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Postprandial Hyperlipidemia and Atherosclerosis

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COI Disclosure

Shizuya YAMASHITA, MD, PhD, FAHA, FJCC

① Consultation fees: Kowa, Sanwakagaku Kenkyusho, Skylight Biotec

② Stock ownership/profit: none

③ Patent fees: none

④ Remuneration for lecture: MSD, Bayer, Kowa

⑤ Manuscript fees: none

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⑦ Scholarship fund: none

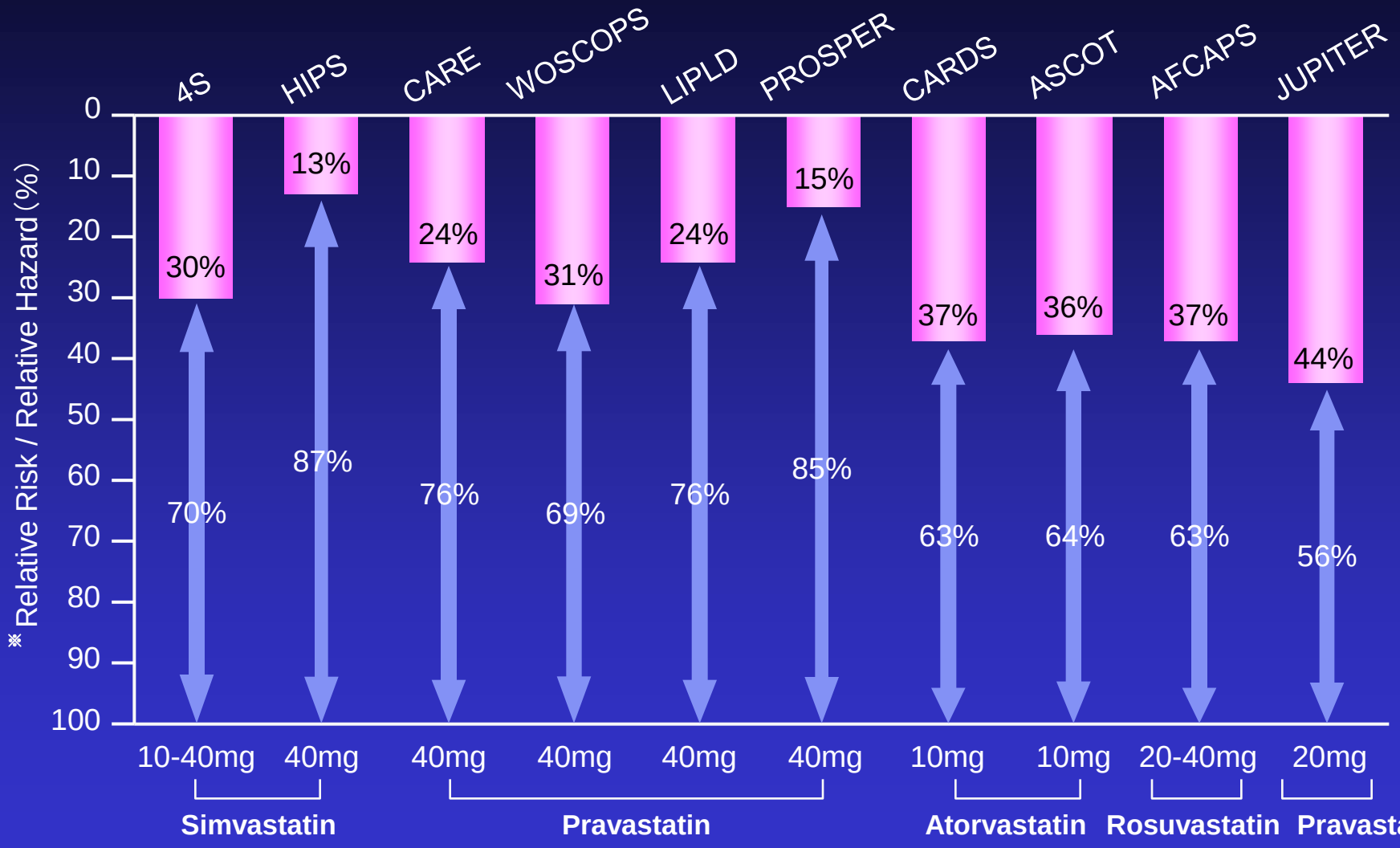
⑧ Affiliation with endowed department: none

⑨ Other remuneration such as gifts: none

Topics

- Residual Coronary Risks
- Clinical Significance of Hypertriglyceridemia and Increased Remnants
- Methods for Evaluation of Remnants
- Apo B-48 Levels in Relation to Diseases
- Postprandial Hyperlipidemia and Atherosclerosis
- Treatment of Postprandial Hyperlipidemia

Residual Coronary Risks



Chapman MJ et al. *Pharmacol Therapeutics* 2010;126:314-345.

Statin can reduce the CV risk by 20-35%, but there are still residual event risks after cholesterol-lowering therapy. Furthermore, coronary plaques regress very limitedly on IVUS and we cannot usually see the widening of vessel lumen.

↓

The reduction of LDL-C alone may not be adequate?

↓

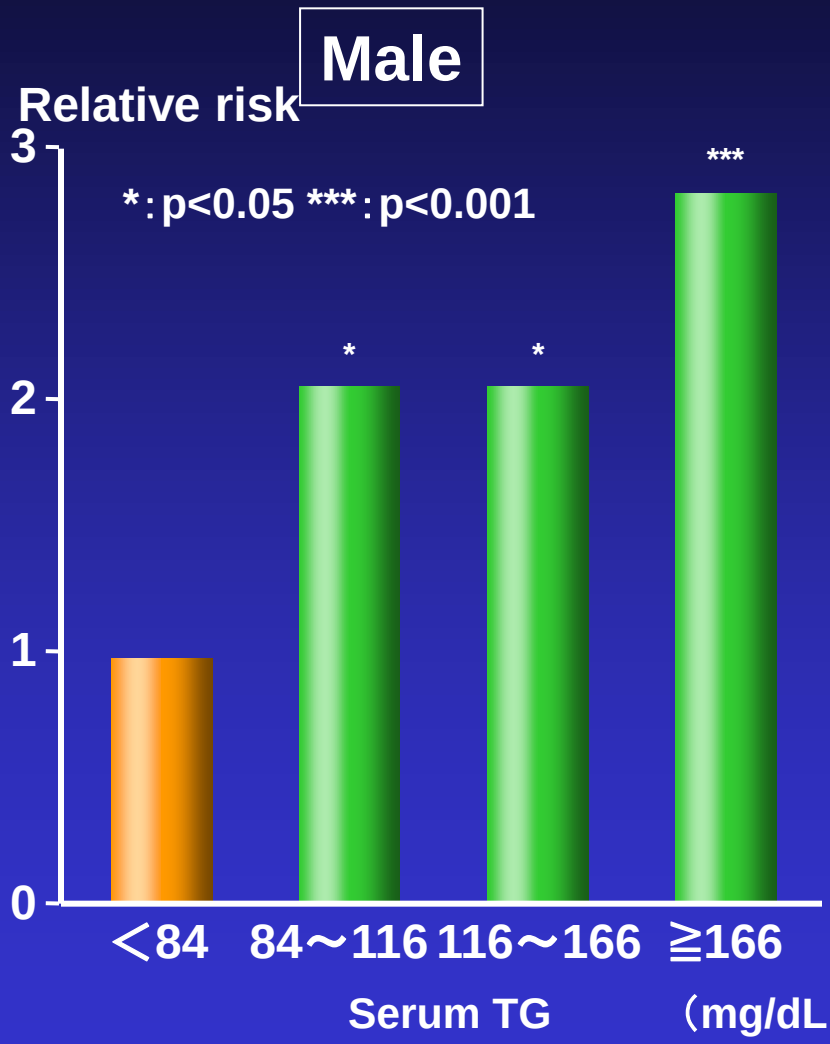
Beyond LDL-cholesterol

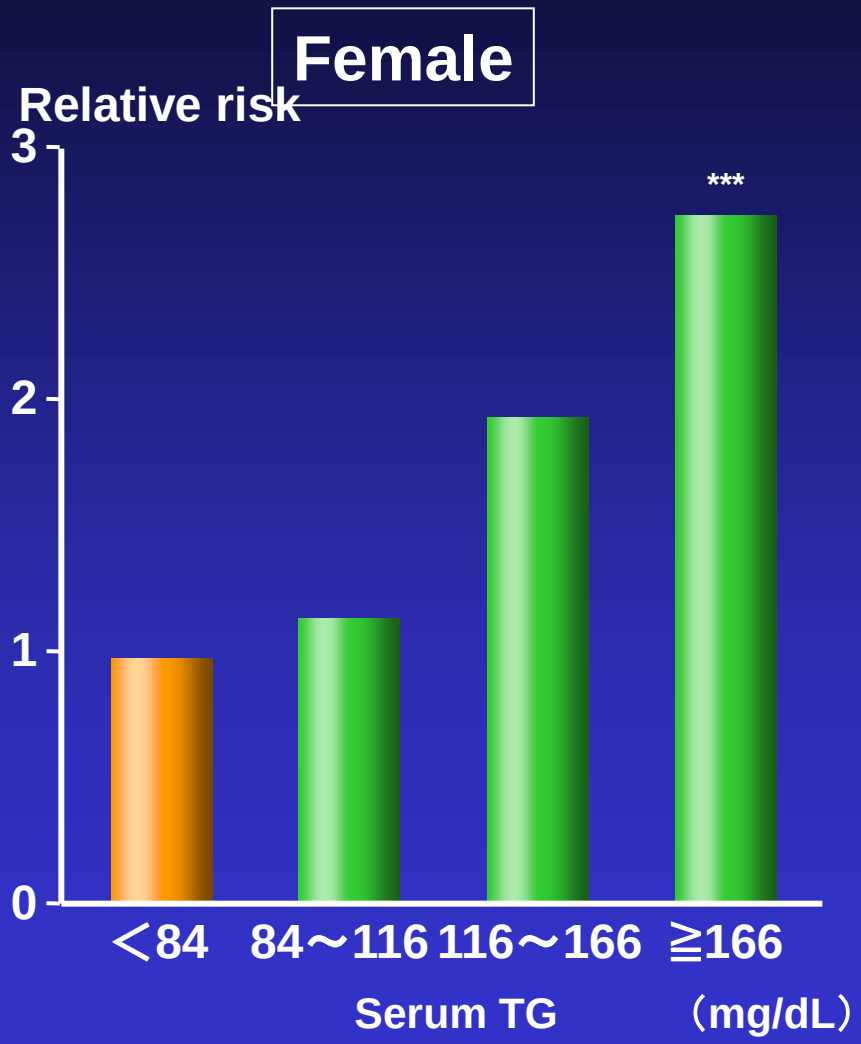
Beyond LDL-cholesterol (Residual risk)

- *Hypertension*
- *Diabetes mellitus*
- *Metabolic syndrome*
- *Low HDL-C*
- *Hypertriglyceridemia and postprandial hyperlipidemia*
- *Inflammation*
- *Smoking*

Triglycerides and Coronary Heart Disease
（11,068 Japanese Cases Followed for 15.5 Years）

