infarction

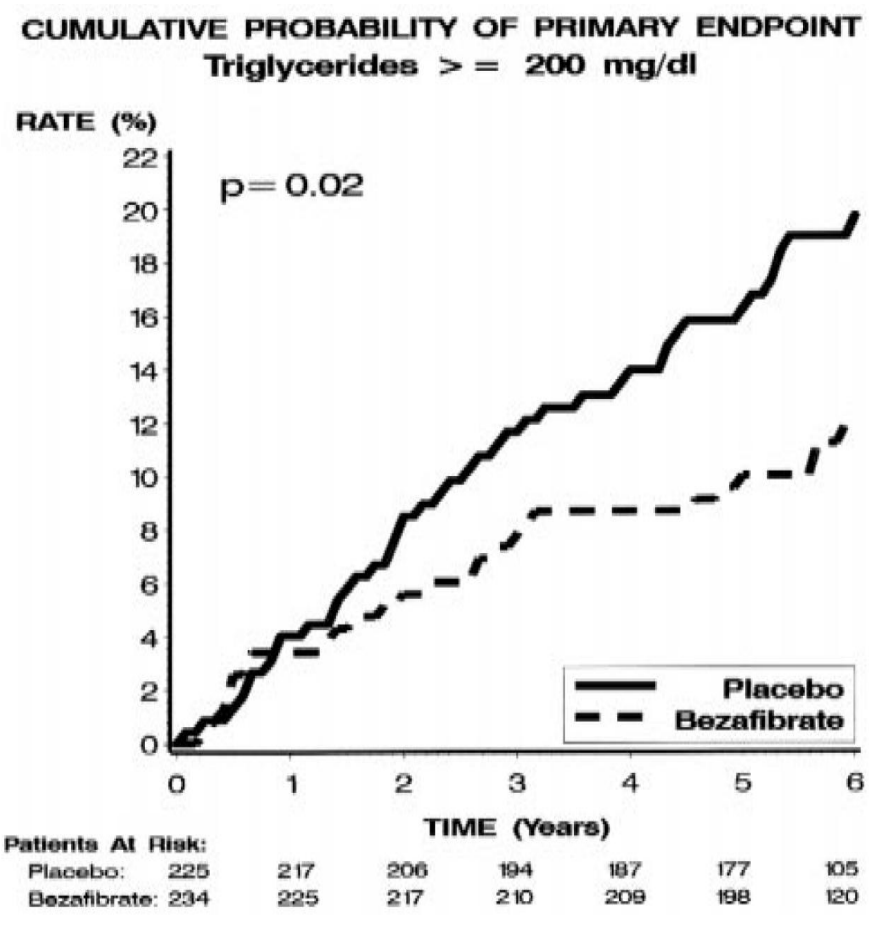


Mortality



Bezafibrate Infarction Prevention Study (BIP)

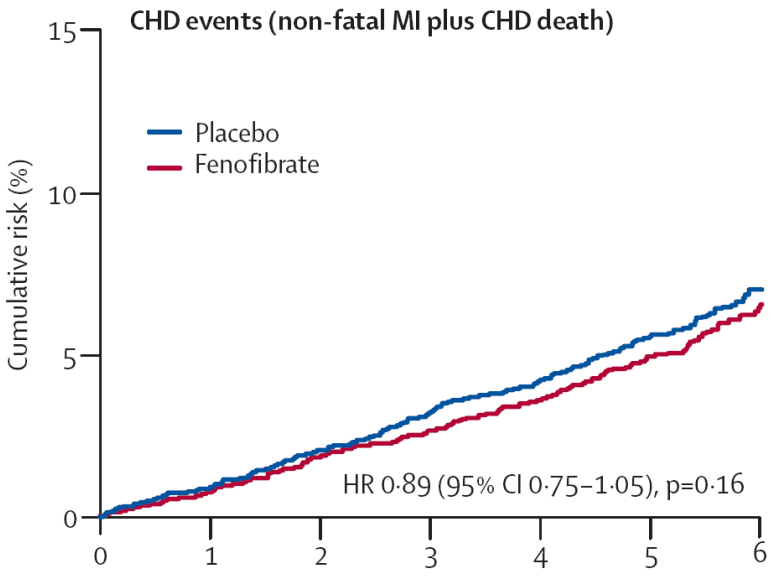




Circulation. 2000;102:21-27

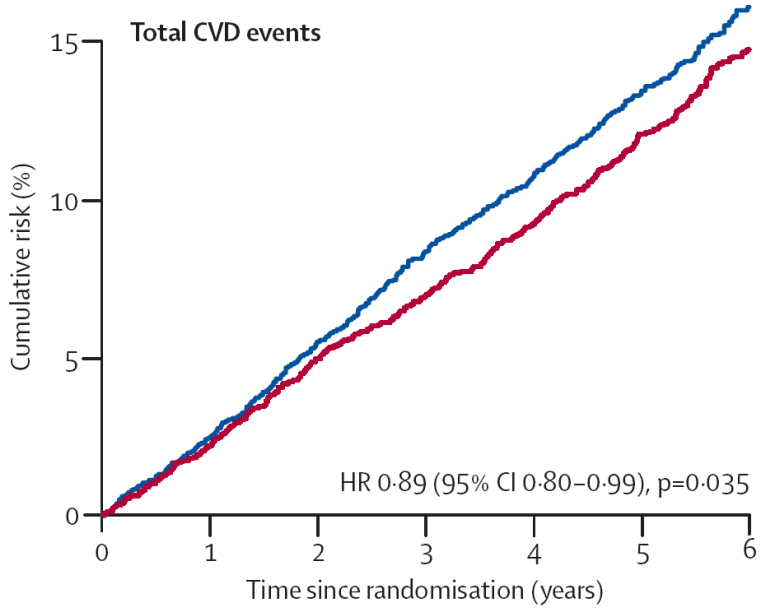
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

- **9795 participants aged 50–75 years, with type 2 DM, and no statin, TC 3.0–6.5 mmol/L and TC/HDL-C ≥ 4.0 or TG 1.0–5.0 mmol/L**
- **placebo and a fenofibrate**
- **Follow-up over the 5 years**
- **End point: CHD death or non-fatal MI**



Numbers at risk

Placebo	4900	4835	4741	4646	4547	2541	837
Fenofibrate	4895	4837	4745	4664	4555	2553	850

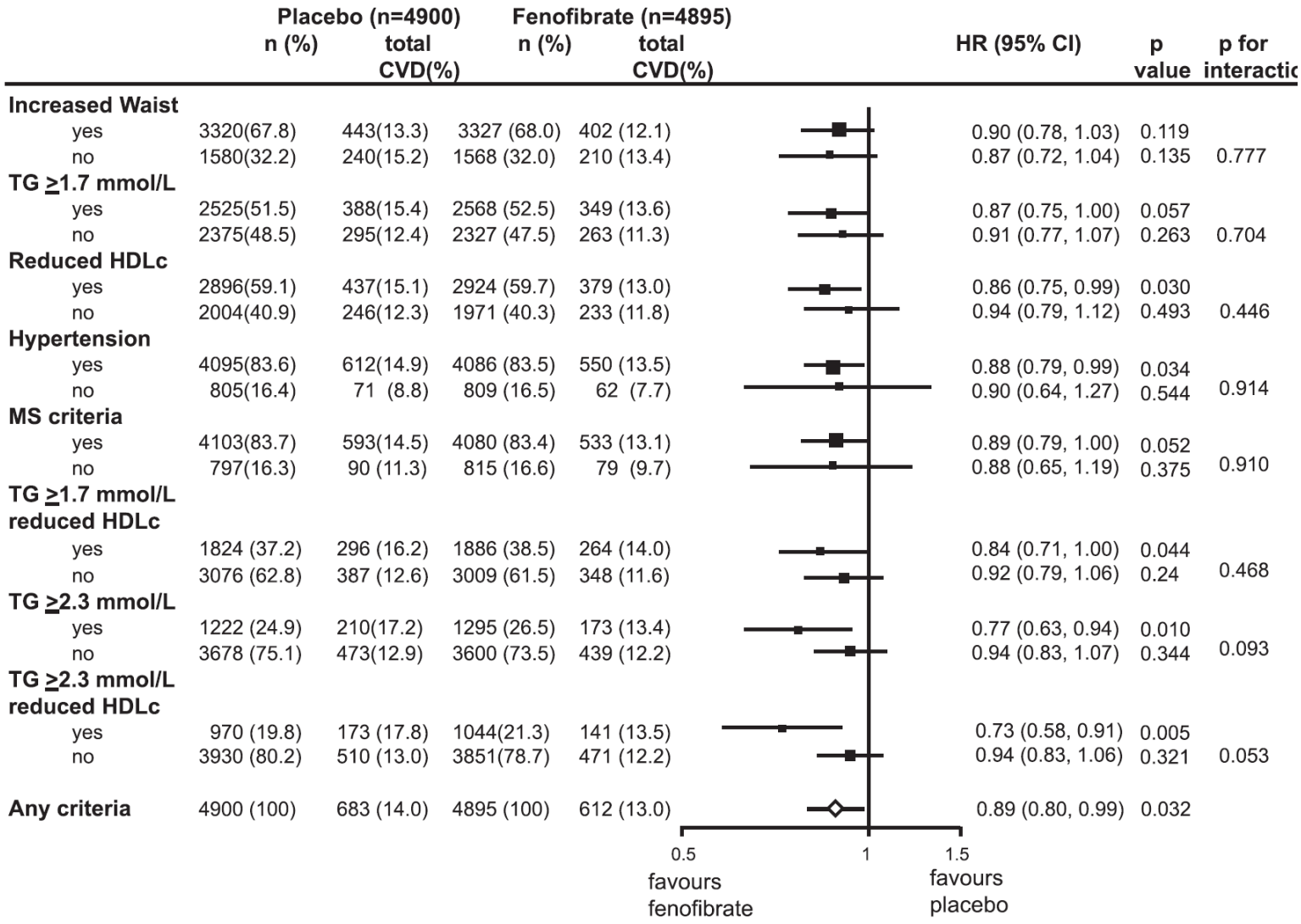


Numbers at risk

Placebo	4900	4762	4586	4419	4257	2340	750
Fenofibrate	4895	4771	4604	4669	4305	2370	775

Lancet 2005; 366: 1849–61

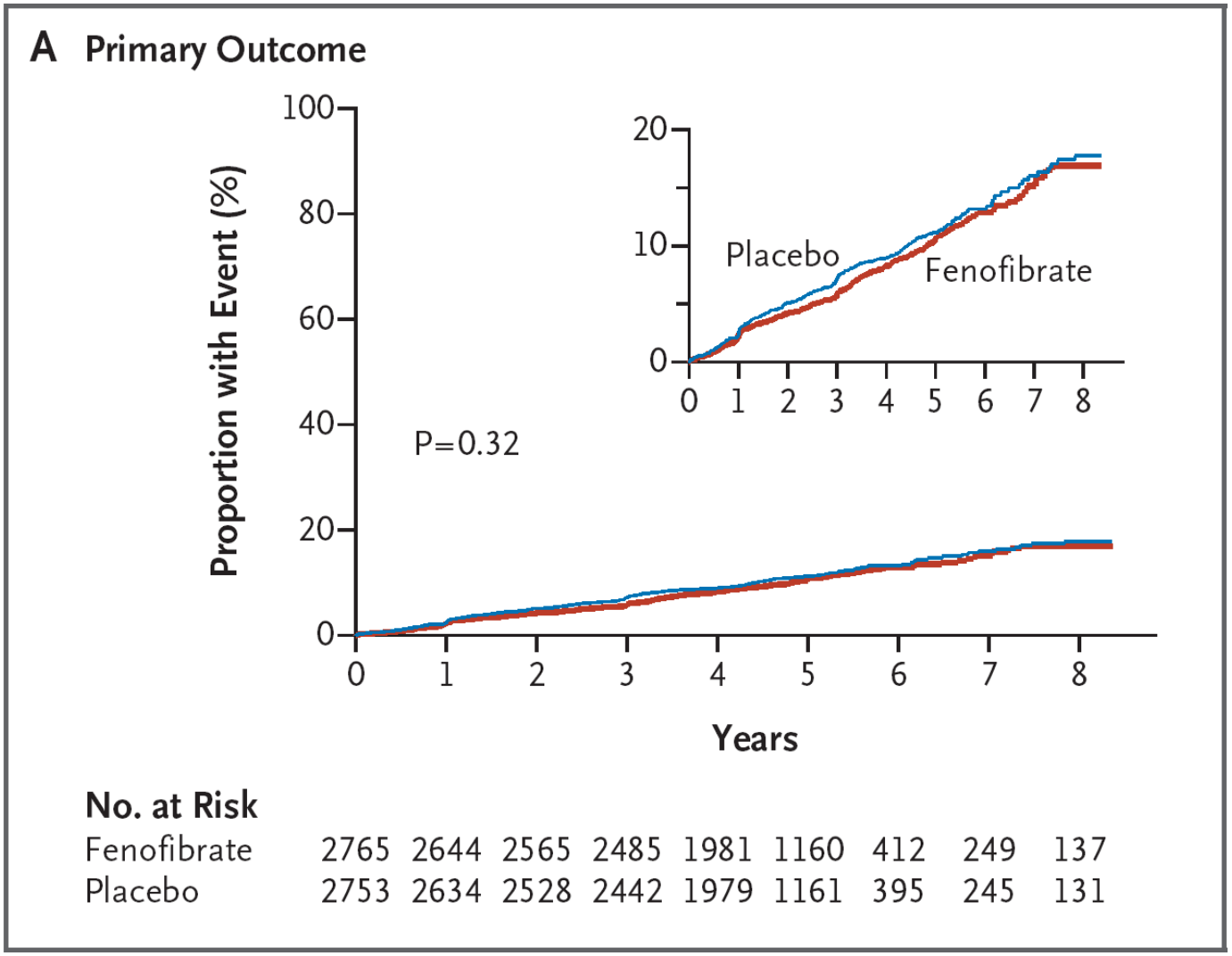
Effects on Cardiovascular Events according to ATP III Metabolic syndrome Criteria (FIELD)



Diabetes Care 32:493–498, 2009

Effects of Combination Lipid Therapy in Type 2 DM

The ACCORD Study Group

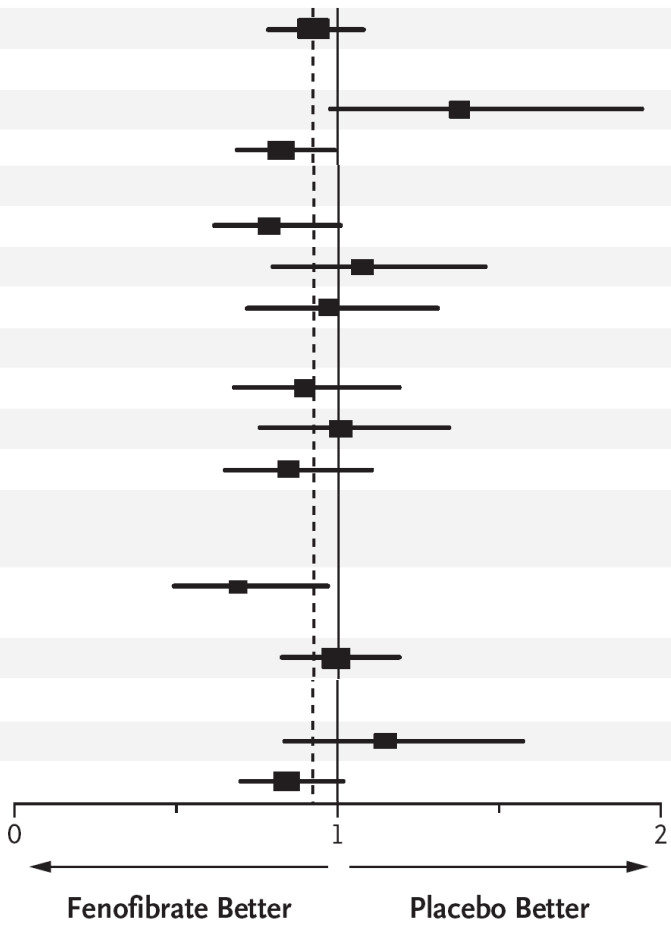


ACCORD; N Engl J Med 2010;362:1563-74.

Effects of Combination Lipid Therapy in Type 2 DM

The ACCORD Study Group

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)	
HDL cholesterol			0.24
≤34 mg/dl	12.24 (964)	15.56 (906)	
35–40 mg/dl	10.12 (860)	9.47 (866)	
≥41 mg/dl	9.08 (925)	8.99 (968)	
Triglycerides			0.64
≤128 mg/dl	9.88 (891)	11.29 (939)	
129–203 mg/dl	10.50 (924)	9.86 (913)	
≥204 mg/dl	11.13 (934)	12.84 (888)	
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)	
Race			0.09
Nonwhite	9.70 (856)	8.22 (888)	
White	10.90 (1909)	12.71 (1865)	

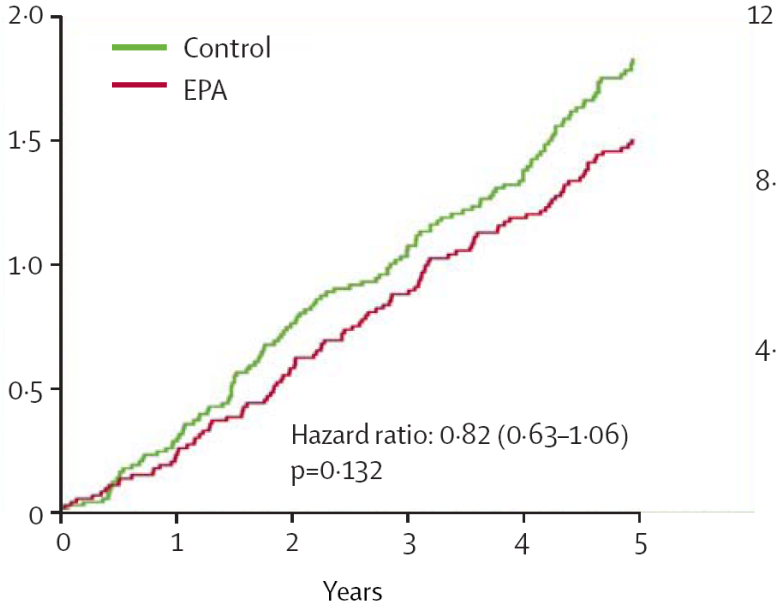


ACCORD; N Engl J Med 2010;362:1563-74.

Japan EPA Lipid Intervention Study (JELIS)

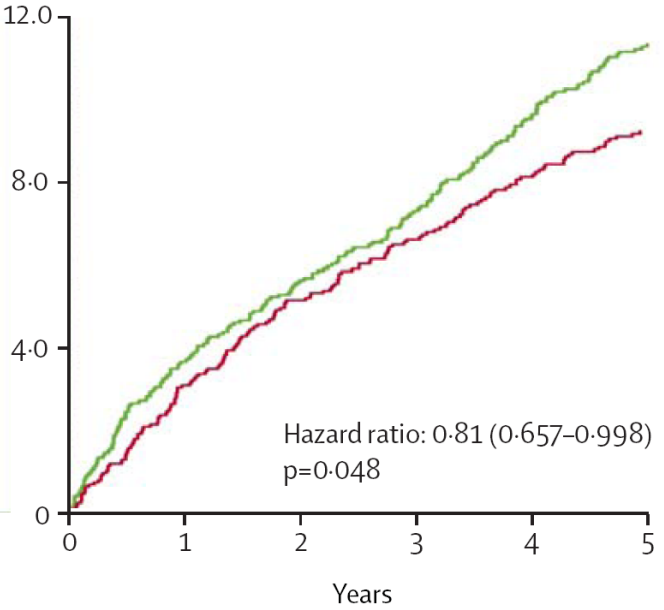
- **18 645 patients with total cholesterol ≥ 6·5 mmol/L**
- **Statin and 1800 mg of EPA or control**
- **Primary endpoint: sudden cardiac death, fatal and non-fatal myocardial infarction, and other nonfatal events including unstable angina pectoris, angioplasty, stenting, or CABG**
- **5 year FU**

Primary Prevention



7478	7204	7103	6841	6678	6508
7503	7210	7020	6823	6649	6482

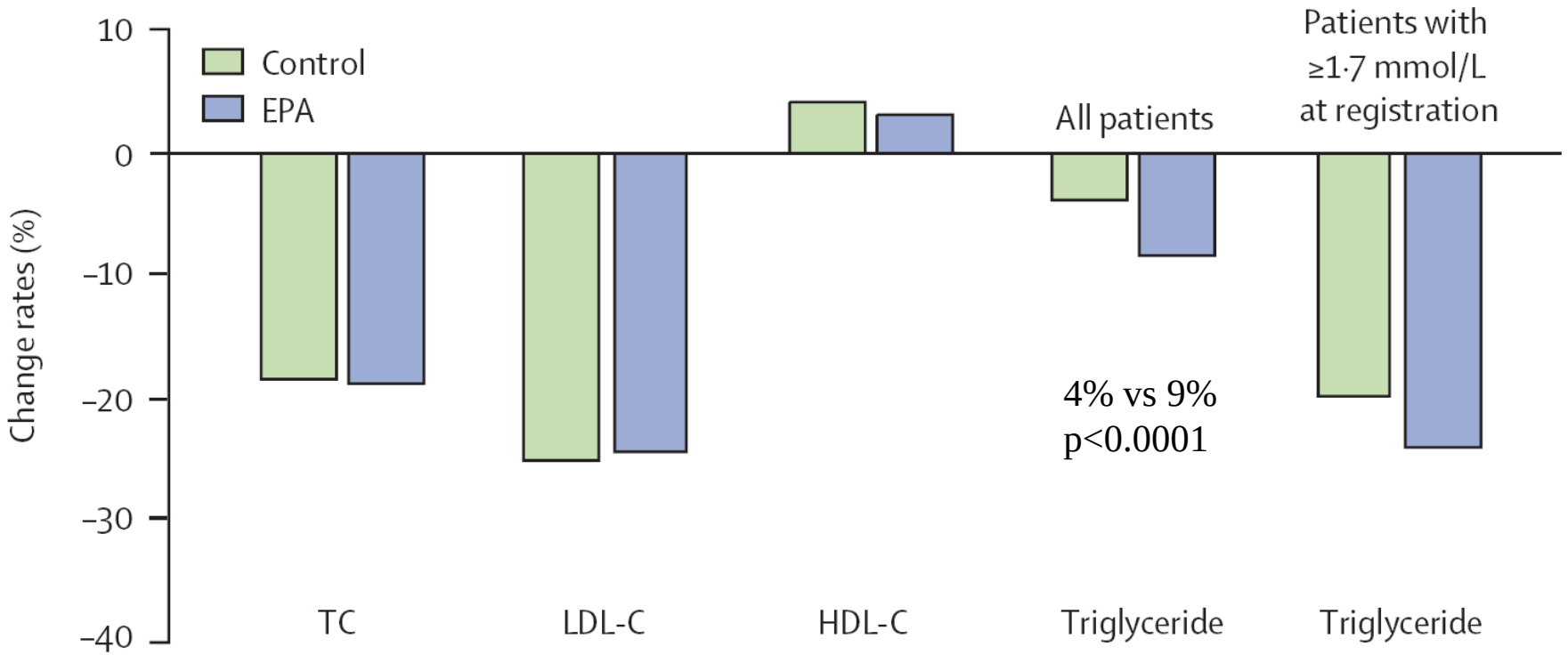
Secondary Prevention



1841	1727	1658	1592	1514	1450
1823	1719	1638	1566	1504	1442

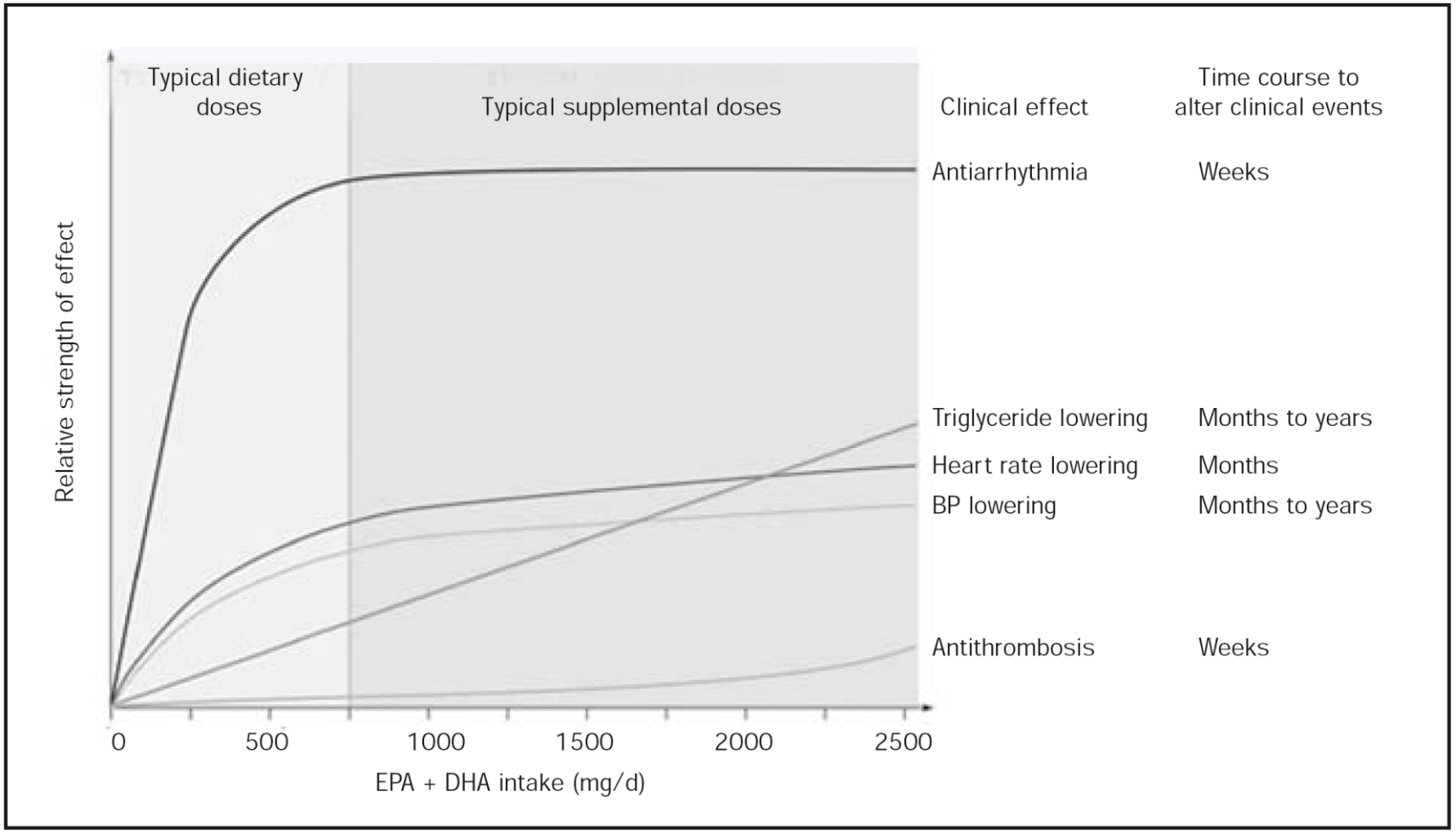
Lancet 2007; 369: 1090–98

Percentage Changes in Lipid Profile (JELIS)



Lancet 2007; 369: 1090–98

Schema of potential dose responses and time courses for fish or fish oil intake



JAMA. 2006;296(15):1885-1899.