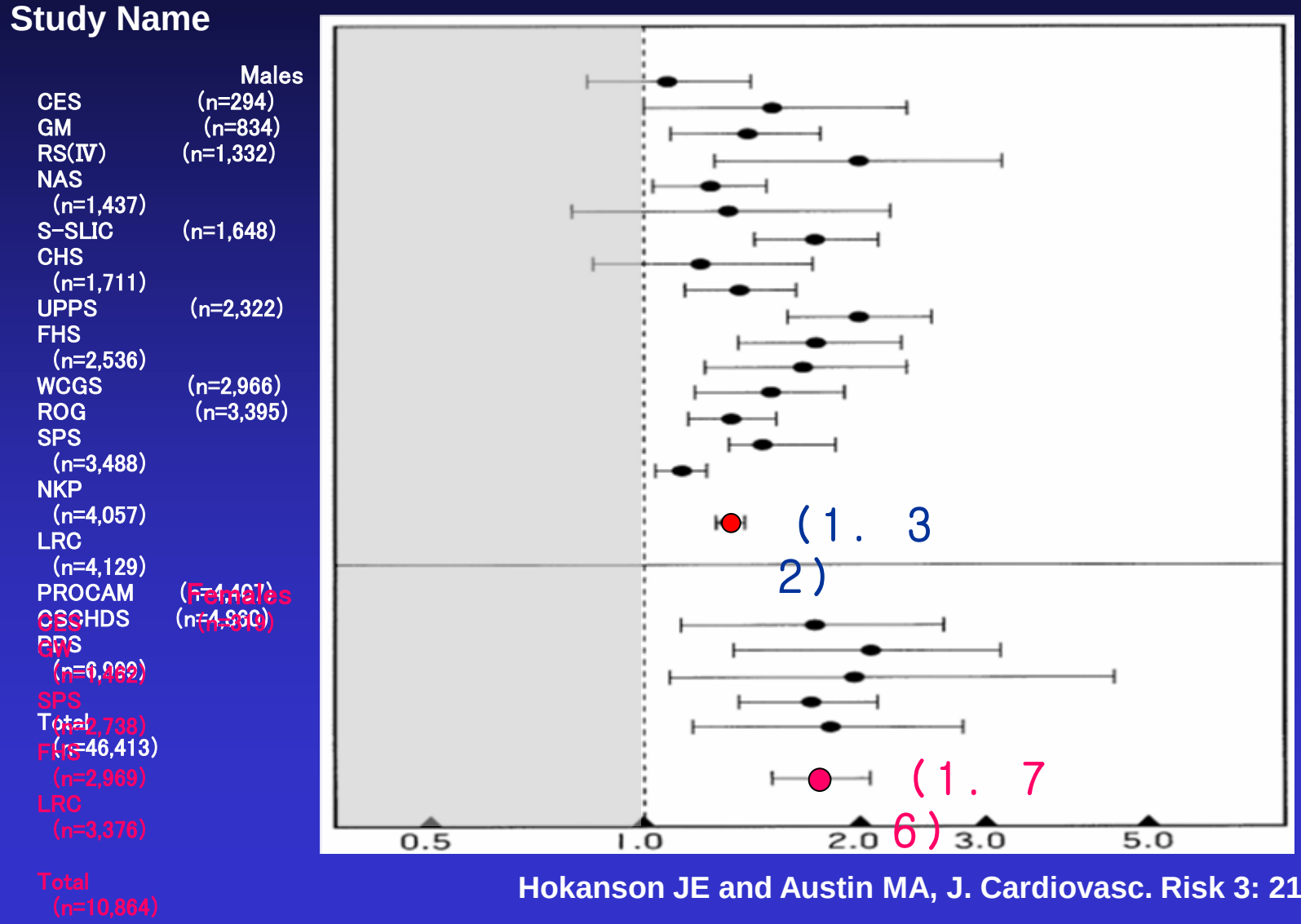
(Matched for Age, BMI, TC, Smoking, BP, Alcohol, Blood sugar, Time after Meal, and Menopause）





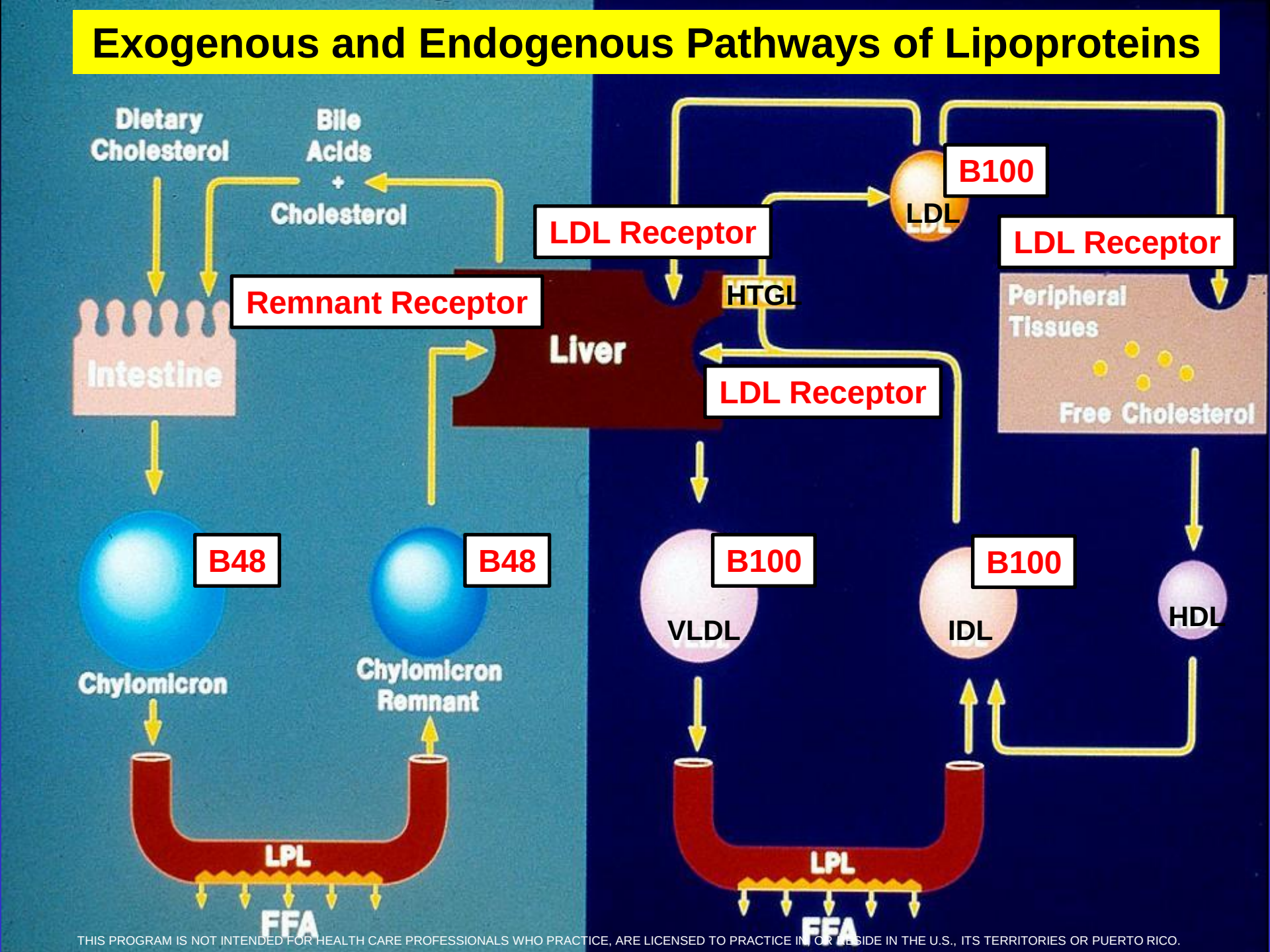
Iso H. et al. ：Am J Epidemiol. 2001；153：490-499

Plasma TG Level Is A Risk Factor For Cardiovascular Disease Independent of HDL-C Level: A Meta-analysis of 17 Population-based Prospective Studies

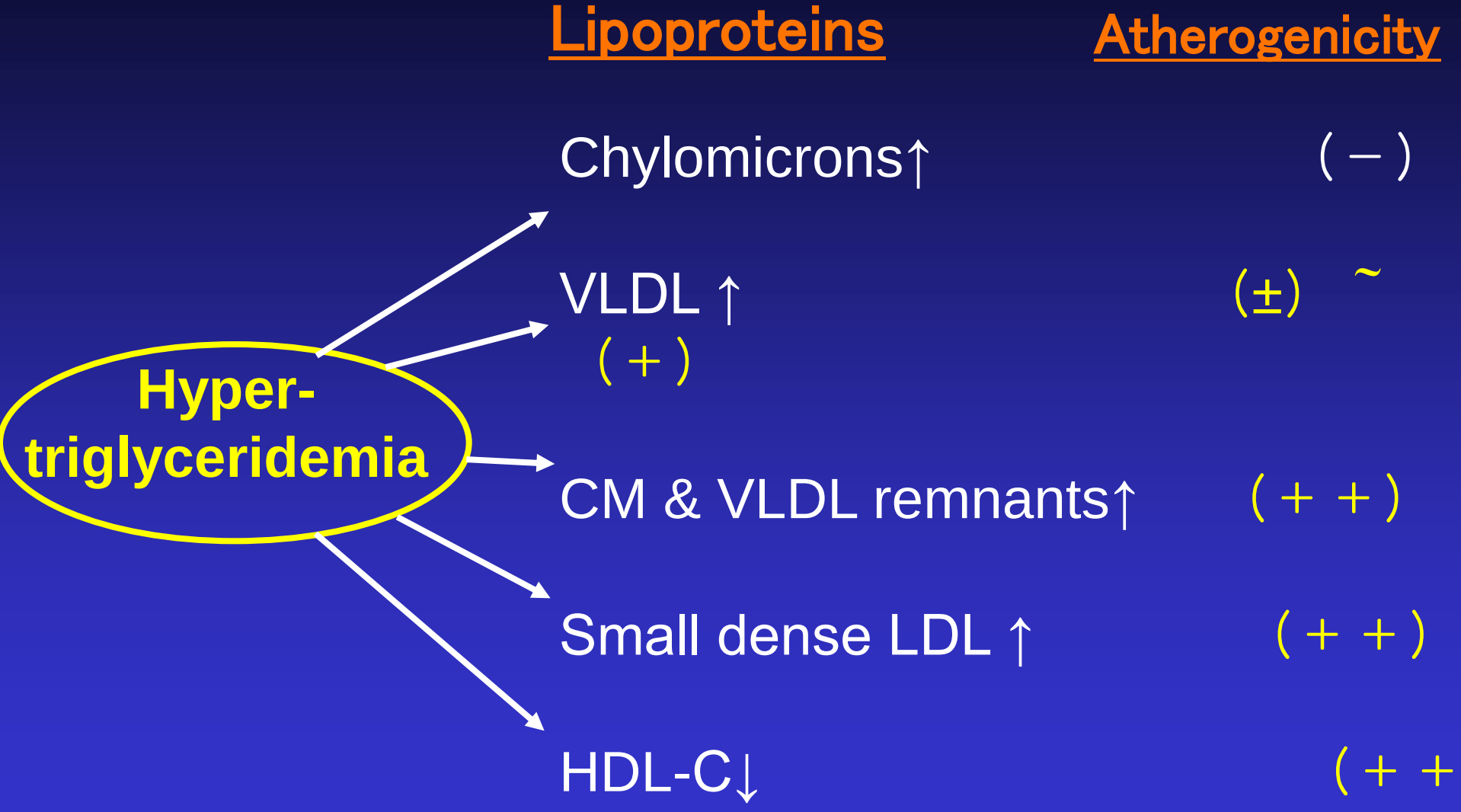


Hokanson JE and Austin MA, J. Cardiovasc. Risk 3: 213-219, 1996

Exogenous and Endogenous Pathways of Lipoproteins



Atheogenicity of Lipoprotein Abnormalities Associated with Hypertriglyceridemia



What Are Remnants ?

Chylomicron → (LPL) → Chylomicron Remnant

VLDL → (LPL) → IDL (VLDL Remnant) → (HTGL) → LDL

Serum lipids and lipoproteins in patients with myocardial Infarction

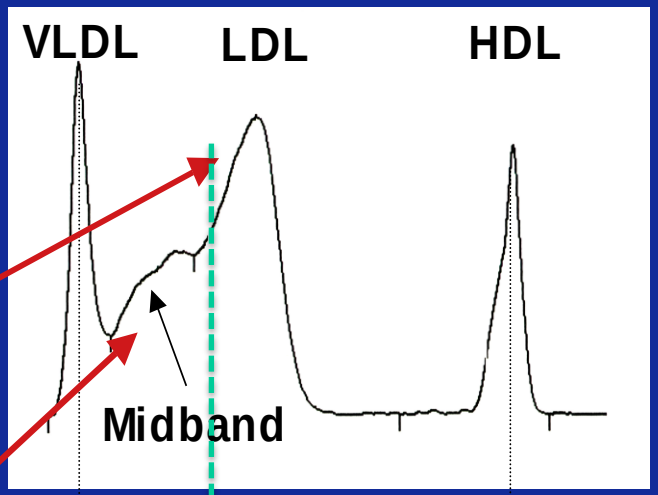
	Myocardial Infarction	Control
Male		
Number	70	23
T-CH	208±44	197±31
TG	158±84*	116±63
HDL-C	36±8***	48±14
VLDL-C	24±18	16±15
VLDL-TG	83±73	59±52
VLDL-(C/TG)	0.31±0.07*	0.27±0.08
IDL-C	11±5*	8±4
IDL-TG	15±10*	10±6
LDL-C	136±41	124±27
Female		
Number	27	10
T-CH	237±47	209±45
TG	161±57***	82±21
HDL-C	41±11**	57±19
VLDL-C	24±23*	8±5
VLDL-TG	77±84	30±15
VLDL-(C/TG)	0.31±0.07	0.26±0.10
IDL-C	17±9*	9±5
IDL-TG	20±8***	10±5
LDL-C	156±36	135±27

Determination of Remnants

- **Electrophoresis**
  - Agarose electrophoresis（broad β pattern）
  - PAG electrophoresis （midband, broad β pattern）
- **Ultracentrifugation**
  - IDL-cholesterol
- **Immunoaffinity chromatography**
  - RLP-cholesterol, RLP-TG
- **Direct method（RemL-C）**
- **Apo B-48（ELISA, CLEIA）**

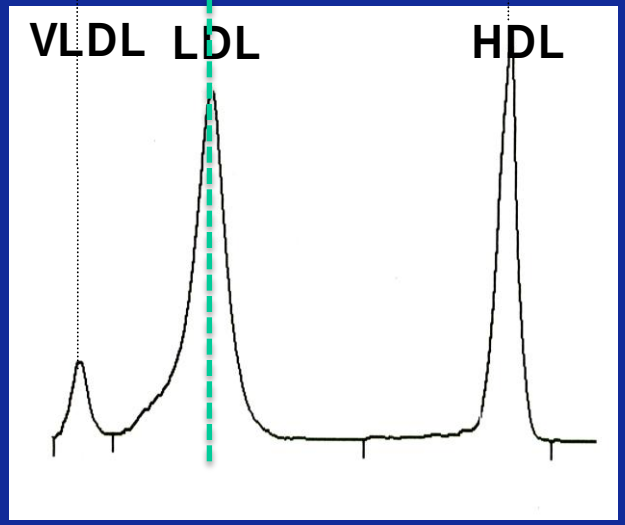
PAG Disc Electrophoresis

Small dense LDL



TC 231 mg/dl
TG 367 mg/dl
HDL-C 35 mg/dl

Remnants



TC 192 mg/dl
TG 85 mg/dl
HDL-C 56 mg/dl

Methods for Measuring RLP-C（JIMRO）

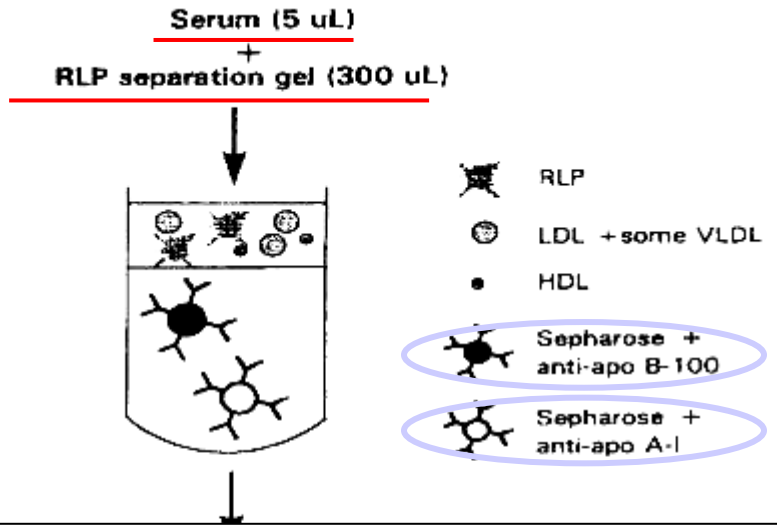
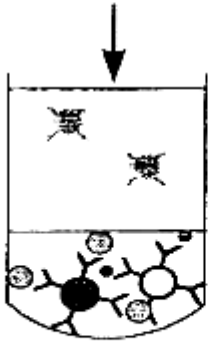


Fig. 1 *Schematic procedure of separation and determination of remnant-like particles.*

FDA Approved：
- Risk for CHD（2000）
- Diagnosis of Familial Type III Hyperlipidemia（1999）

Incubation with Anti Apo A-Ⅰ、B-100 Antibodies Attached with Sepharose Beads for 3 Hours

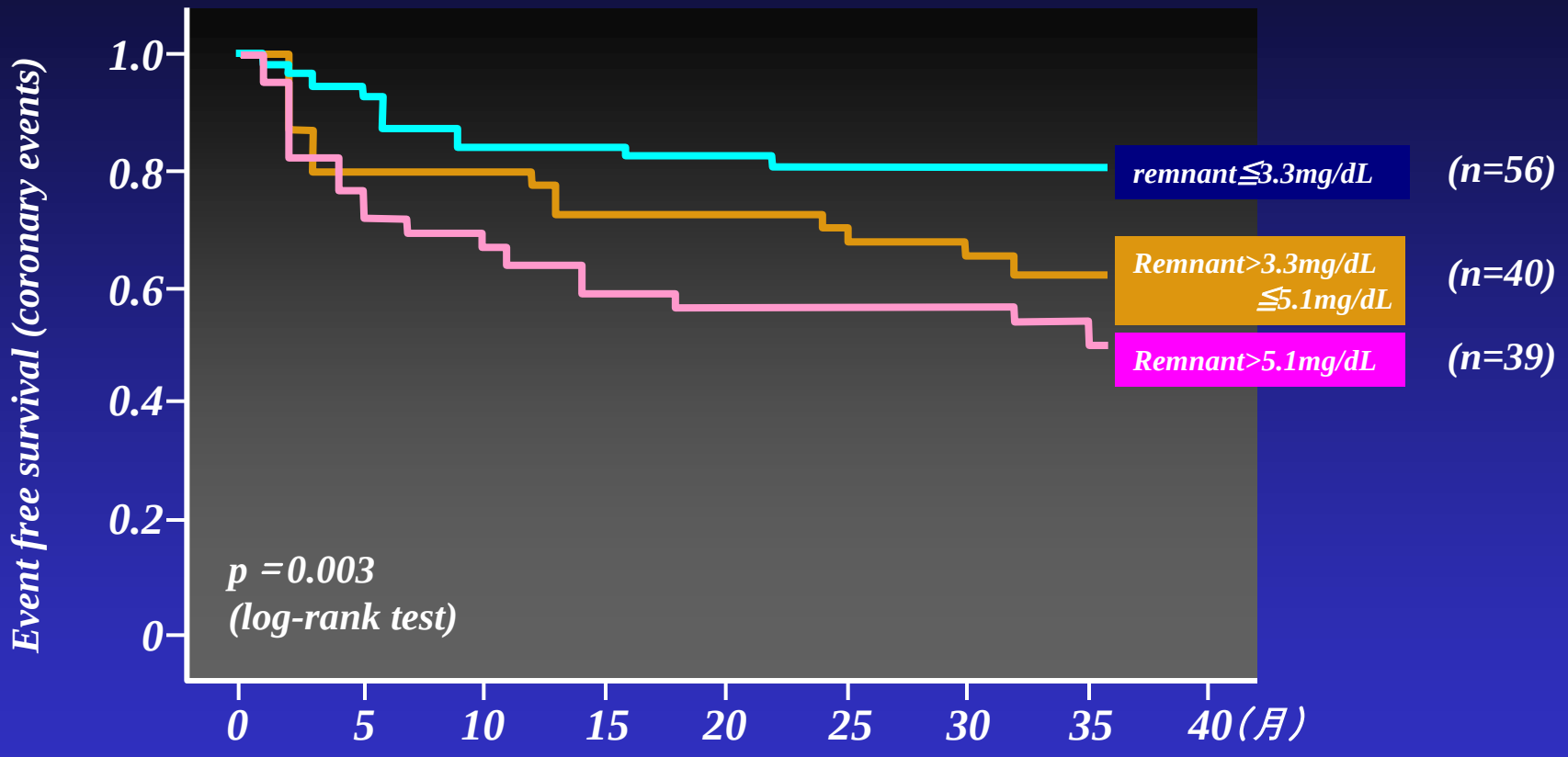
Low-speed centrifugation



→ Remnant-like Particles (RLP)：Unadsorbed Fraction

Adsorbed lipoproteins Precipitated

Remnants Are the Critical Risk Factor of Cardiovascular Events



Subjects：patients with cardiovascular events 147 cases male97 cases, age 65±9.7 years
Study duration： 26.8±13.9 months

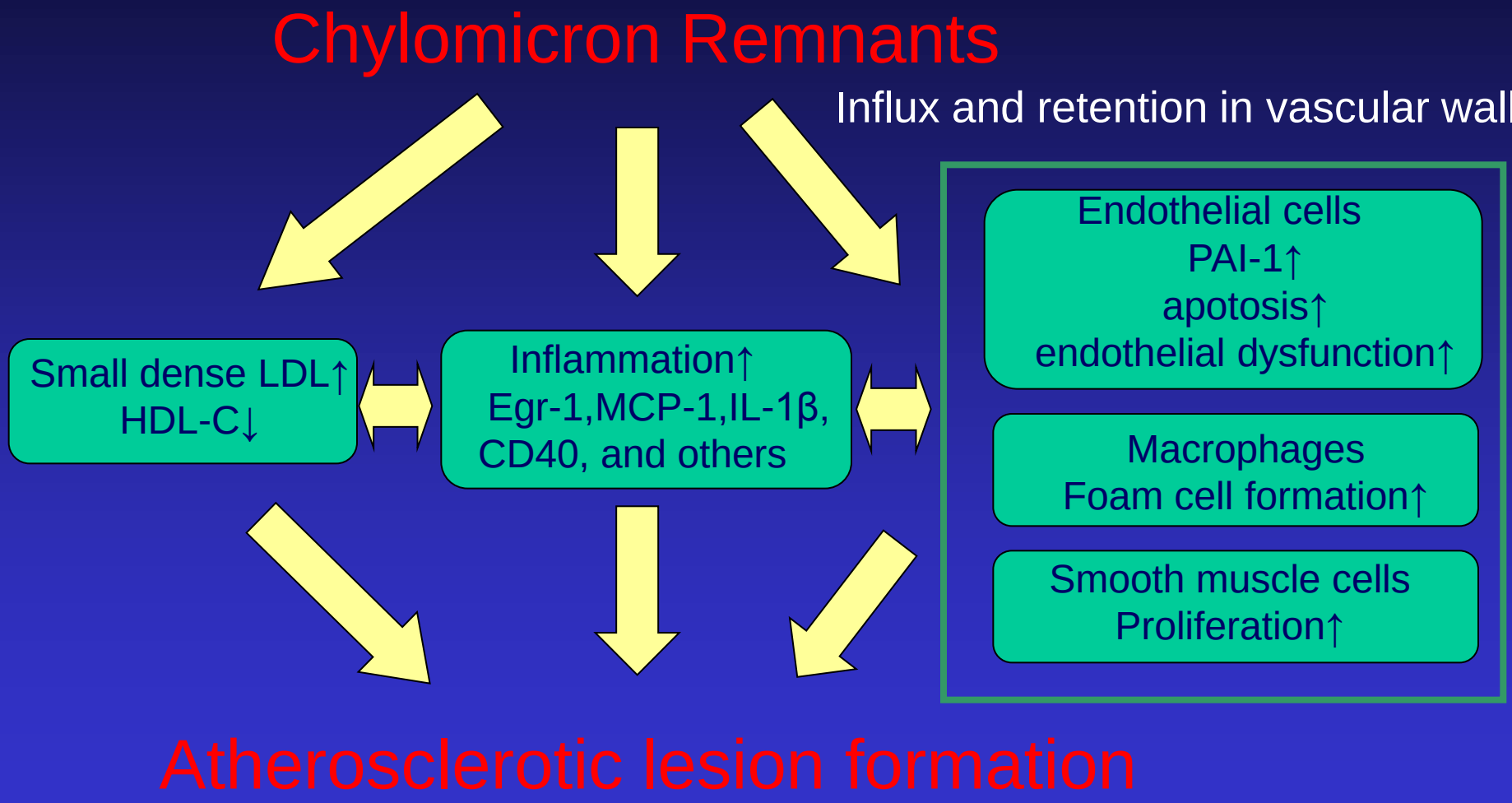
Kugiyama K. et al.: Circulation 1999: 99; 2858-2860.