증례

55세 여자

운동시 흉통, 피부 병변

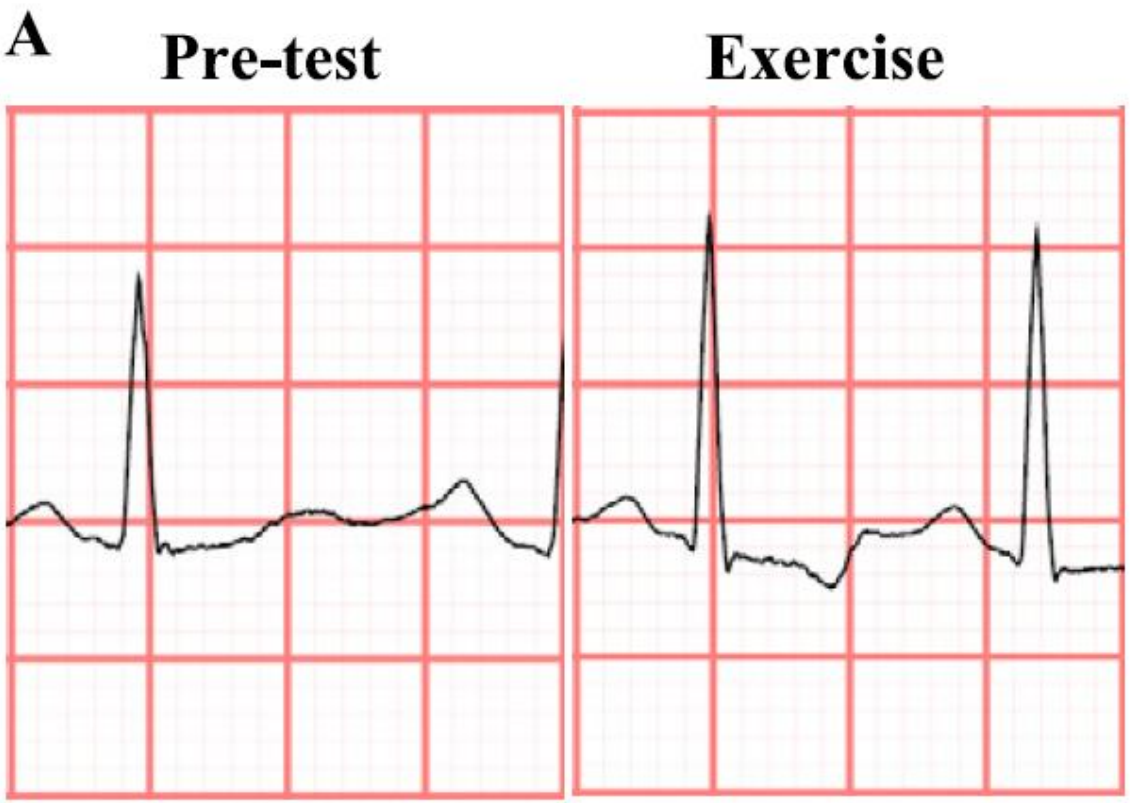
콜레스테롤 747 mg/dL

HDL 콜레스테롤이 50 mg/dL

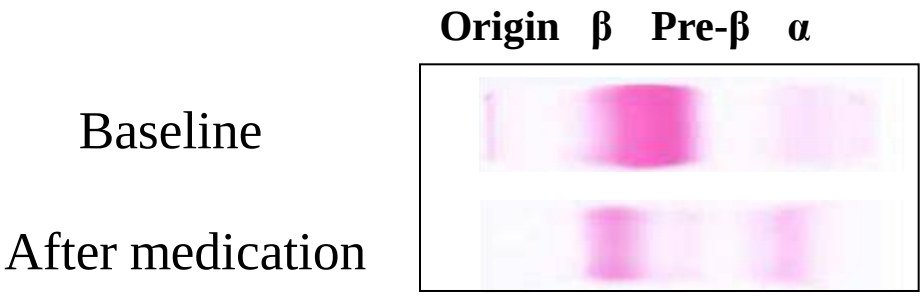
중성지방이 1,315 mg/dL

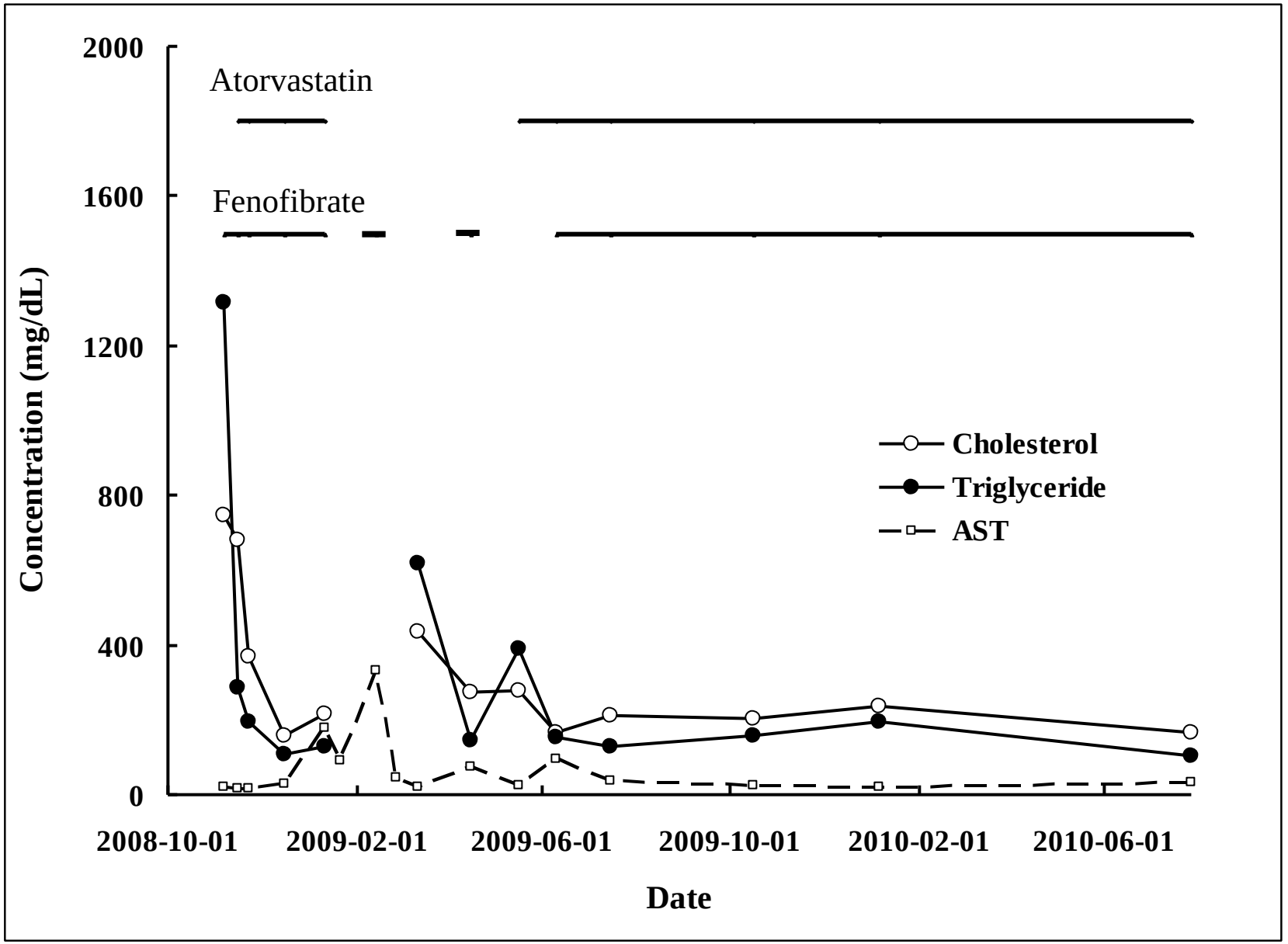
계산된 LDL 콜레스테롤은 ? mg/dL

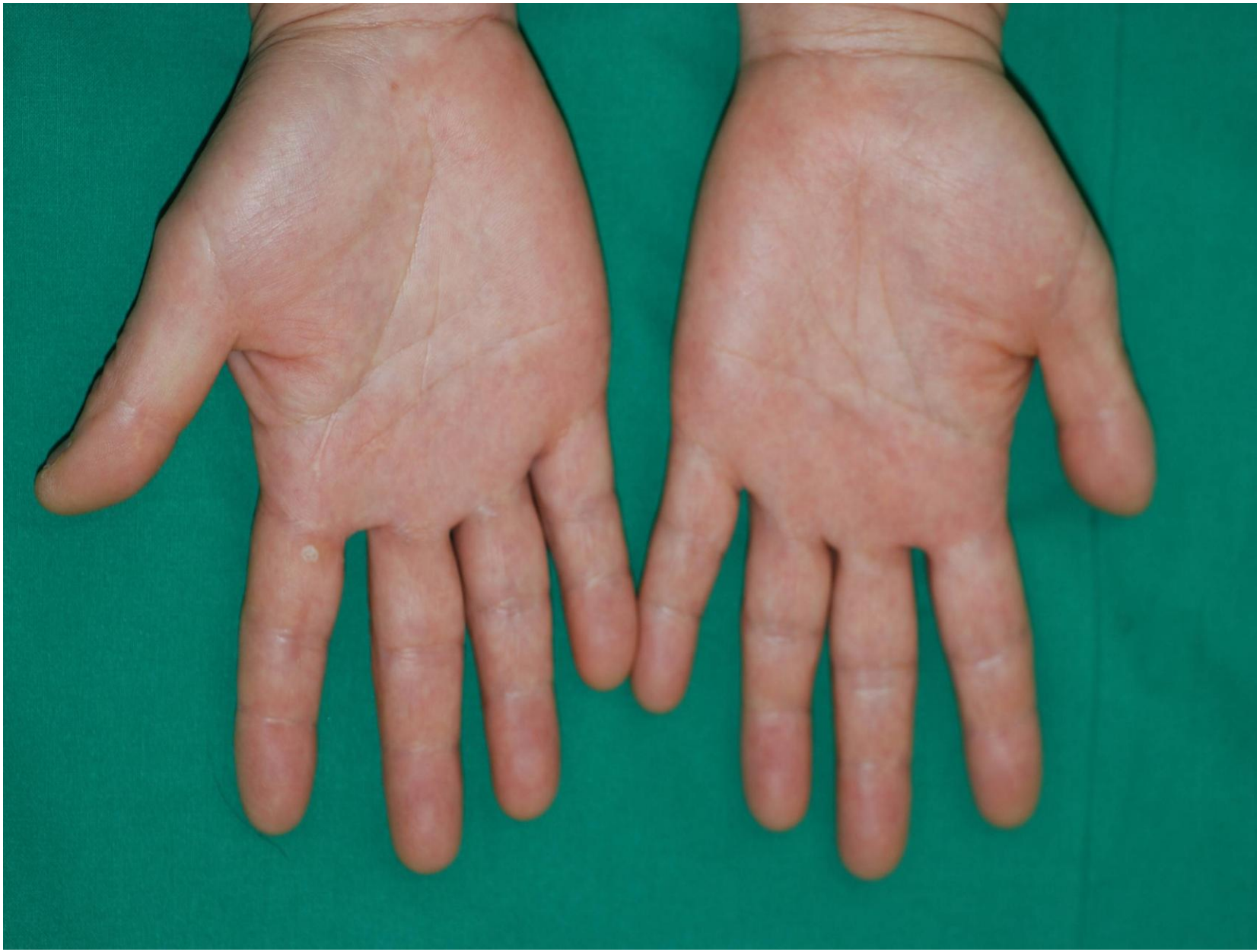
운동부하심전도



Lipoprotein Agarose Gel Electrophoresis

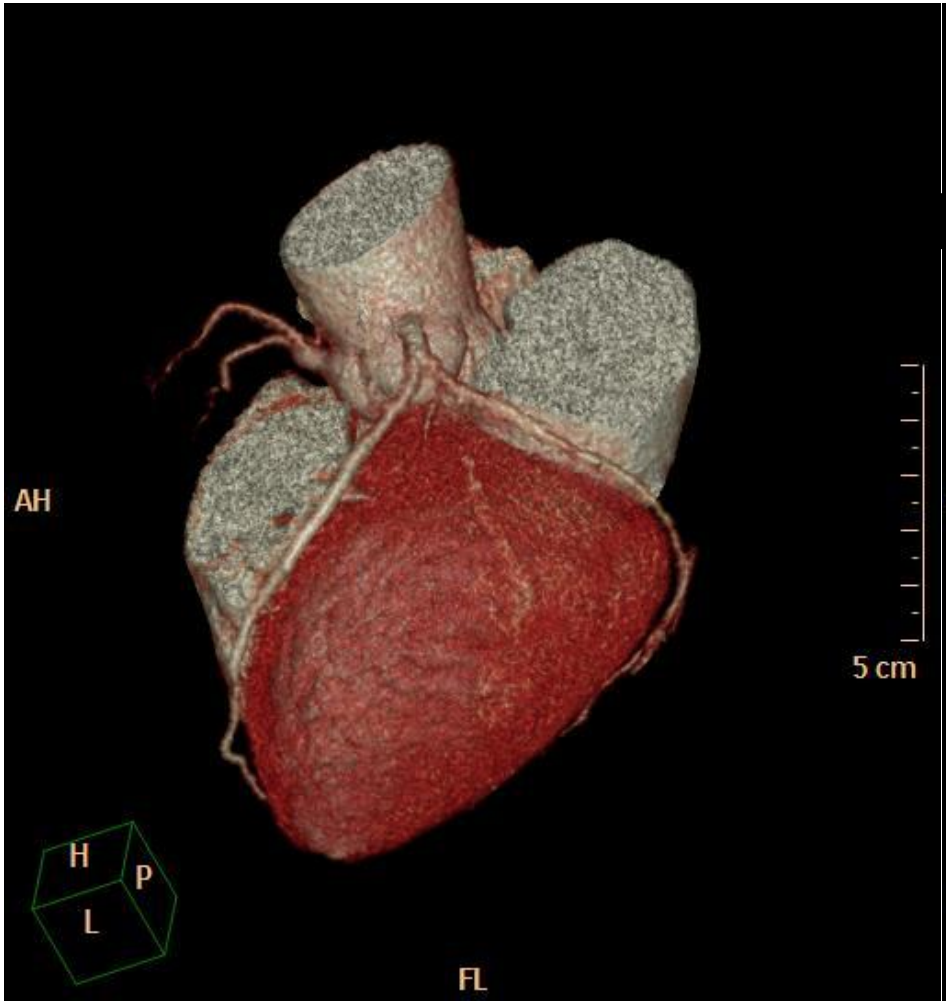



2000
1600
1200
800
400
0
Concentration (mg/dL)
Atorvastatin
Fenofibrate
Cholesterol
Triglyceride
AST
2008-10-01
2009-02-01
2009-06-01
2009-10-01
2010-02-01
2010-06-01
Date

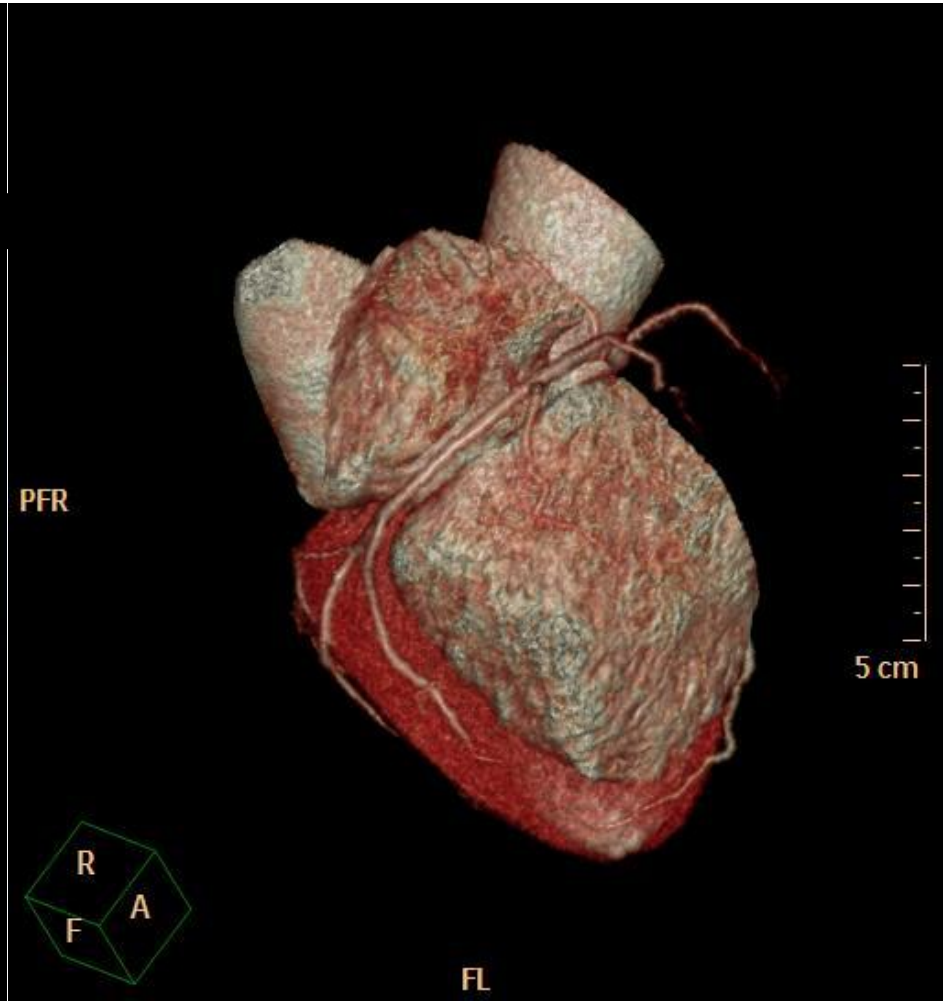


운동부하심전도

A



B



Type III Hyperlipoproteinemia