Why Are Remnants Important?

- Chylomicron remnants and VLDL remnants (IDL) are taken up by macrophages without oxidation, forming foam cells

- It is important to assess the increase of remnants and decrease them, which leads to the attenuation of development of atherosclerotic cardiovascular diseases

Chylomicron Remnants Contribute to Form Atherosclerotic Lesions Via Several Mechanisms

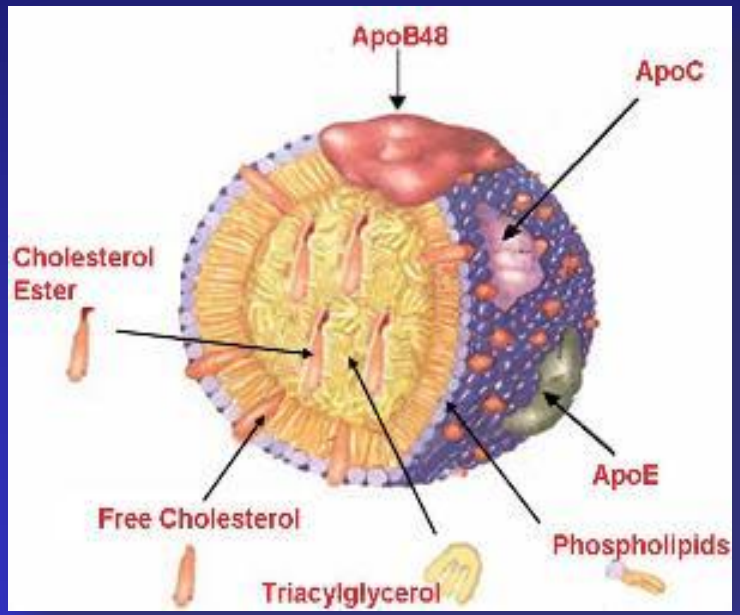


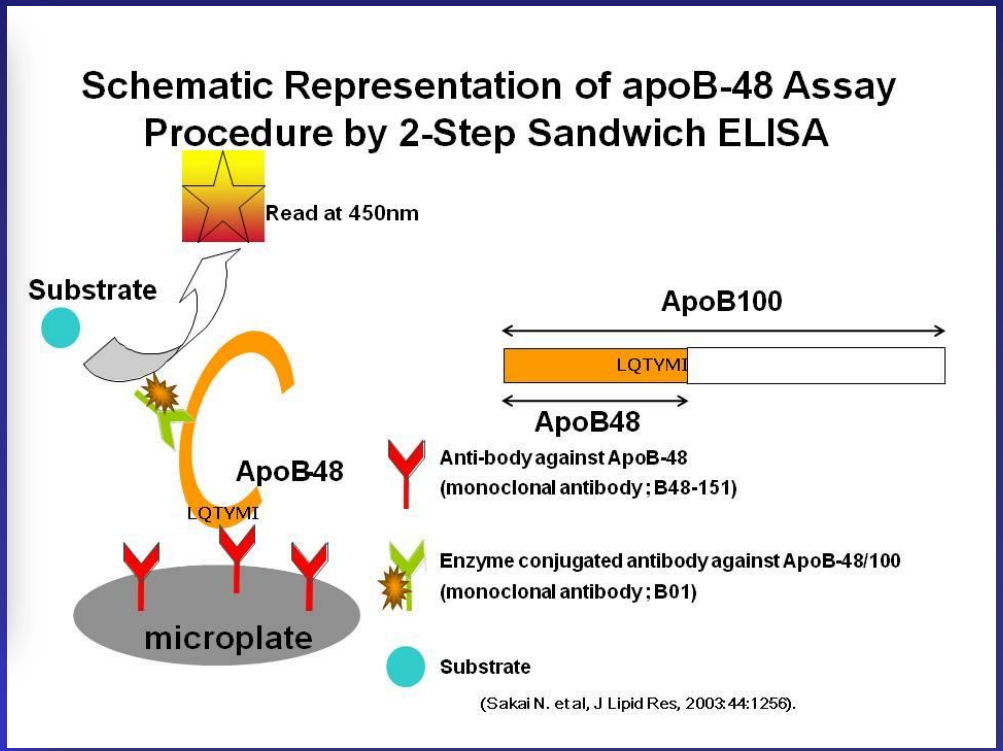
Fujioka Y, et al: J Atheroscler Thromb 16:145-154, 2009

Measurement of fasting serum apoB-48 levels in normolipidemic and hyperlipidemic subjects by ELISA[1]

Naohiko Sakai,[2,3,*] Yoshiaki Uchida,[2,†] Koji Ohashi,[*] Toshiyuki Hibuse,[*] Yasuhiko Saika,[*] Yoshiaki Tomari,[*] Shinji Kihara,[*] Hisatoyo Hiraoka,[*] Tadashi Nakamura,[*] Satoru Ito,[4,†] Shizuya Yamashita,[*] and Yuji Matsuzawa[*]

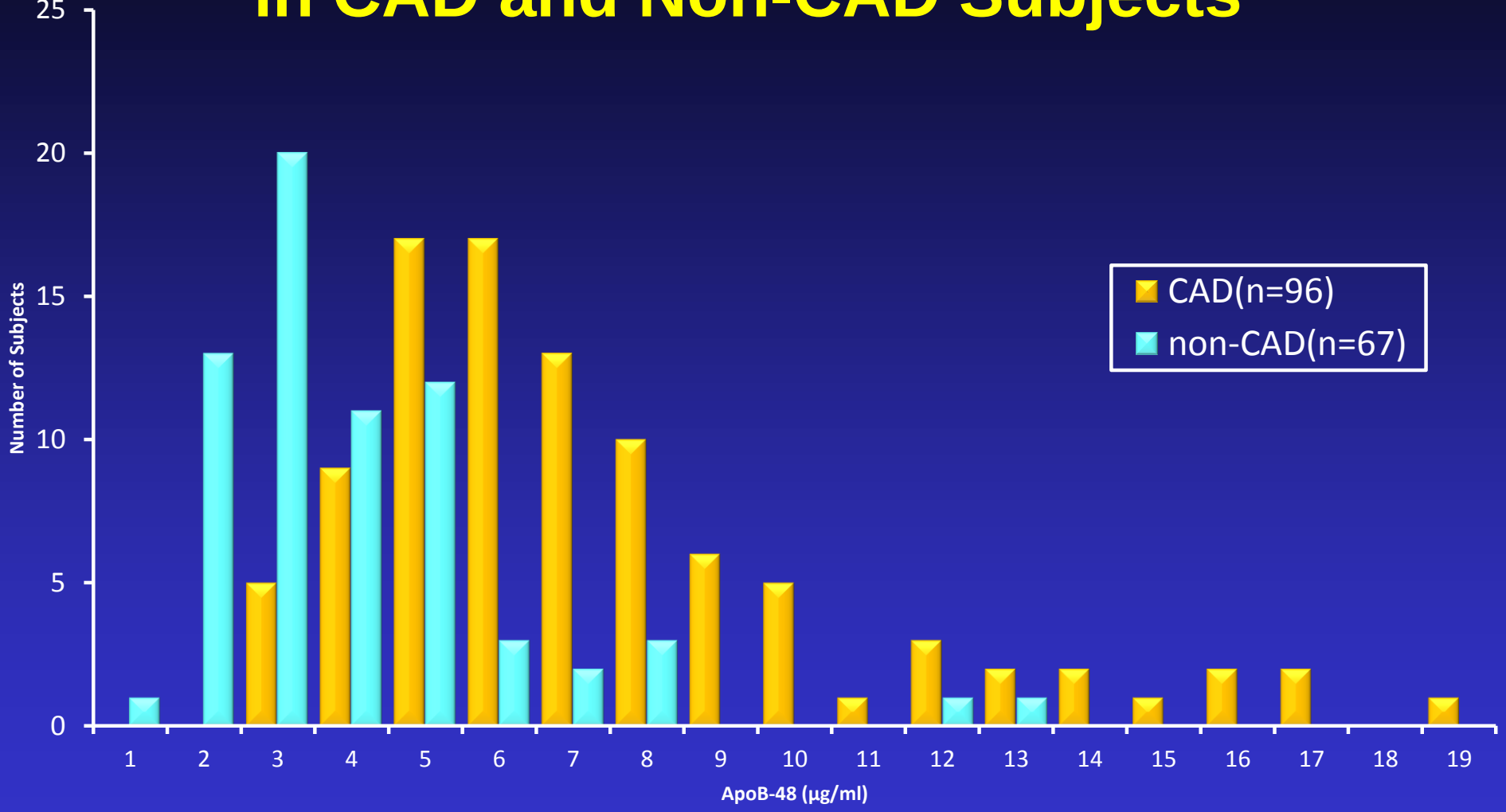
Department of Internal Medicine and Molecular Science,[*] Osaka University Graduate School of Medicine, B5, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; and Diagnostic Research Laboratories,[†] Fujirebio, Inc., 51 Komiya-cho, Hachioji, Tokyo 192-0031, Japan





Sakai N. et al: J Lipid Res 44: 1256, 2003

Distribution of Fasting Serum Apo B48 Levels in CAD and Non-CAD Subjects

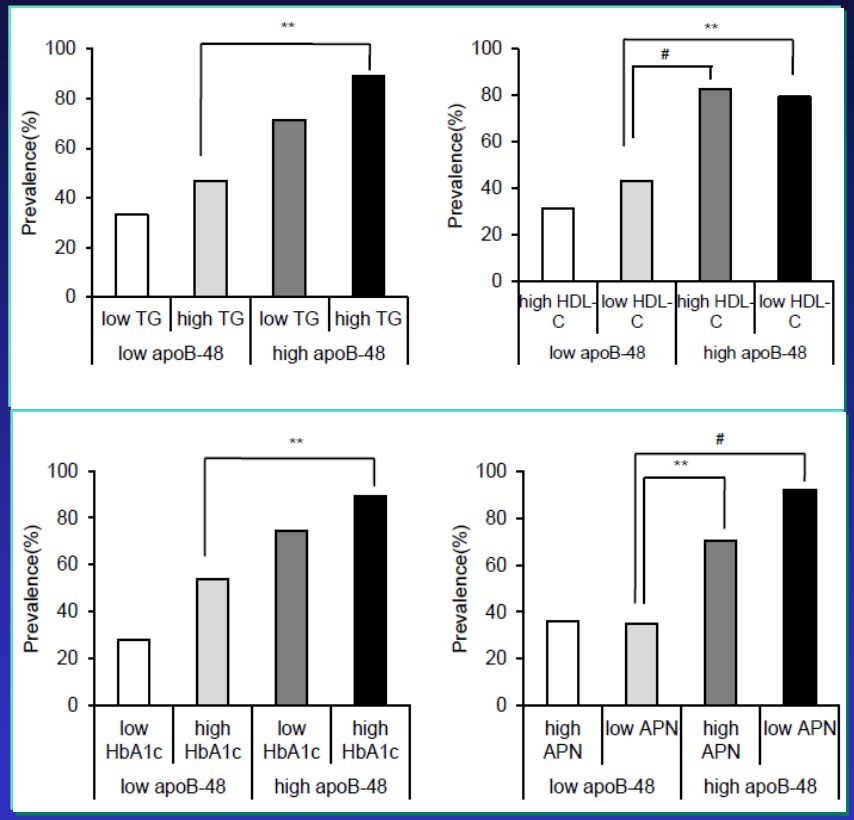


Masuda D. et al: Eur J Clin Invest 2013

Fasting ApoB-48 Level Is Correlated with Prevalence of Coronary Heart Disease

	Univariate p value	Multivariate p value
age	0.1581	-
sex	0.3698	-
Log-BMI	0.4645	-
Smoking	0.0492	-
TC	0.7440	-
LDL-C	0.8508	-
HDL-C	0.0085	0.3721
TG	0.0017	0.1098
Systolic BP	0.9747	-
Diastolic BP	0.6757	-
FPG	0.0081	0.6110
HbA1c	0.0008	0.3036
Log-apoB-48	<0.0001	<0.0001
Log-APN	0.0239	0.6039

Univariate and Multivariate Analyses of correlations between CHD and various parameters
Univariate;Pearson's correlation analysis,
Multivariate;Stepwise multiple regression analysis.



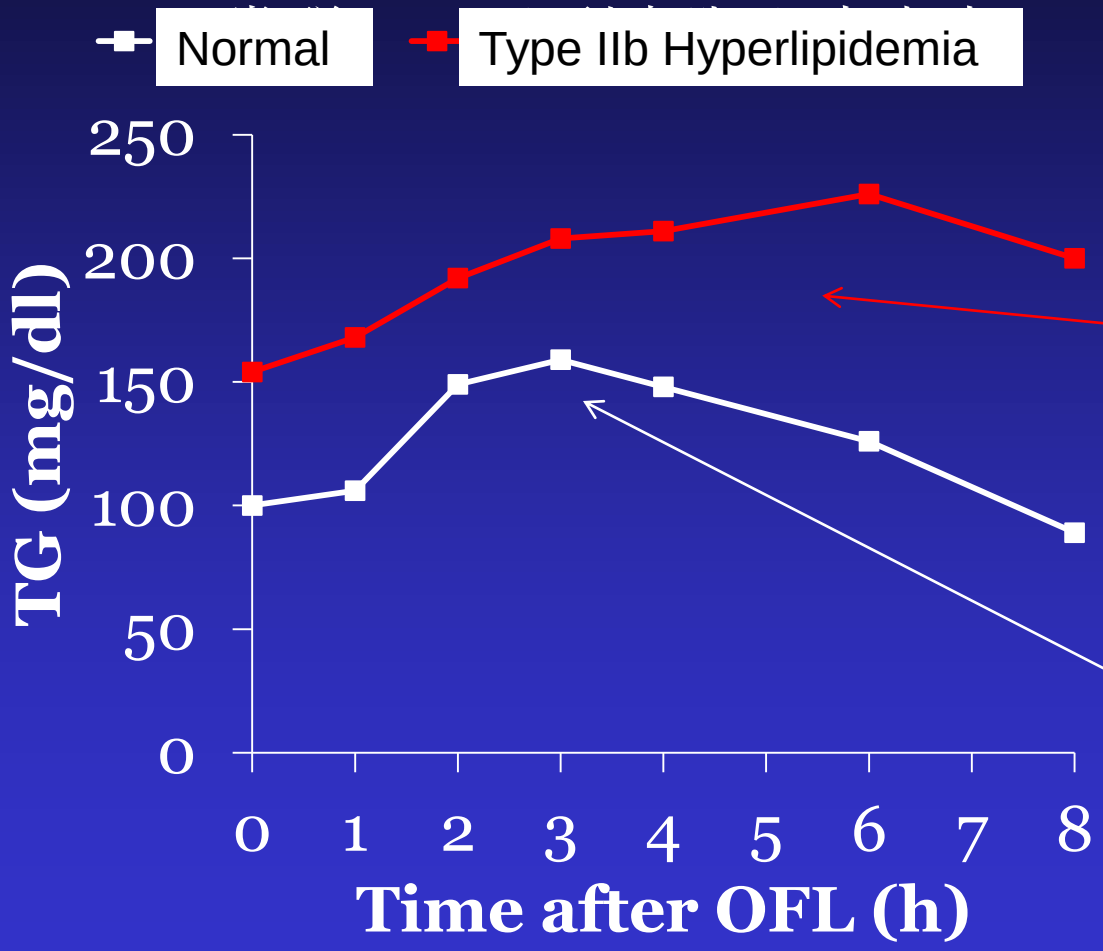
Masuda D, et al, Eur J Clin Invest

Postprandial Hyperlipidemia

- Increased TG-rich chylomicron remnants after meals
- Hypertriglyceridemia is prolonged after meals
- Highly atherogenic state

Zilversmit DB: Circulation 60:473-85, 1979

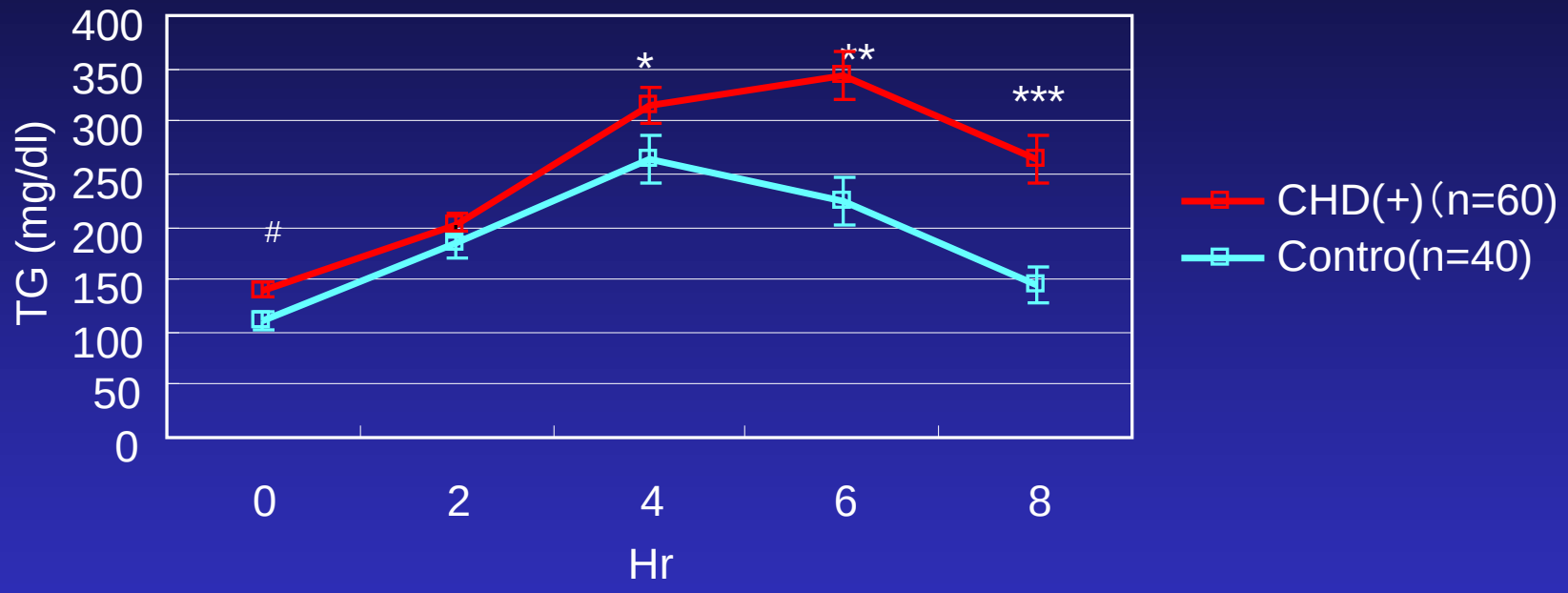
Postprandial Hyperlipidemia in Patients with Type IIb Hyperlipidemia



- TG peak is prolonged
- TG reduction is impaired
- High TG level at fasting

- TG peak is 3-4 h after meal in control subjects
- Returns to fasting TG level after 6-8 h

Postprandial Hyperlipidemia in Patients with Coronary Heart Disease



 # P<0.05 (CHD(+) vs control)

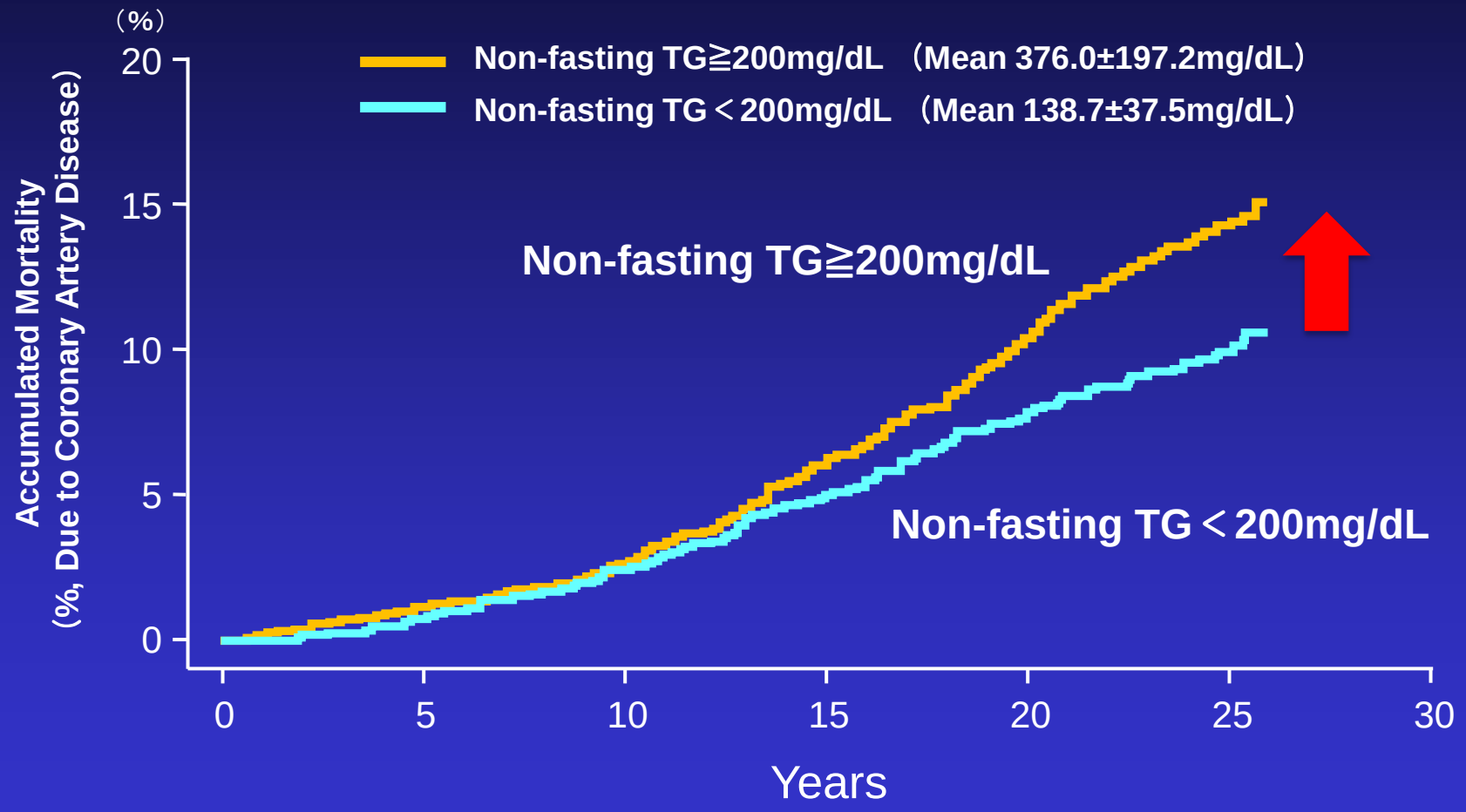
*** P<0.05 (CHD(+) vs control) ,** P<0.01(CHD(+) vs control),*** P<0.01 (CHD(+) vs control)**

fatty meal contained 729 kcal per square meter of body surface and consisted of 5.3 g protein, 24.75 g carbohydrate, 240 mg cholesterol, and 65.2 g fat (from heavy whipping cream) with a polyunsaturated to saturated fat ratio of 0.06