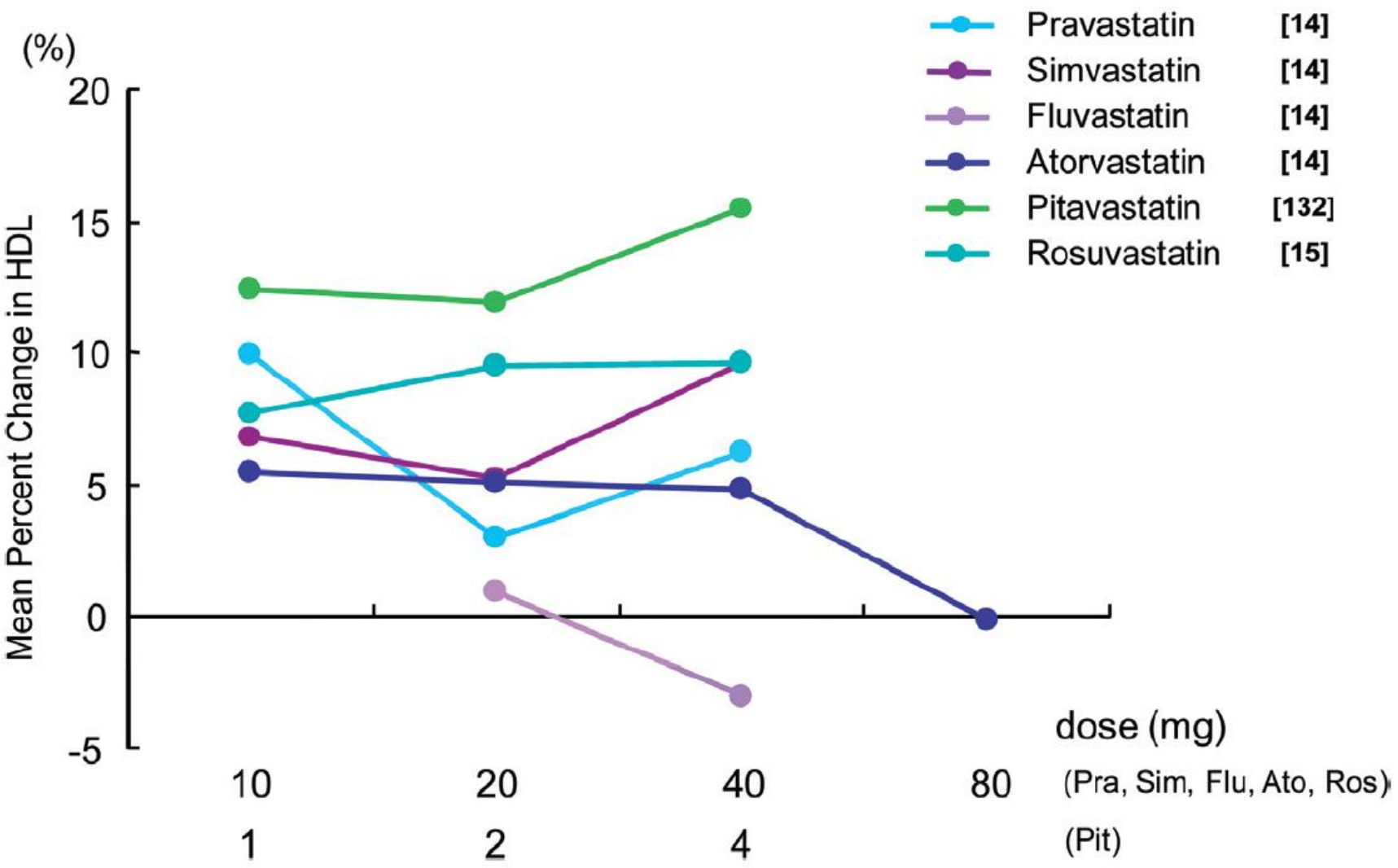
경청해 주셔서 감사합니다.

고지혈증 치료제

약 제	효과			부작용	금기	임상연구결과
	LDL-C	HDL-C	중성지방			
HMG-CoA reductase inhibitor (statin)	↓↓↓	↑↑	↓	Myopathy 간효소 상승	절대: 활동성 및 만성 간질환 상대: 특수 약제의 병용*	주요 관상동맥사건, 관상동맥사망, 관상동맥시술 및 총사망률의 감소
Bile acid sequestrant	↓↓	↑	↑	위장관 불편감, 변비, 타약제의 흡수장애	절대: dysbetalipoproteinemia 중성지방 400mg/dL 초과 상대: 중성지방 200 mg/dL 초과	주요 관상동맥사건 및 관상동맥사망 감소
Nicotinic acid	↓↓	↑↑↑	↓↓	안면홍조, 혈당상승, 요산증가, 상부위장관 불편감, 간독성	절대: 만성간질환, 심한 통풍 상대: 당뇨병, 고요산혈증, 소화성궤양	주요 관상동맥사건의 감소 총사망률의 감소가능
Fibrates	↓**	↑↑	↓↓↓	소화불량, 담석, 근육병증	절대: 중증의 신질환, 중증의 간질환	주요 관상동맥사건의 감소

* : Cyclosporin, macrolide 항생제, 항진균제, cytochrome P-450 억제제.
** : 중성지방만이 높은 경우 증가시킬 수 있음.