Patsh JR et al: *ATVB* 12:1336-1345, 1992

Postprandial Hyperlipidemia Is a Risk for Coronary Artery Disease Mortality

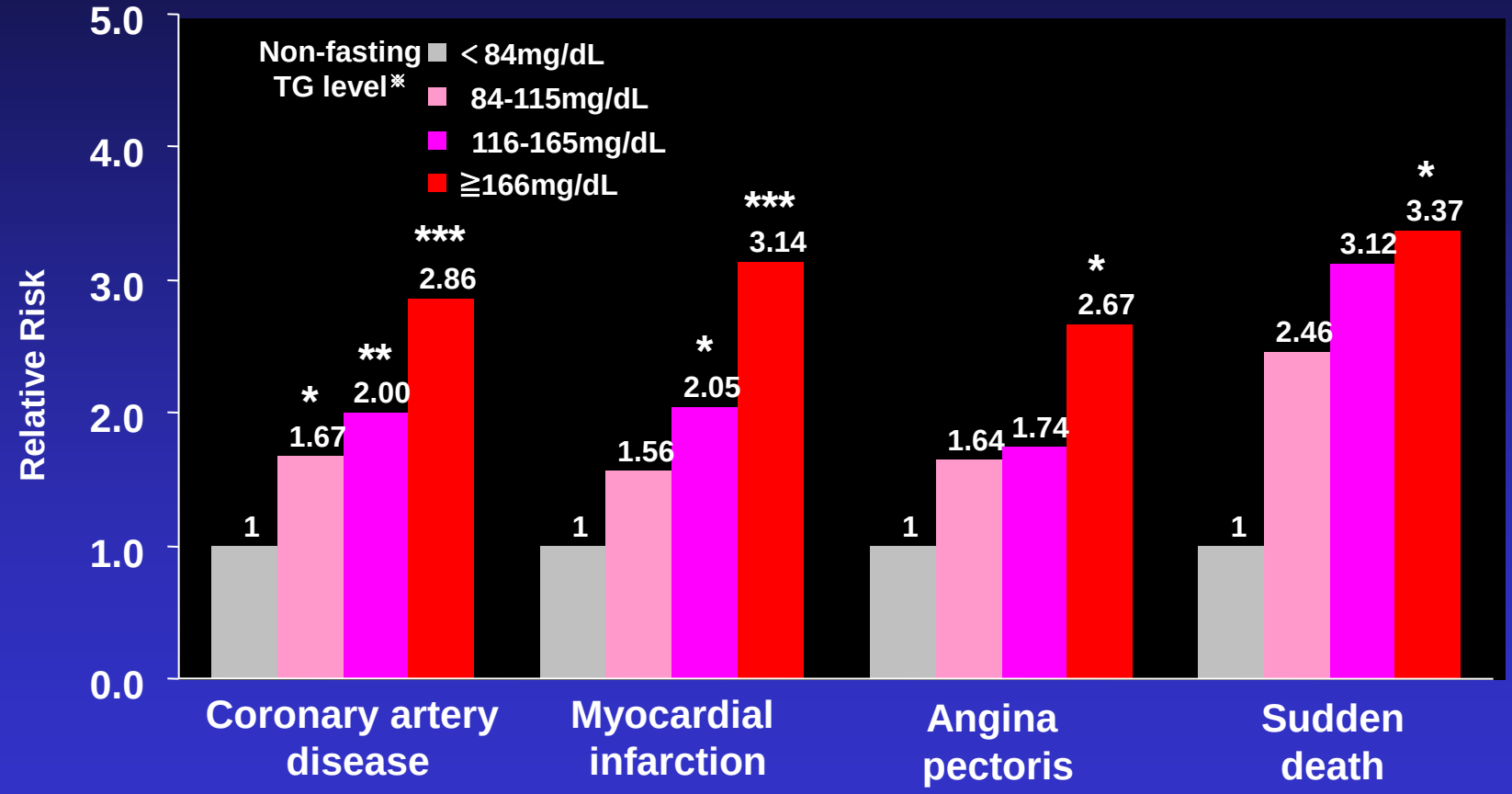
■Subjects Enrolled in MRFIT Study (n=2,809)



Eberly LE et al.: *Arch Intern Med* 163: 1077-1083, 2003

Postprandial Hyperlipidemia (Non-fasting Hypertriglyceridemia) Is a Critical Risk Factor of Cardiovascular Events in a Japanese Population

■Subjects：Normocholesterolemic Japanese (n=1,068)



*p<0.05, **p<0.01, ***p<0.001

Iso H et al.: *Am J Epidemiol* 153: 490-499, 2001

Copenhagen City Heart Study

Odds Ratio for Ischemic Stroke in Relation to Non-fasting TG and Total Cholesterol Levels

TG(mg/dL)	Patients number(%) ／Events	TG	Total Chol	Total Chol (mg/dL)	atients number(%) ／Events
Females					
Age-adjusted					
＜89	2,210 (29) / 183	p<0.001	p=0.17	＜193	1,167 (15) / 76
89～176	3,985 (53) / 451			193～231	2,246 (30) / 218
177～265	985 (13) / 146			232～270	2,197 (29) / 259
266～353	241 (3) / 29			271～308	1,300 (17) / 187
354～442	96 (1) / 17	8		309～347	480 (6) / 69
≧443	62 (1) / 11	15		≧348	189 (2) / 28
Multivariate adjusted *					
＜89	2,210 (29) / 183	p<0.001	p=0.18	＜193	1,167 (15) / 76
89～176	3,985 (53) / 451			193～231	2,246 (30) / 218
177～265	985 (13) / 146			232～270	2,197 (29) / 259
266～353	241 (3) / 29			271～308	1,300 (17) / 187
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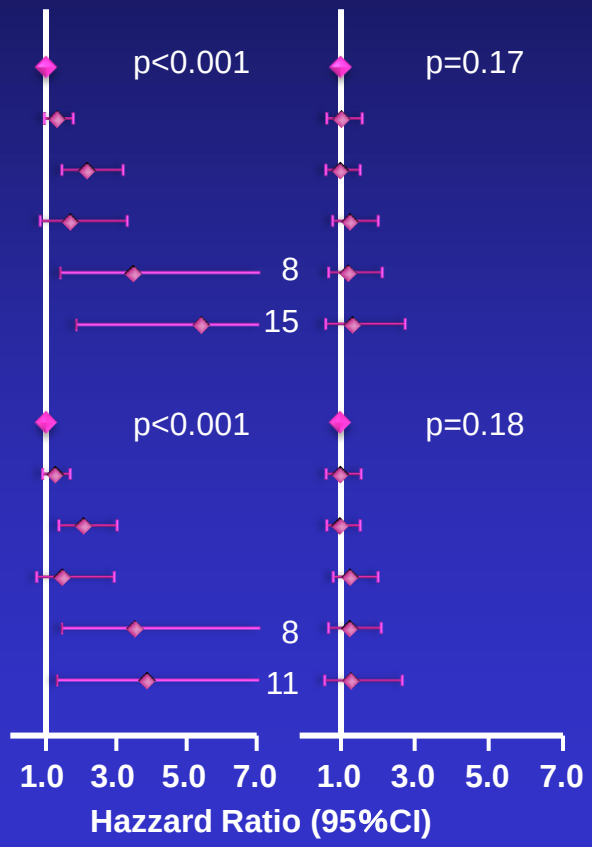


Varbo A, et al: Ann Neurol (in press)

Factors and Diseases Affecting Postprandial Hypertriglyceridemia

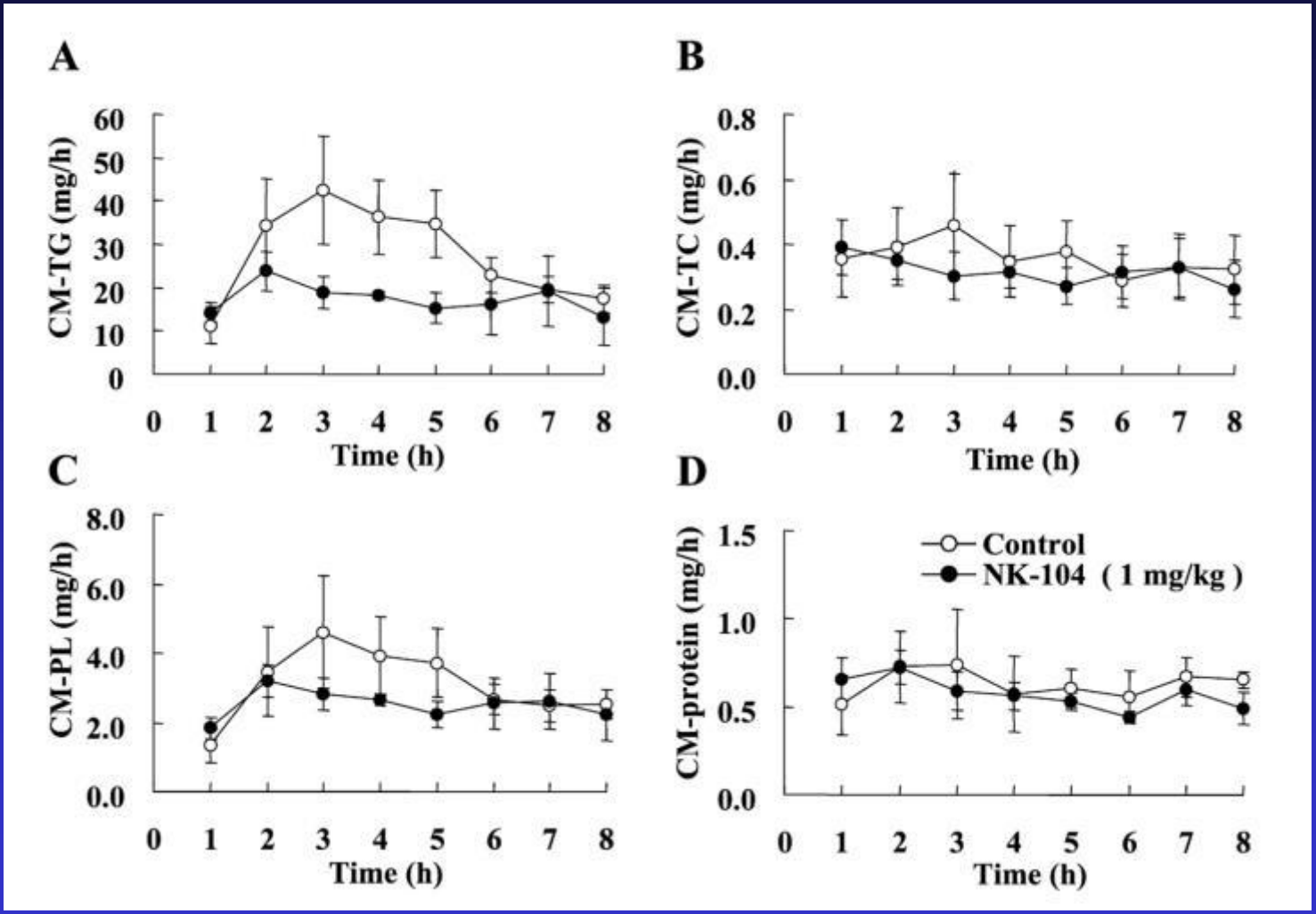
	Extent of change in postprandial lipaemia
Dietary factors	
Amount of fat (meal)	+++
Type of fat (meal)	+/ − (depending on type of fat)
Type of fat (habitual diet)	+/ − (depending on type of fat)
Carbohydrates	++
Protein (meal)	No / − (depending on type of protein)
Alcohol	++
Fibre	No / − (depending on type of fibre)
Lifestyle factors	
Physical exercise	− −
Tobacco use	++
Physiological factors	
Gender	+ (males)
Age	+
Menopausal status	+ (postmenauposal status)
Physiopathology	
Fasting triacylglycerolaemia	+++
Central obesity	++
Insulin resistance/type 2 diabetes	++