Effect of Statins on HDL-C Levels

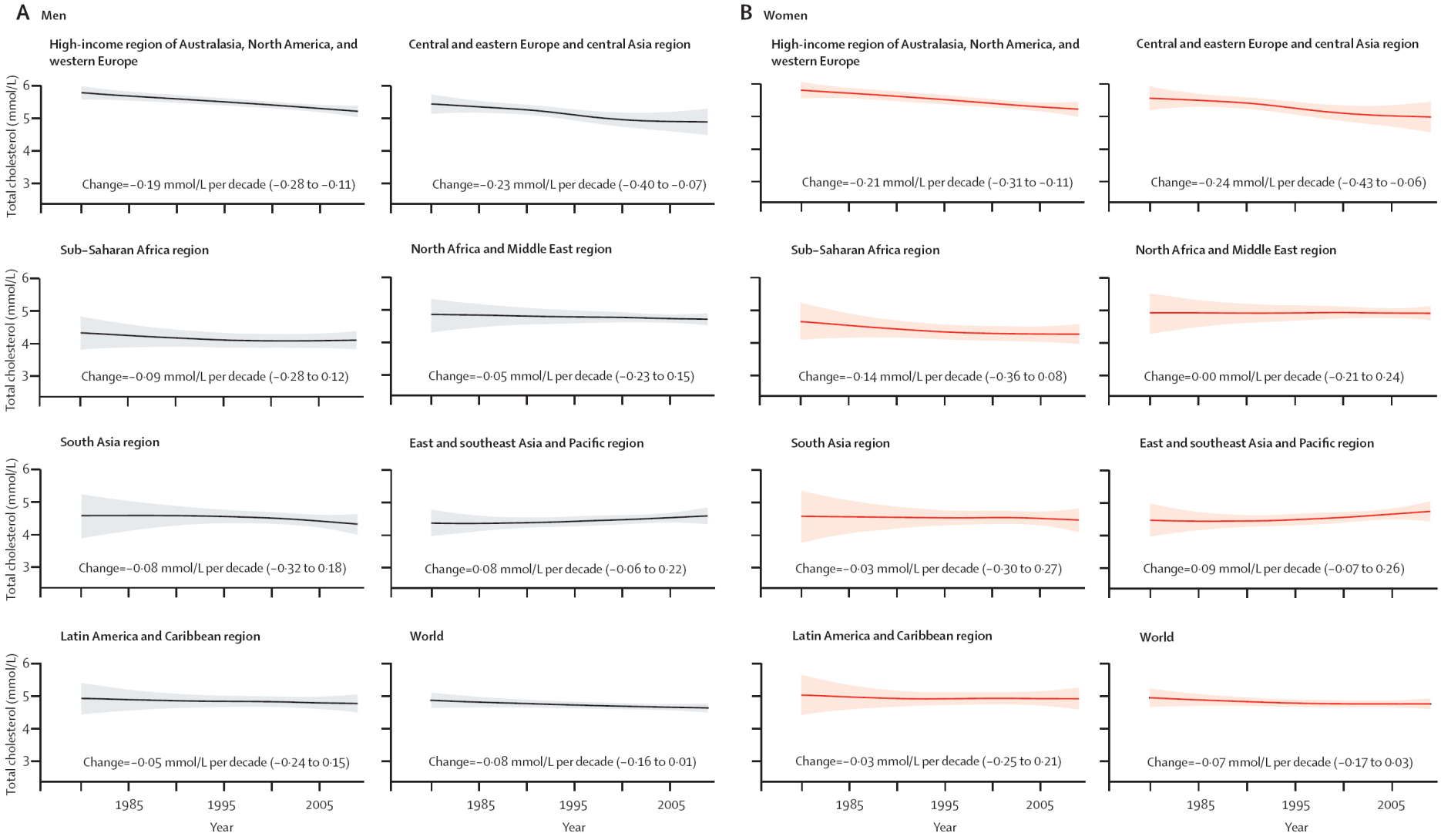


J Atheroscler Thromb. 2010 May;17(5):436

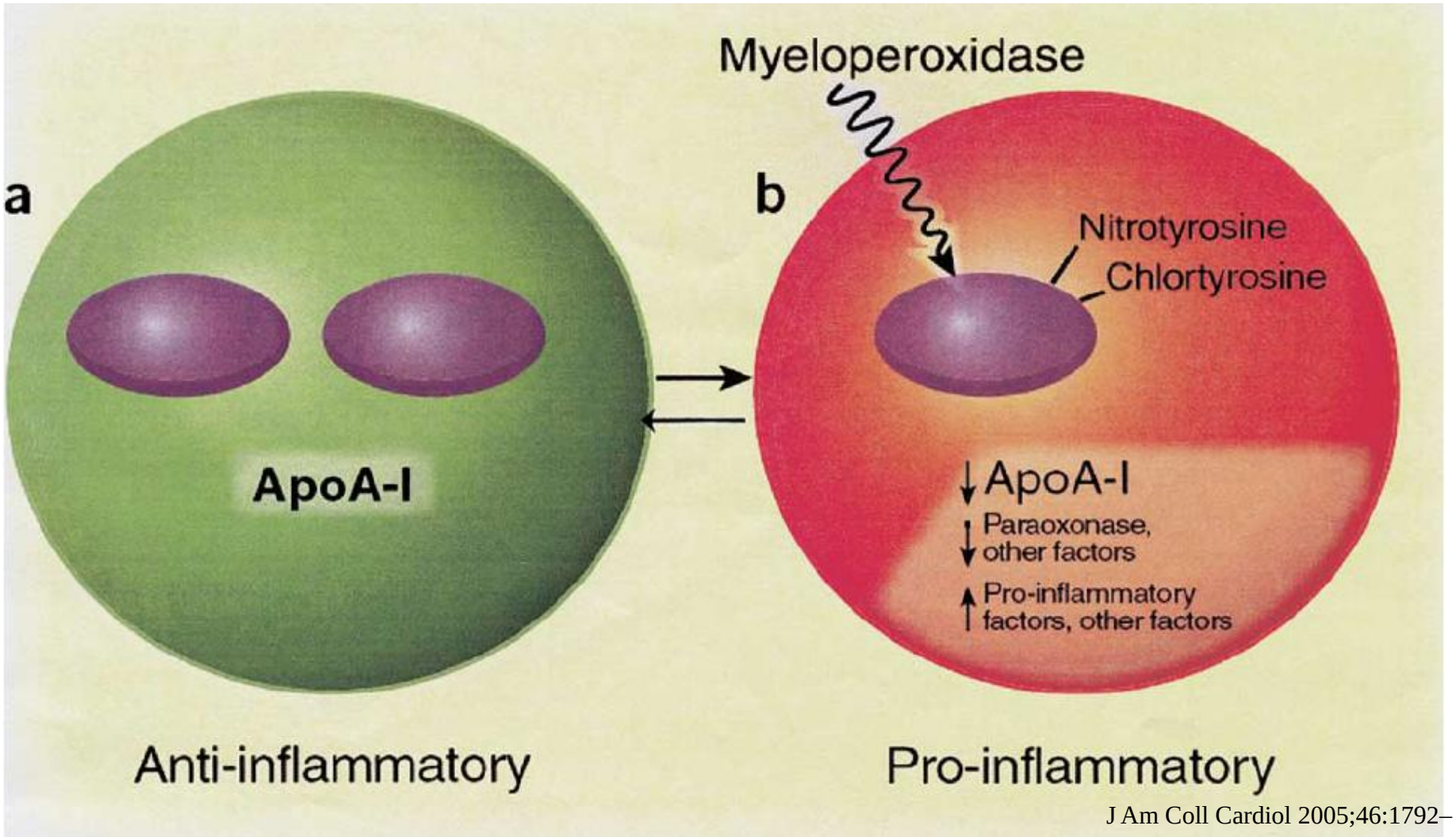
Pharmacokinetic parameters of statins

Statin	Pitavastatin	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Molecular weight	881	1209	433.5	405	446.5	1001	418.15
Origin	Synthetic	Synthetic	Synthetic	Microbial	Semi-synthetic (microbial origin)	Synthetic	Semi-synthetic (microbial origin)
Racemic	No	No	Yes	No	No	No	No
Prodrug	No	No	No	Yes	No	No	Yes
Log *P*	1.49	1.11	1.27	1.70	–0.84	–0.33	1.60
Absorption (%)	80	30	98	31	37	50	65–85
Hepatic excretion (%)	NA	>70	68	>70	66	90	78–87
Bioavailability (%)	>60	12	10–35	<5	17	20	<5
Effect of food on bioavailability (%)	No	Yes (↓ 13)	Yes (↓ 15–25)	Yes (↑ 50)	Yes (↓ 30)	No	No
Protein binding (%)	96	>98	>98	96–98.5	43–54	88	>95
T_{max}	0.5–0.8	2.0–4.0	0.5–1.5	2.8	0.9–1.6	3	1.3–2.4
$T_{1/2}$	11	11–30	0.5–2.3	2.5–3.0	0.8–3.0	20	1.9–3.0
Renal excretion	<2	2	6	30	60	10	13
50% inhibitory concentration (nmol/L)	6.8	15.2	17.9	2.7–11.1	55.1	12	18.1
Lipid-lowering Metabolites	No	Yes, active	Yes, mainly inactive	Yes	Yes, mainly active	No	Yes
Range of dose (mg)	1–4	10–80	20–80	10–80	5–40	5–80	5–80
CYP isoforms primarily involved with metabolic pathway	CYP2C9 Minimally	CYP3A4	CYP2C9	CYP3A4	CYP3A4 Minimally	CYP2C9 Minimally	CYP3A4

Trends in age-standardised mean total cholesterol by region

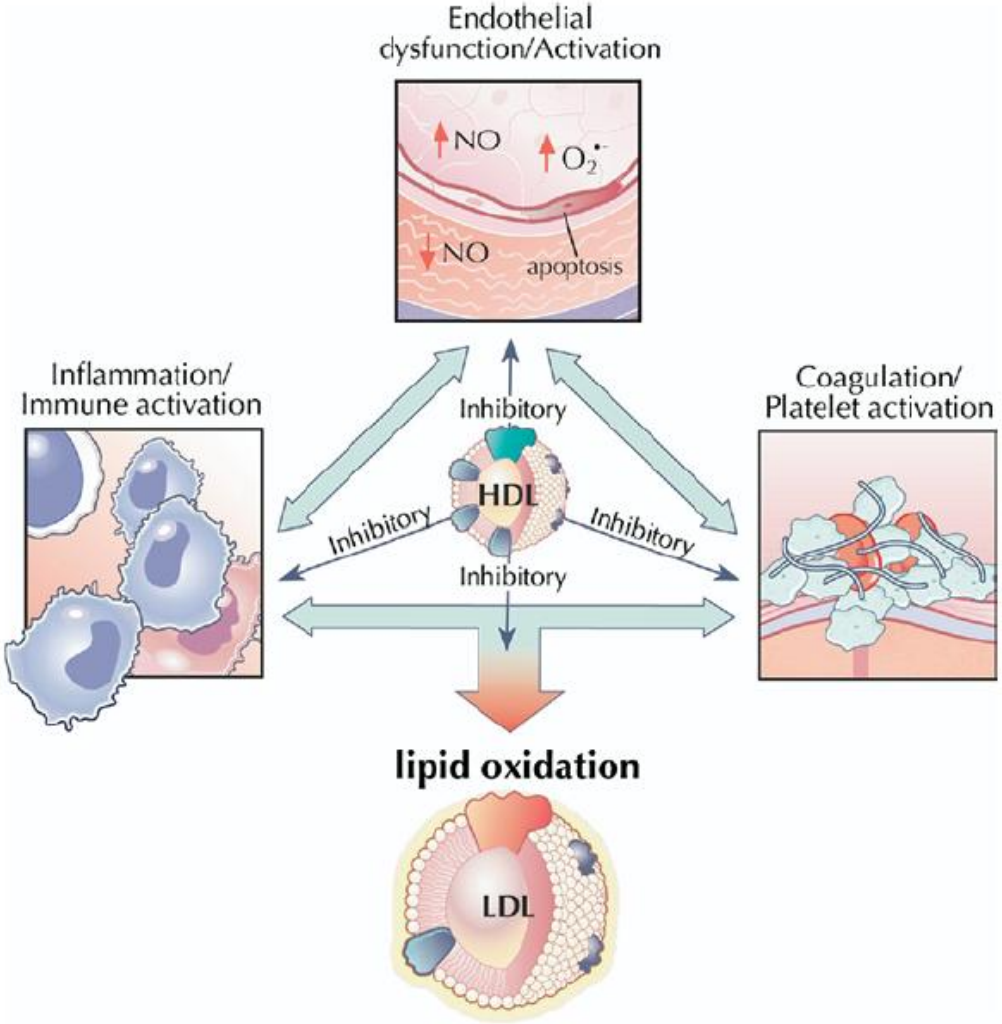


Lancet 2011; 377: 578–86

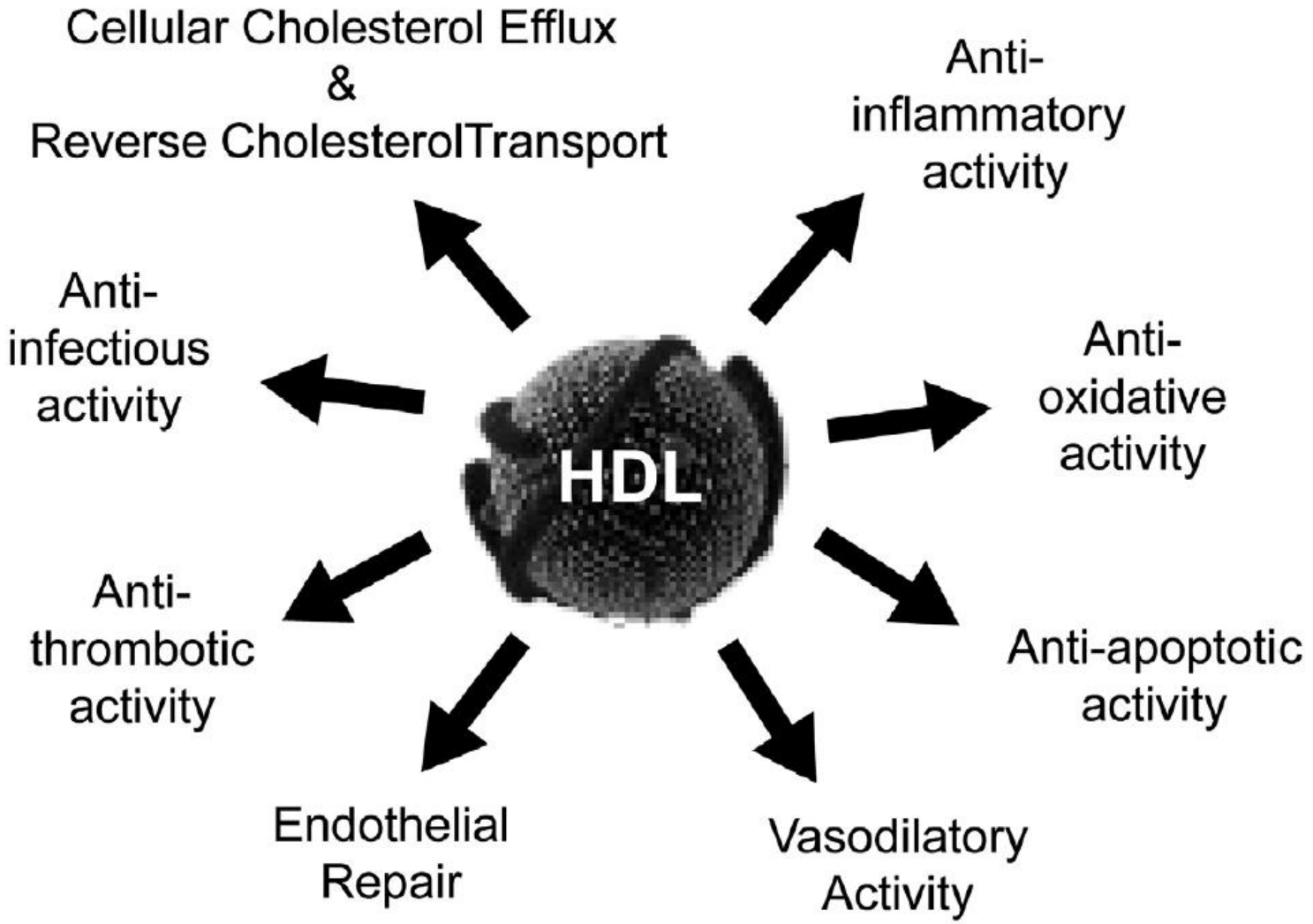


J Am Coll Cardiol 2005;46:1792– 8

HDL Functions Other Than Reverse Cholesterol Transport

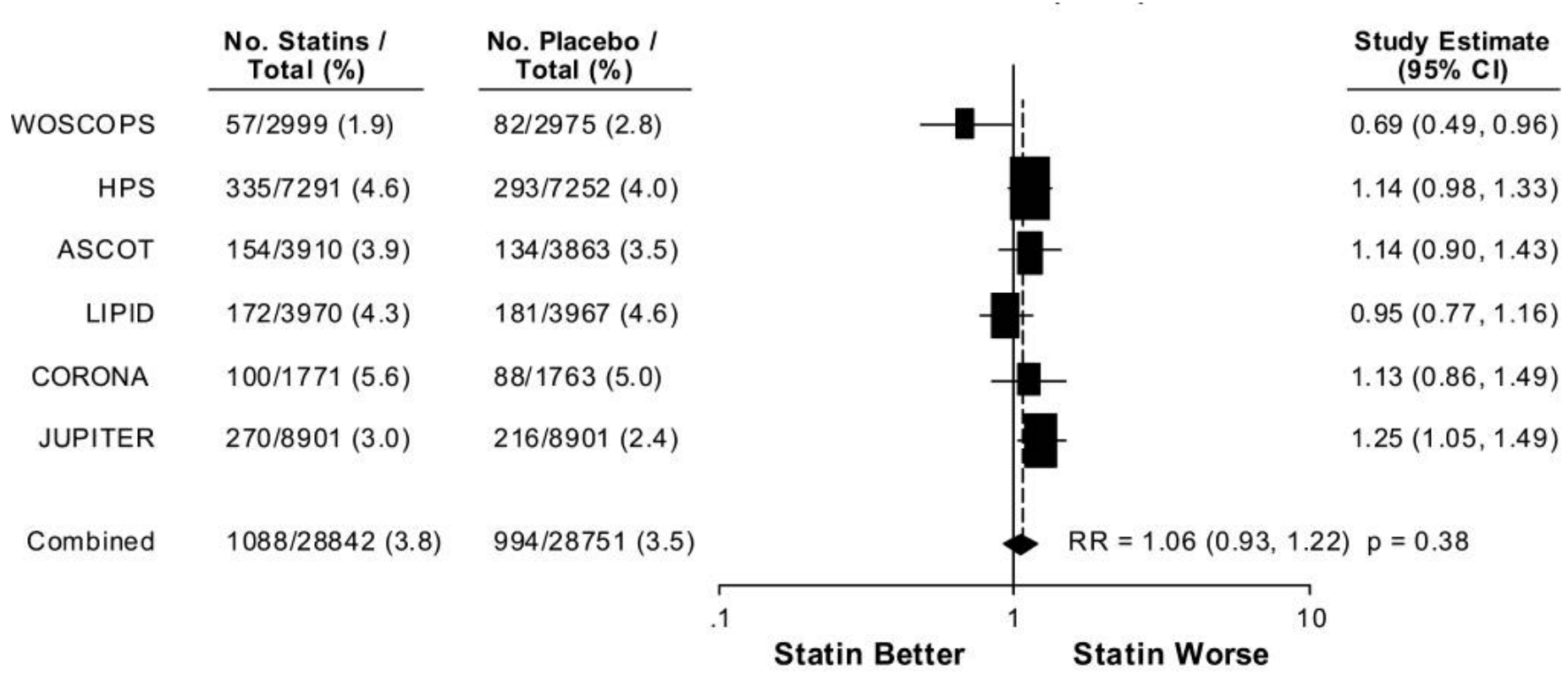


Anti-atherogenic Mechanisms of HDL

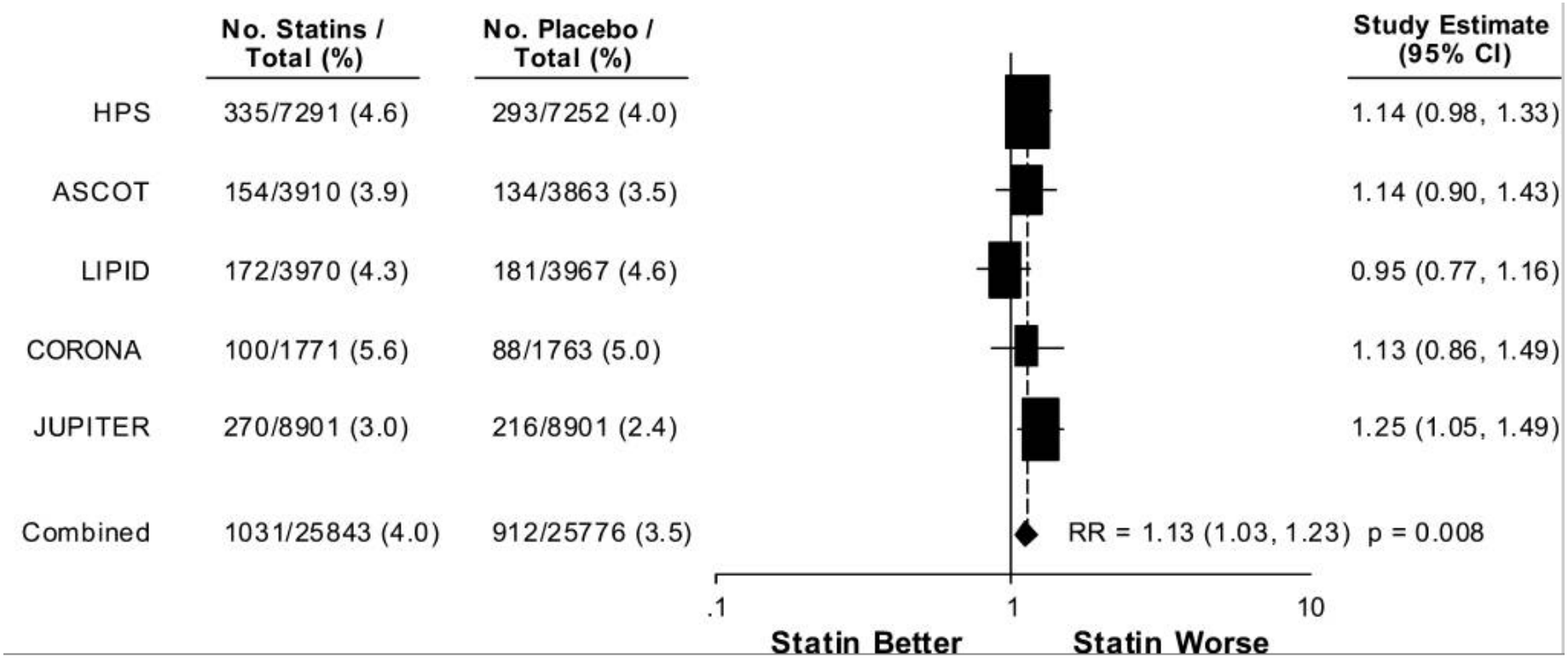


J Atheroscler Thromb. 2010 May;17(5):436

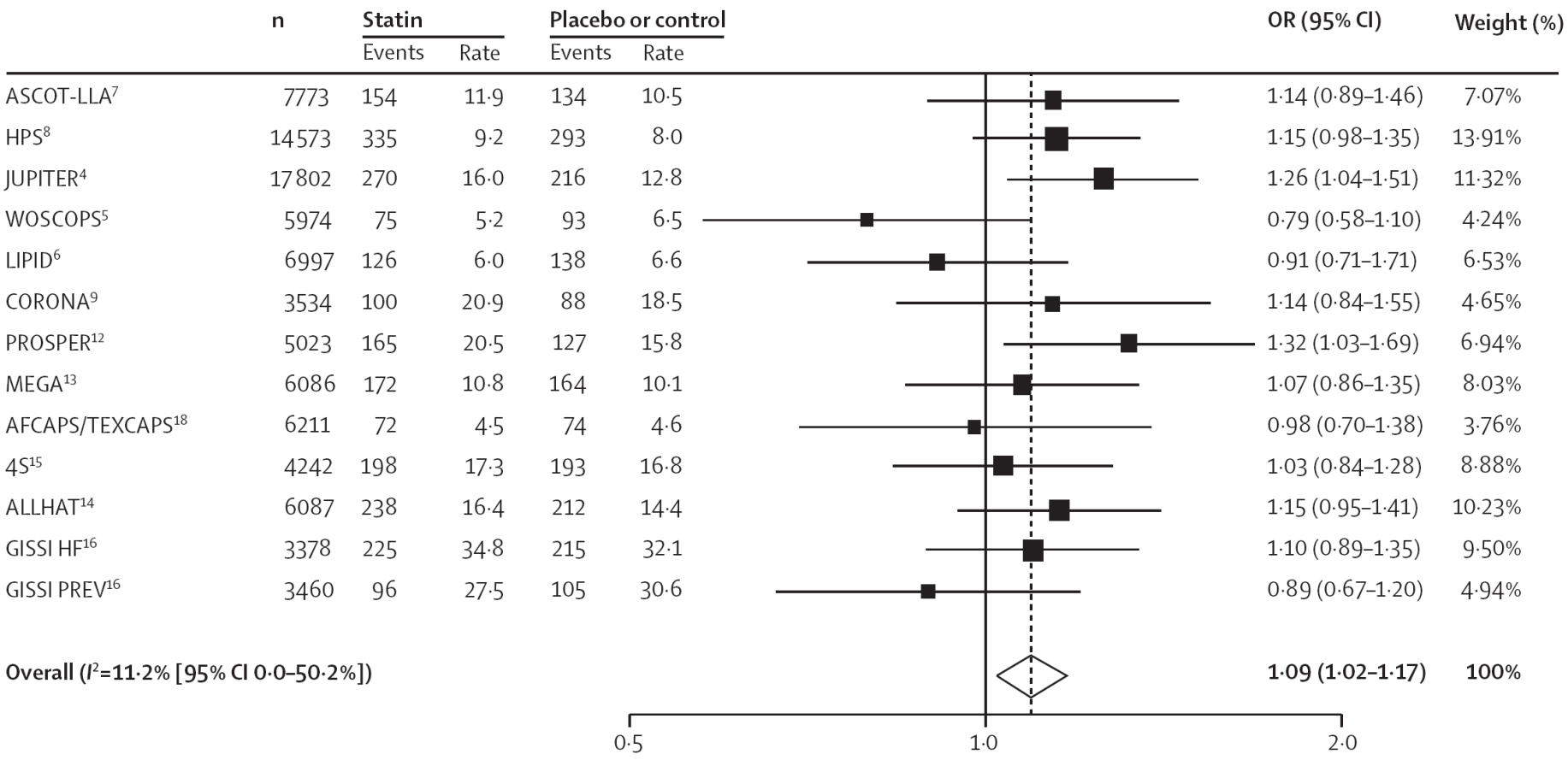
Statins And DM Risk



Statins And DM Risk

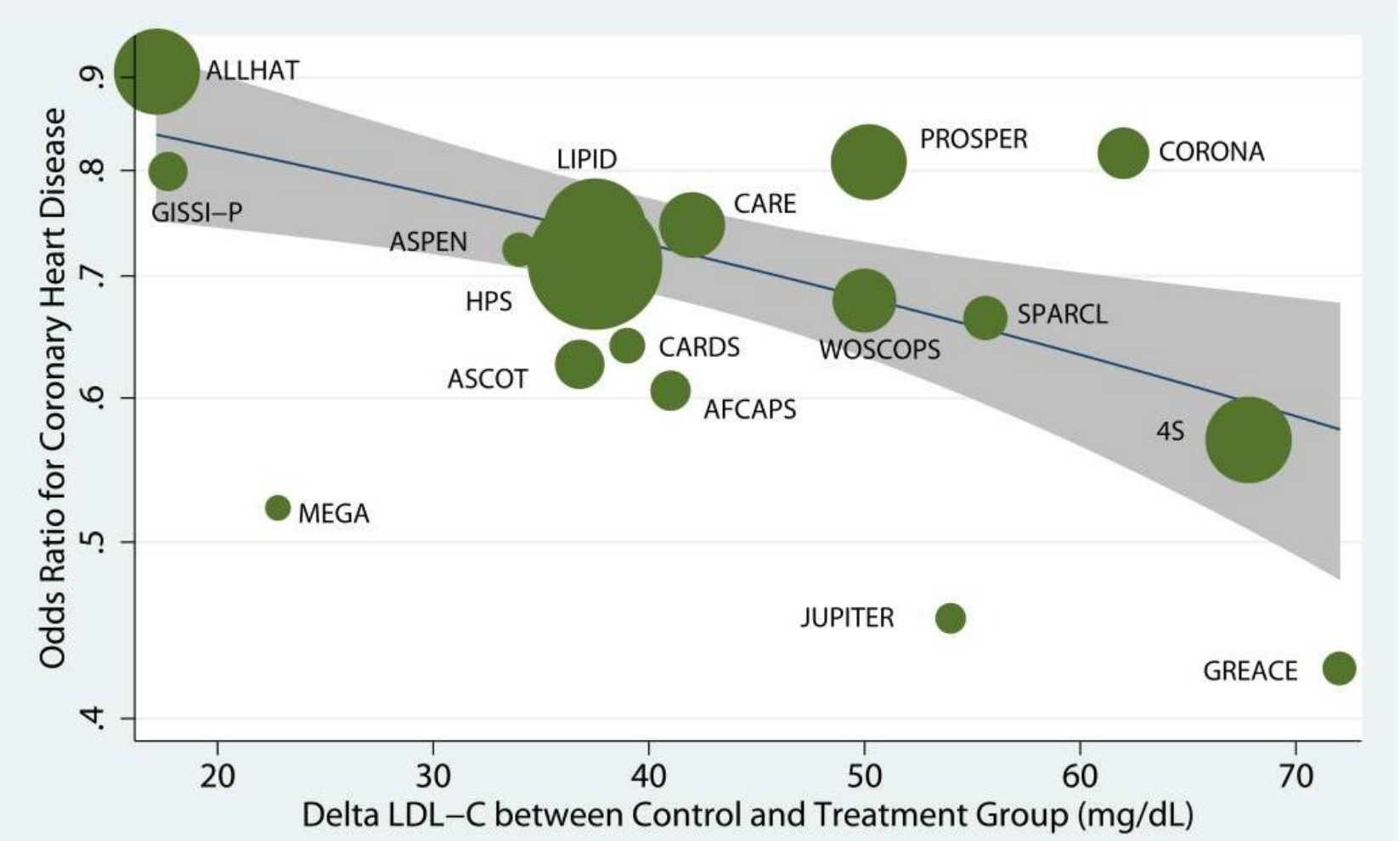


Statins And DM Risk



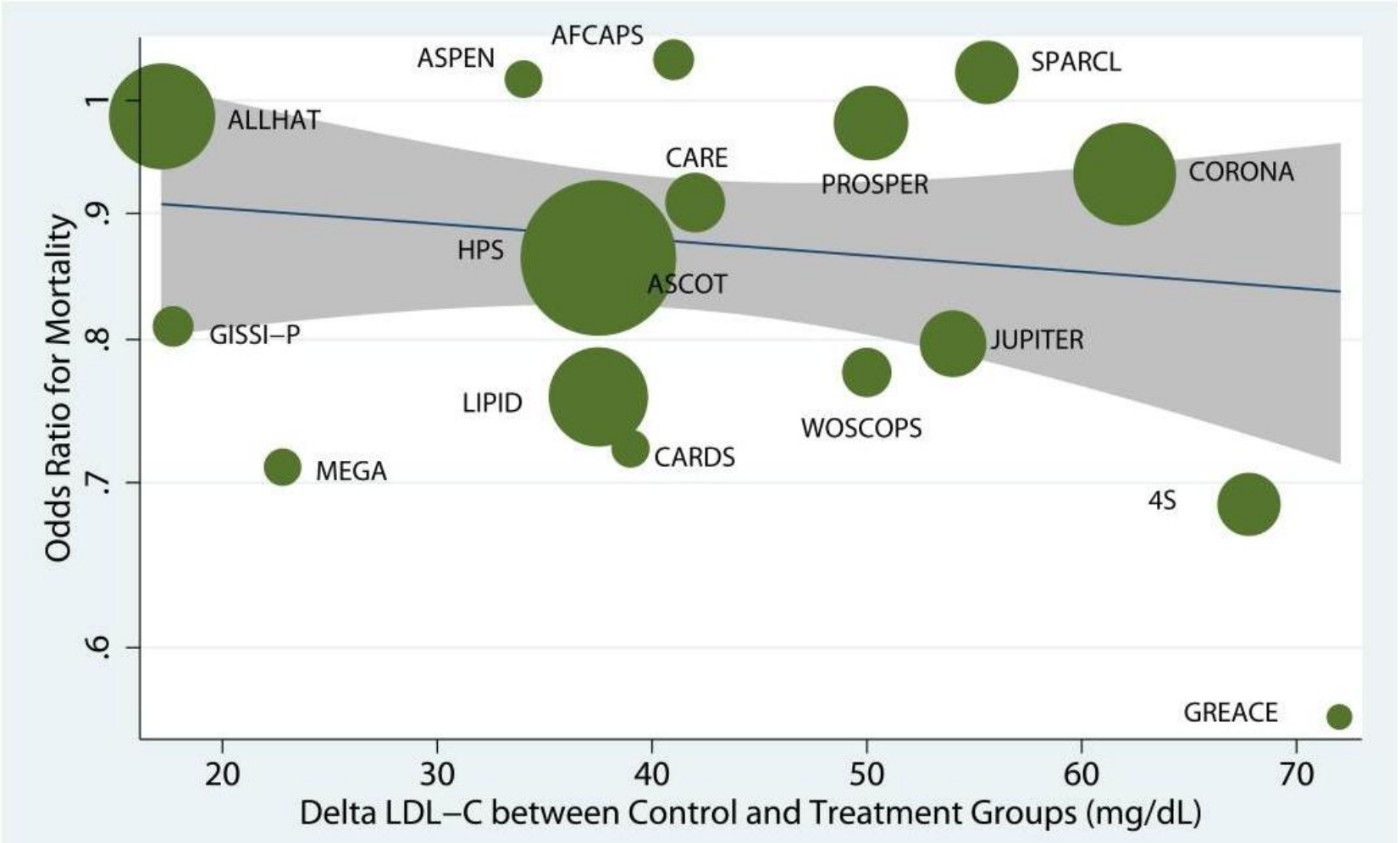