Lopez-Miranda J, et al.: Br J Nutr 98:458-473, 2007

Drug Treatment of Postprandial Hyperlipidemia

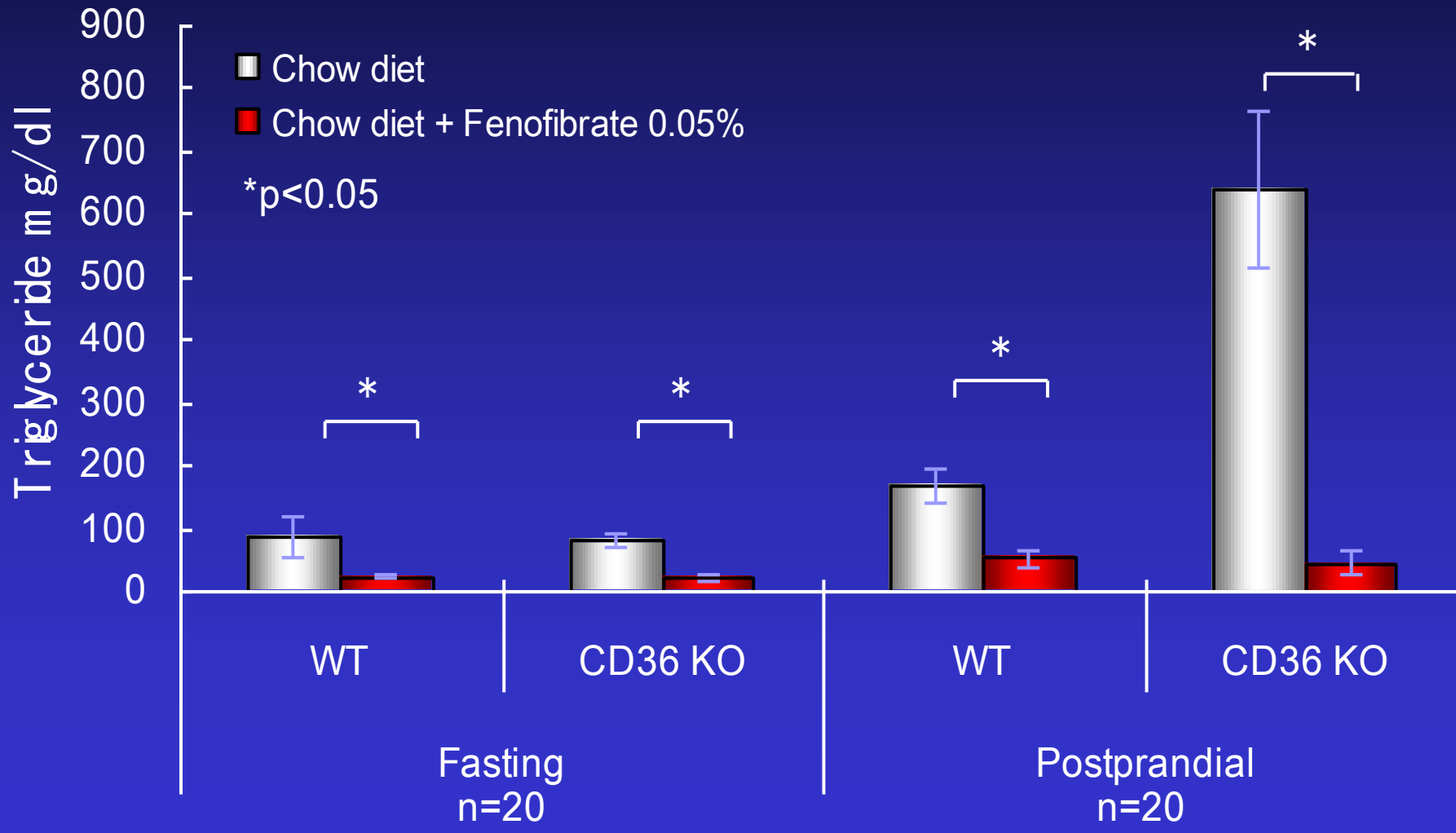
- Statins
- Fibrates
- Inhibitors of intestinal cholesterol transporter (ezetimibe)
- EPA, ω-3 fatty acids (EPA/DHA)
- Anti-diabetic drugs
- Others

Effect of Pitavastatin on Chylomicron Secretion into Lymph after OFL of Rats

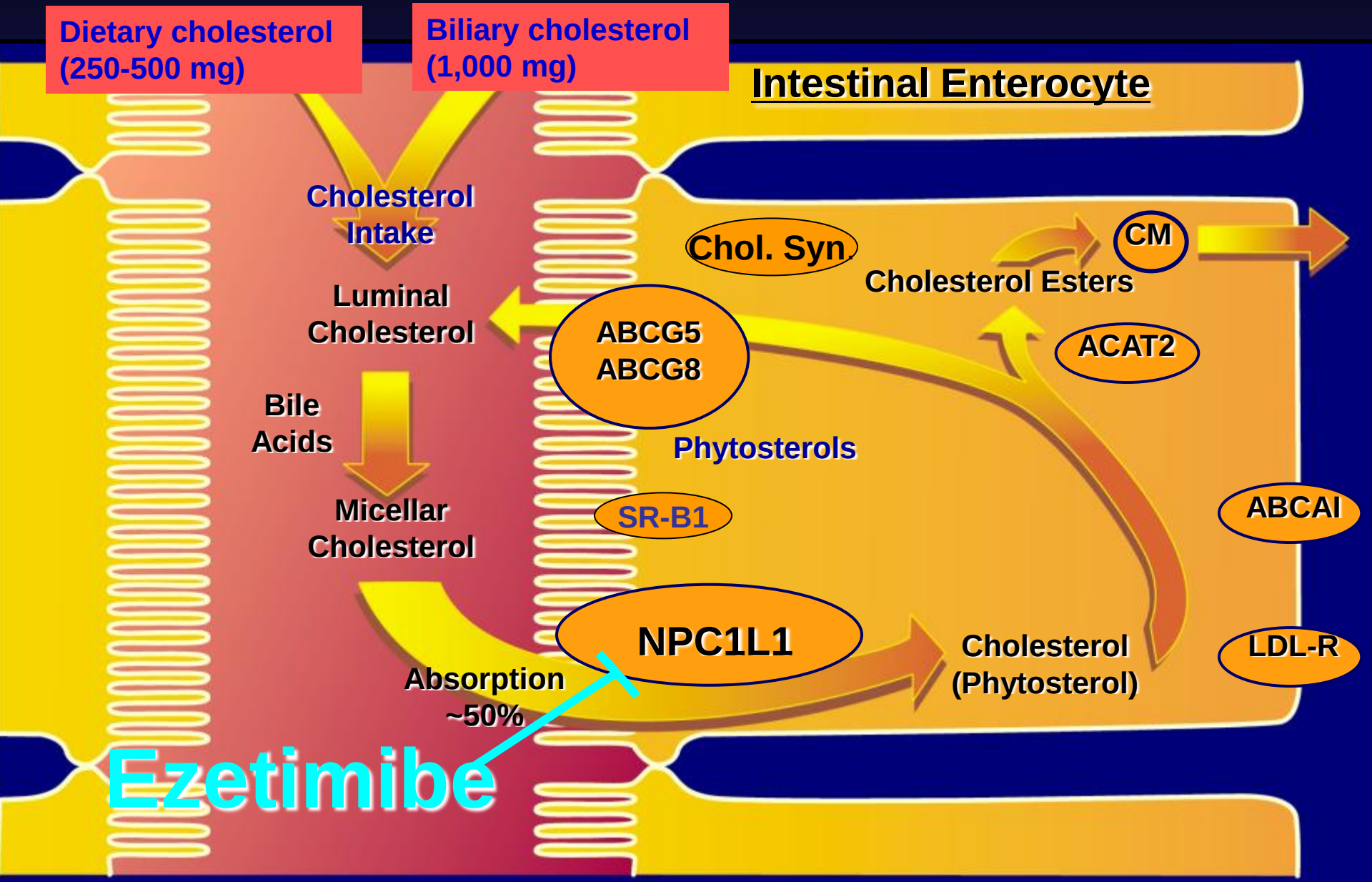


Aoki T. et al. Eur J Pharmacol. 2002

Administration of Fenofibrate Reduces Fasting and Postprandial Plasma Triglyceride Concentrations in Wild-type and CD36-null Mice



Target of Ezetimibe



Subjects

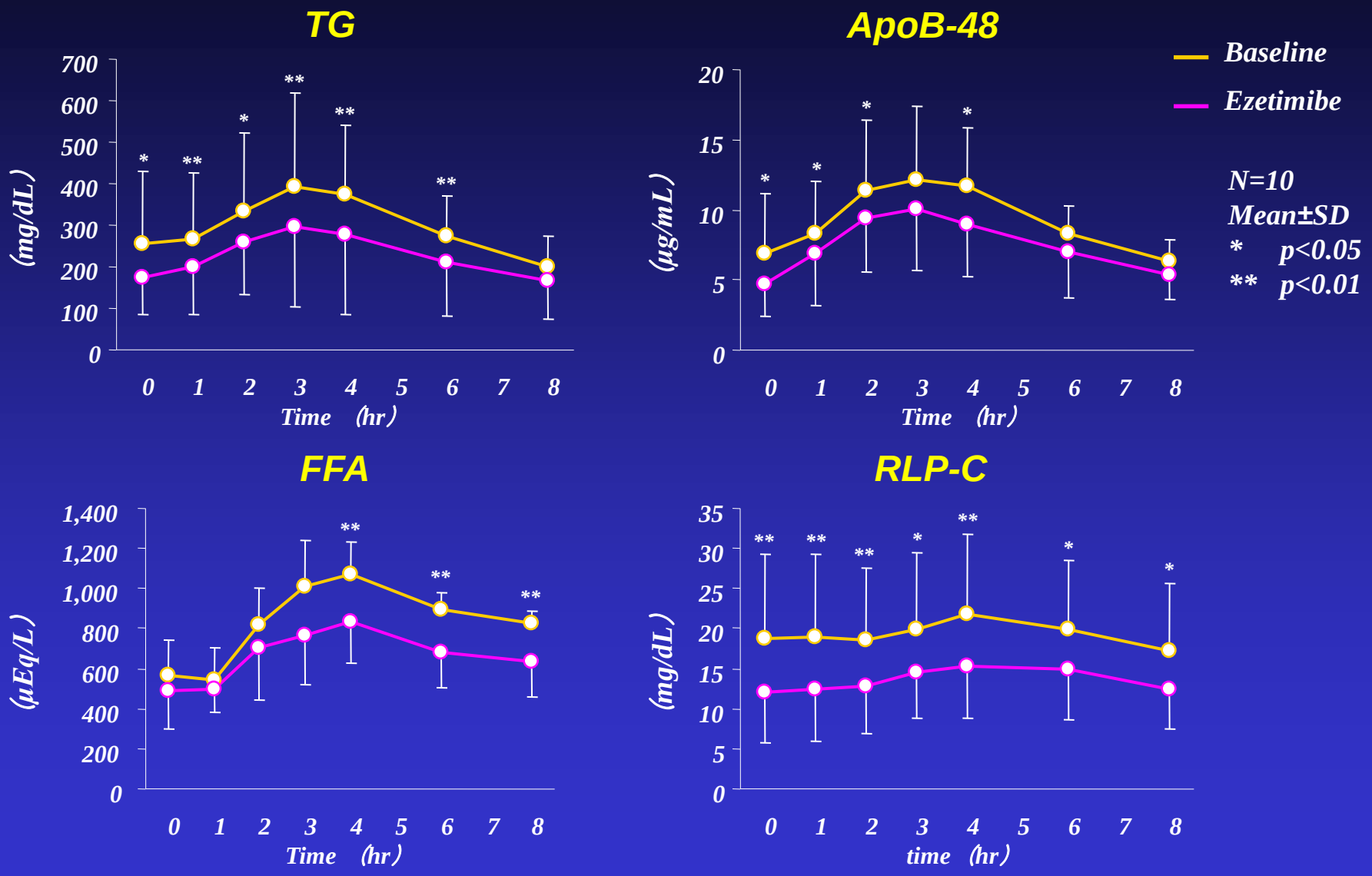
Patients with Type IIb Hyperlipidemia
（n=10, 8 Males and 2 Females）