Lancet 2010; 375: 735–42

Meta-regression of OR for CHD Relative to Absolute Difference in LDL-C between Treatment vs Placebo or Usual care.



Am J Cardiol. 2010 May 1;105(9):1289

Meta-regression of OR for Mortality Relative to Absolute Difference in LDL-C between Treatment vs Placebo or Usual care.



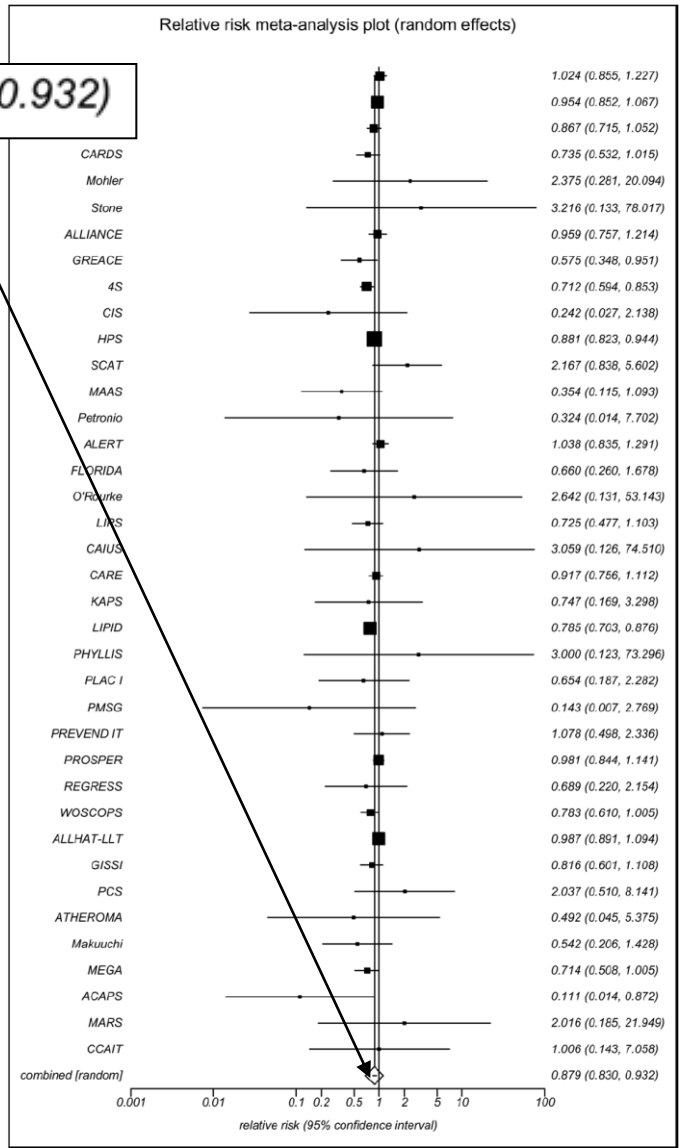
Am J Cardiol. 2010 May 1;105(9):1289

Am J Med. 2008 Jan;121(1):24

Effect of Statin on Stroke

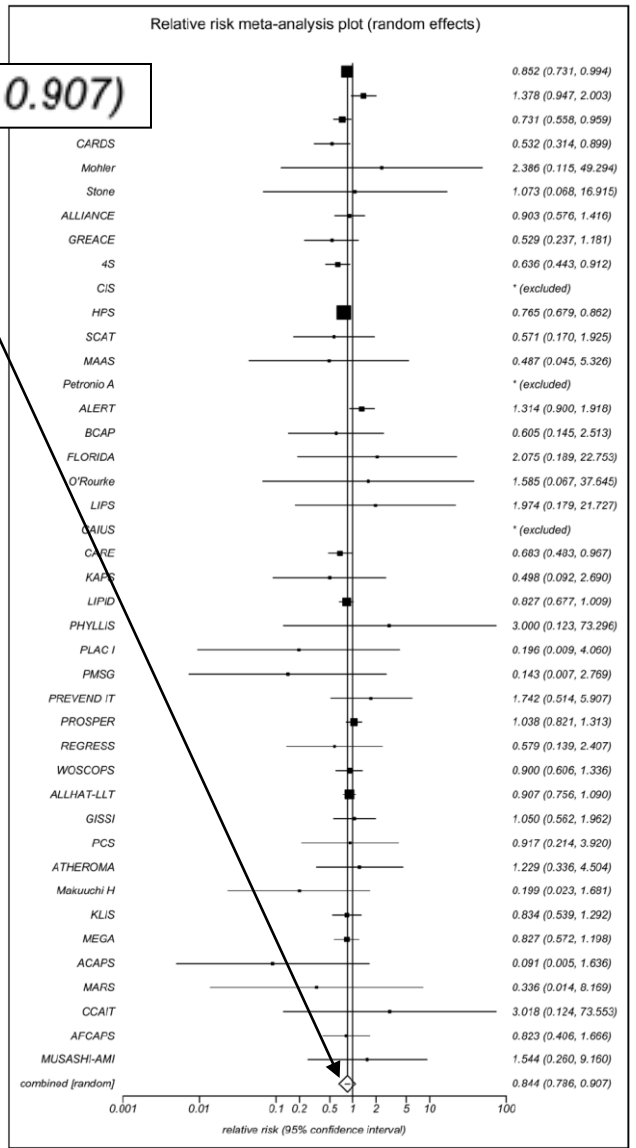
Mortality

0.879 (0.830, 0.932)

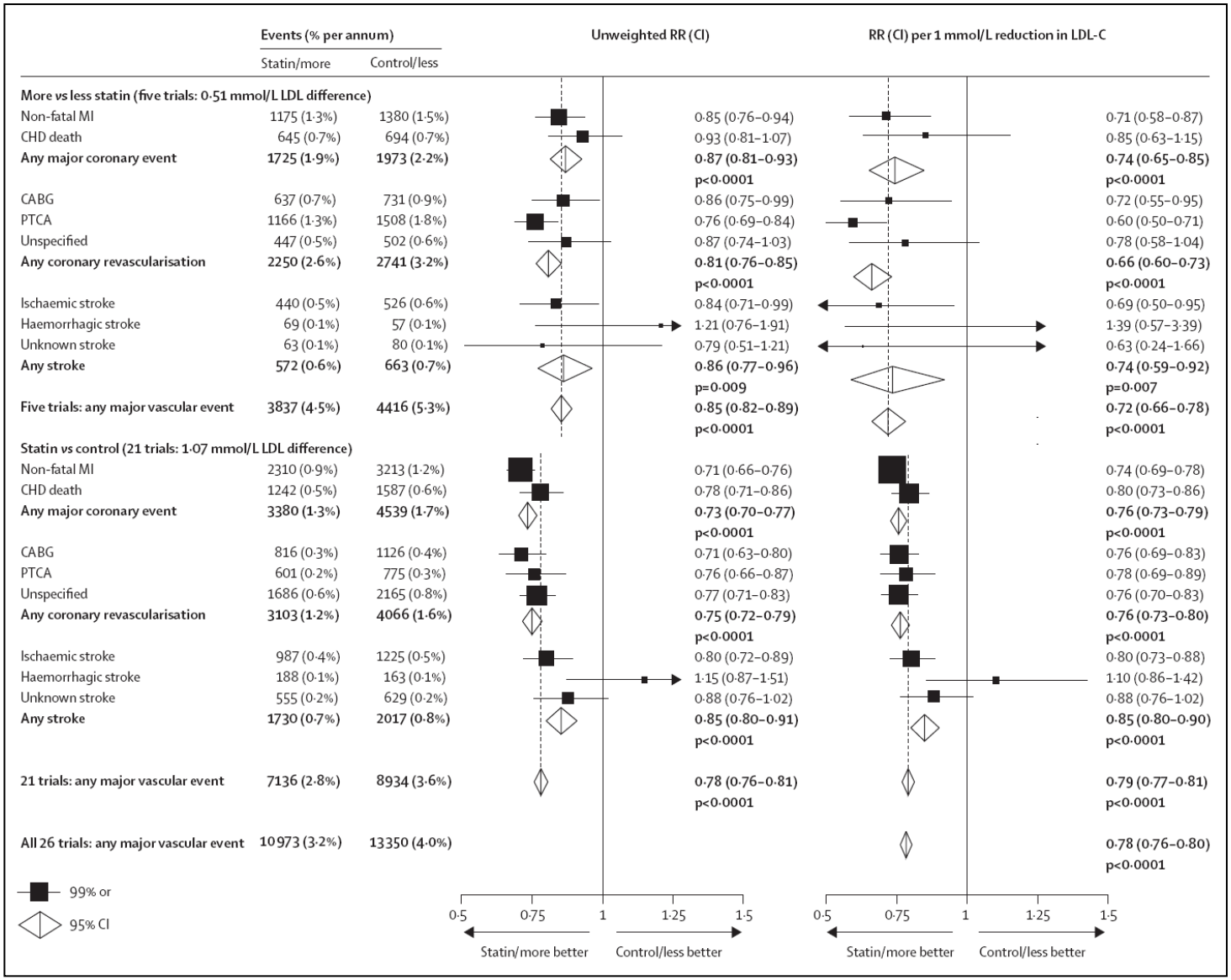


Stroke

0.844 (0.786, 0.907)

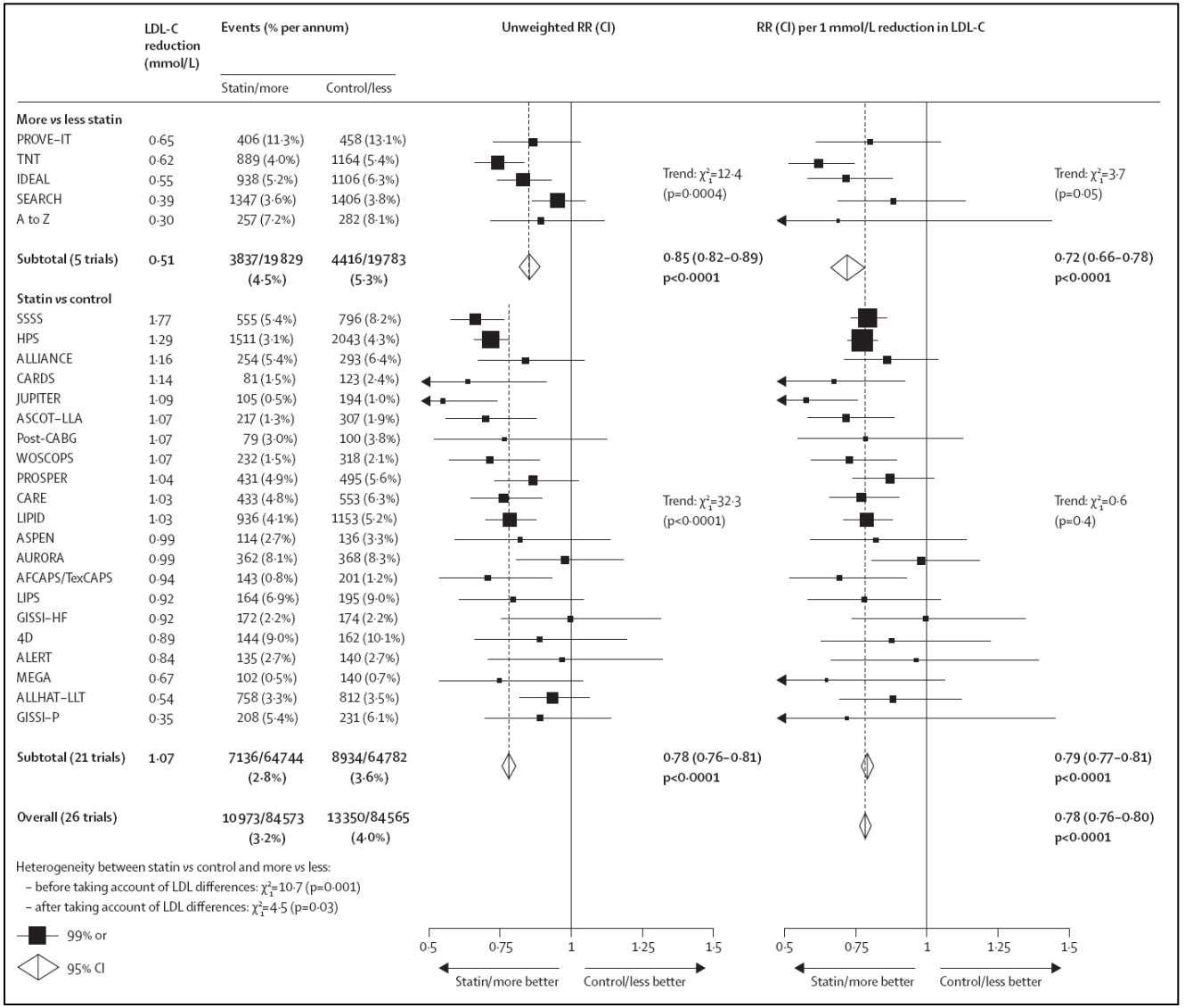


Effects of Statins on Major Vascular Event



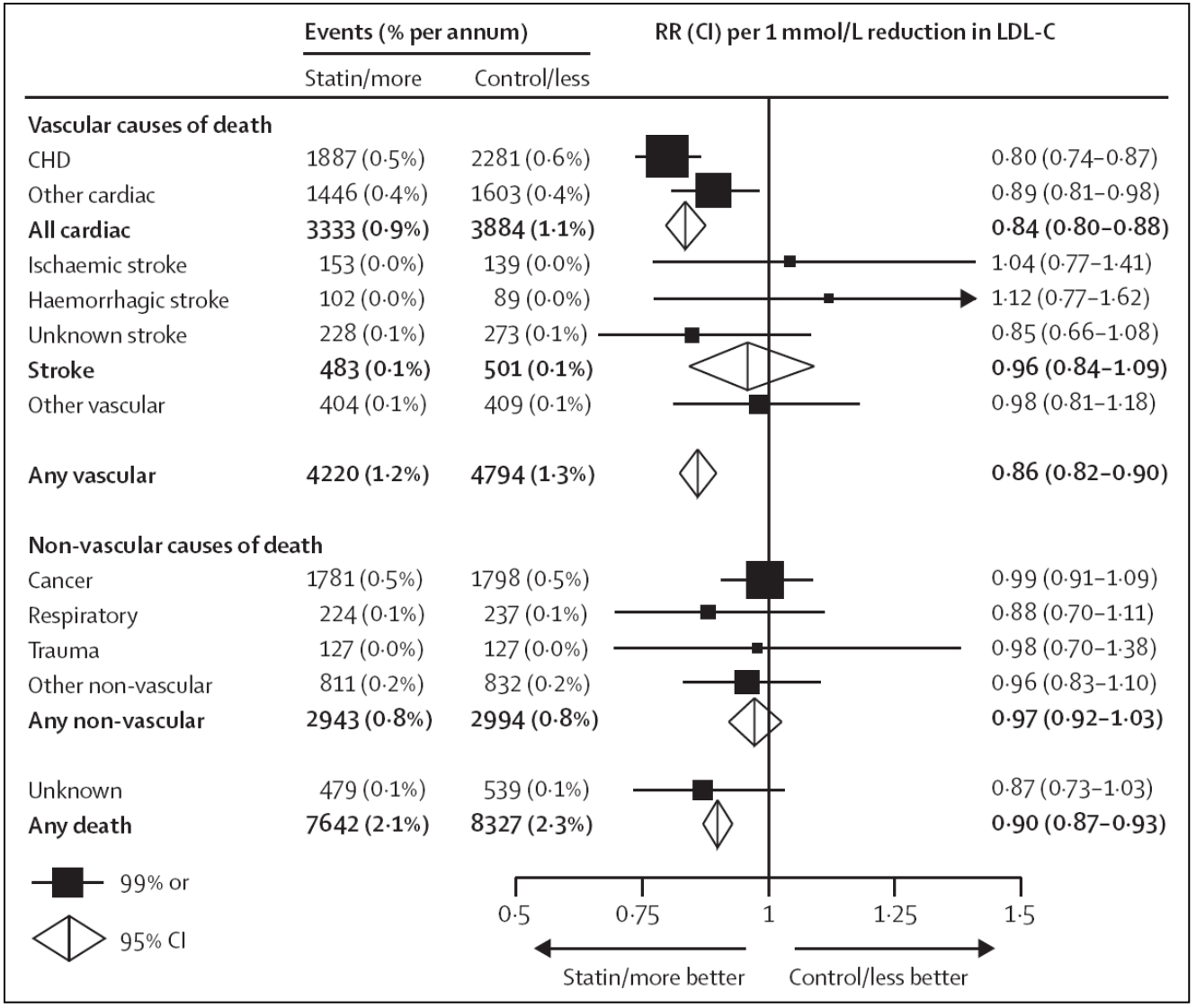
Cholesterol Treatment Trialists' (CTT) Collaboration, Lancet 2010; 376: 1670–81

Effects of Statins on Major Vascular Event



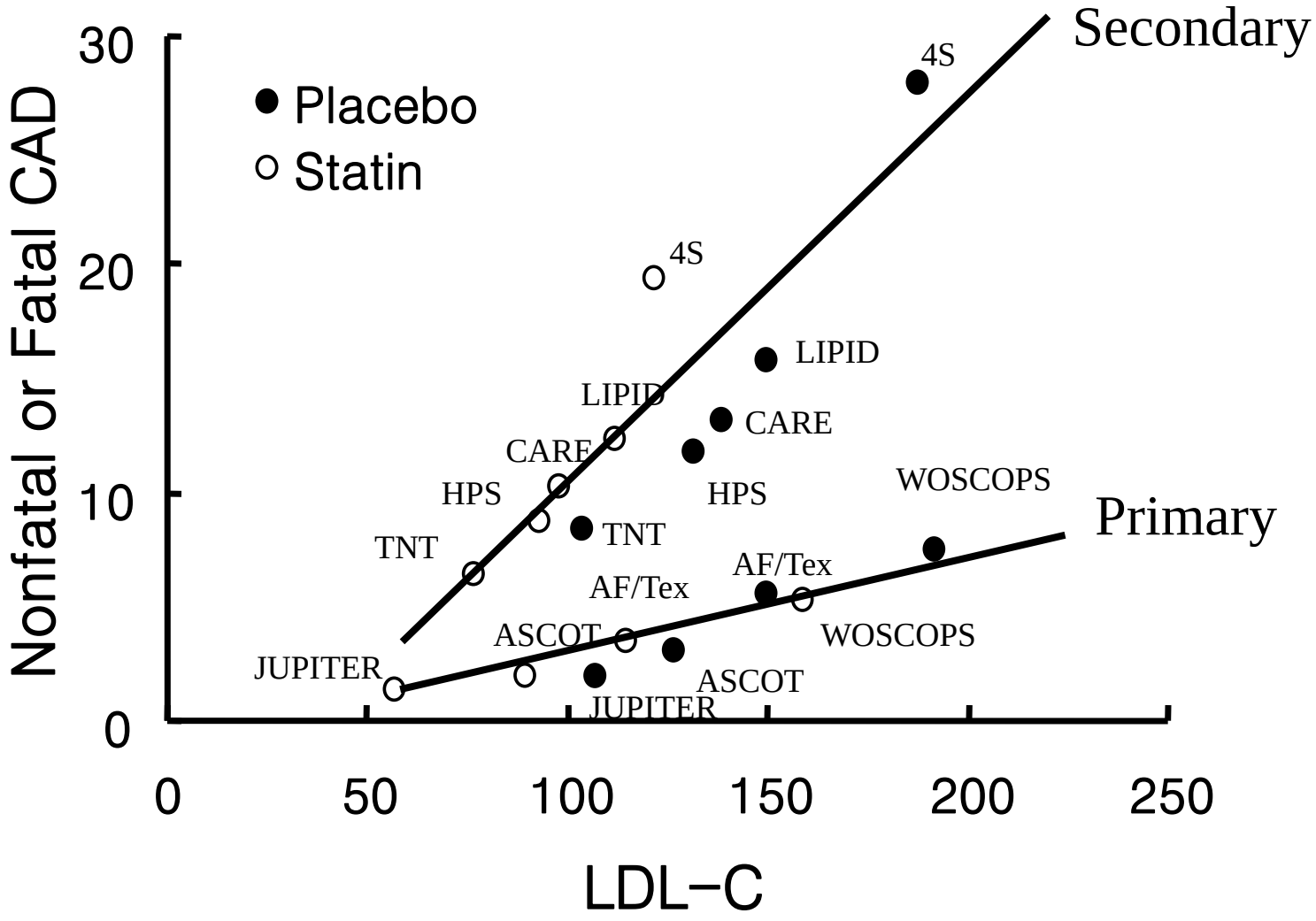
Cholesterol Treatment Trialists' (CTT) Collaboration, Lancet 2010; 376: 1670–81

Effects of Statins on Cause-specific Mortality



Cholesterol Treatment Trialists' (CTT) Collaboration, Lancet 2010; 376: 1670–81

LDL-C and Nonfatal or Fatal CAD



Prevention of CHD with Fibrate

Before HMG CoA Reductase Inhibitor

	Mean TC Difference(%)	Duration (years)	No. of Subjects	All Death	CHD Death	Coronary Event
Primary Prevention						
Helsinki Heart Study	9.9	5	2051/2030	0	0	+
Gemfibrozil						
WHO, Clofibrate	9	5.3	5331/5296	-	0	+
Follow-up		9.6		0	0	
Secondary Prevention						
Coronary Drug Project						
Clofibrate	6.5	6.2	1103/2789	0	0	0
		15		0	0	0
Newcastle, Clofibrate	11	5	244/253		+	

+; Effective, 0: Ineffective, -: Adverse for Prevention of CHD