Age: 51 ± 14 years (34-67)

BMI: 27.1 ± 4.4 kg/m^2

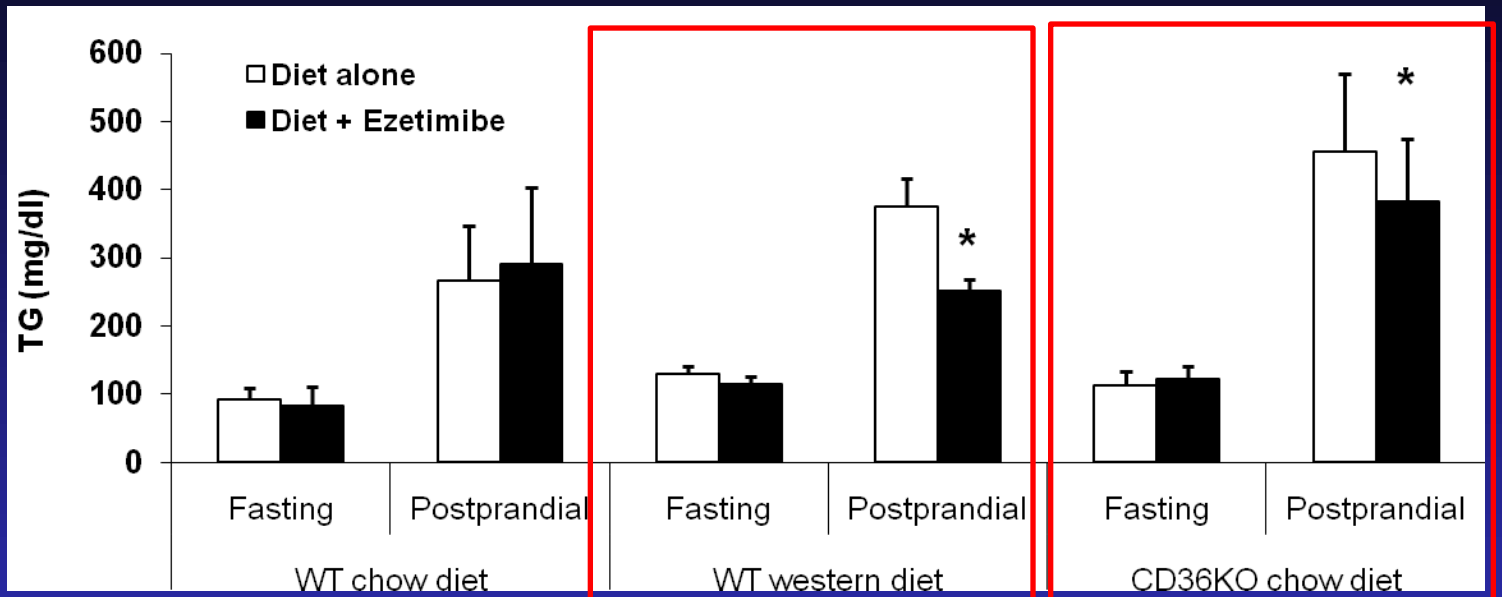
1. **Total chlesterol≥220 mg/dl and TG≥150 mg/dl at fasting**
2. **Patients were administered ezetimibe (10mg/day) with informed consent**
3. **This study was approved by Ethical Committee of Osaka University Hospital**

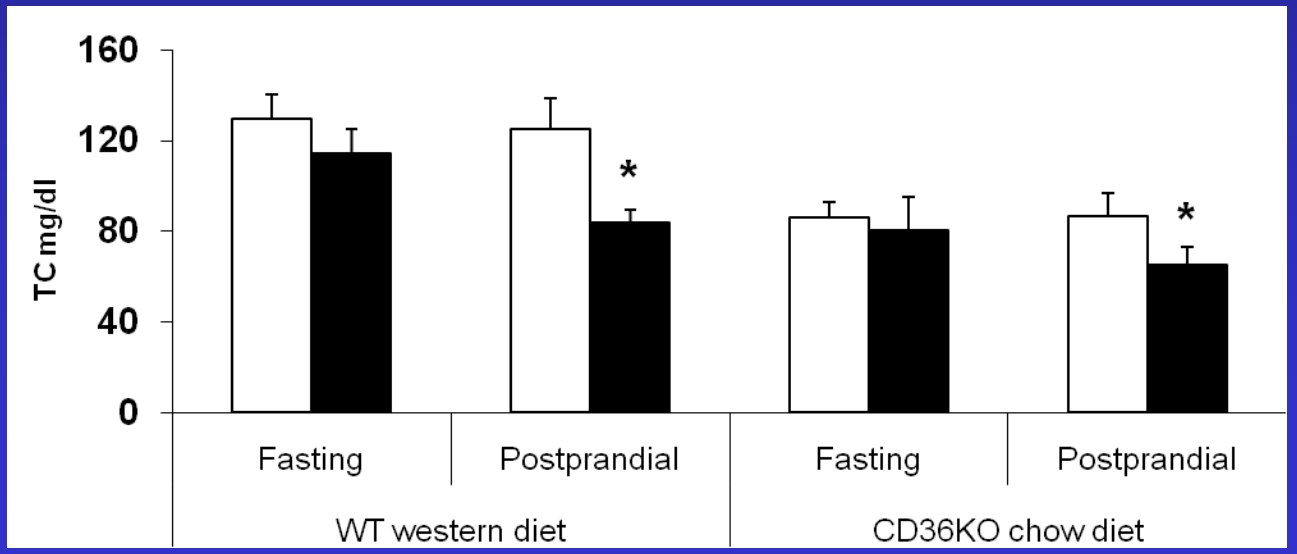
Effects of Ezetimibe on Postprandial Hyperlipidemia



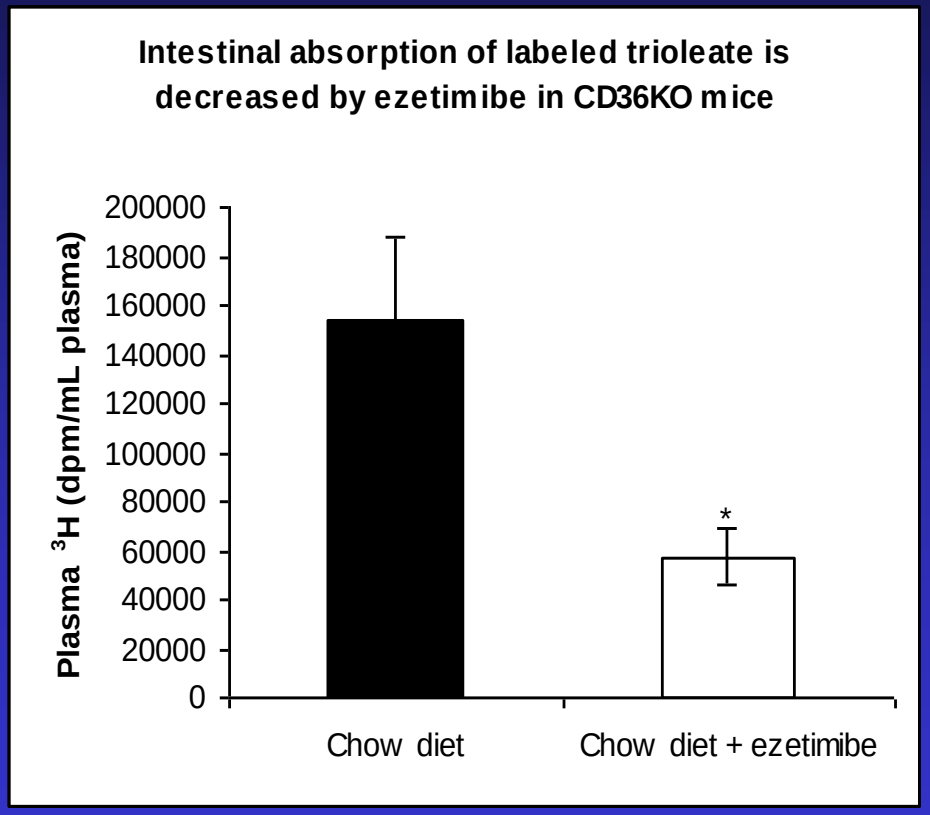
Masuda D, Yamashita S et al.: Eur J Clin Invest 2009; 39: 689-98

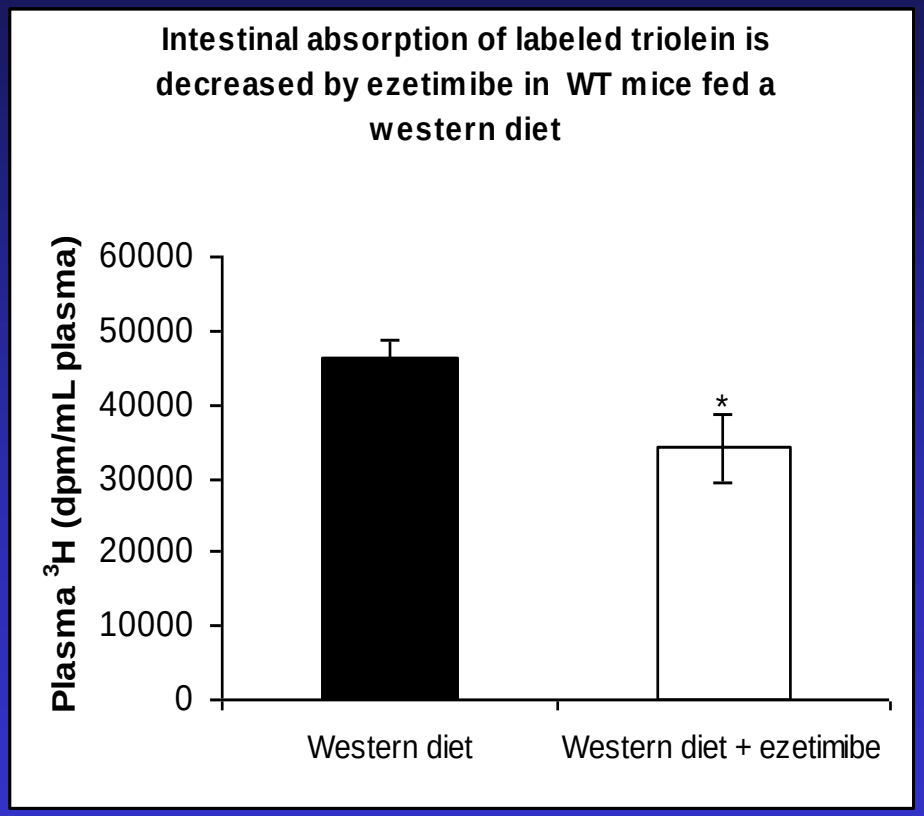
Ezetimibe Reduces Postprandial Cholesterol and TG Levels in WT and CD36KO Mice



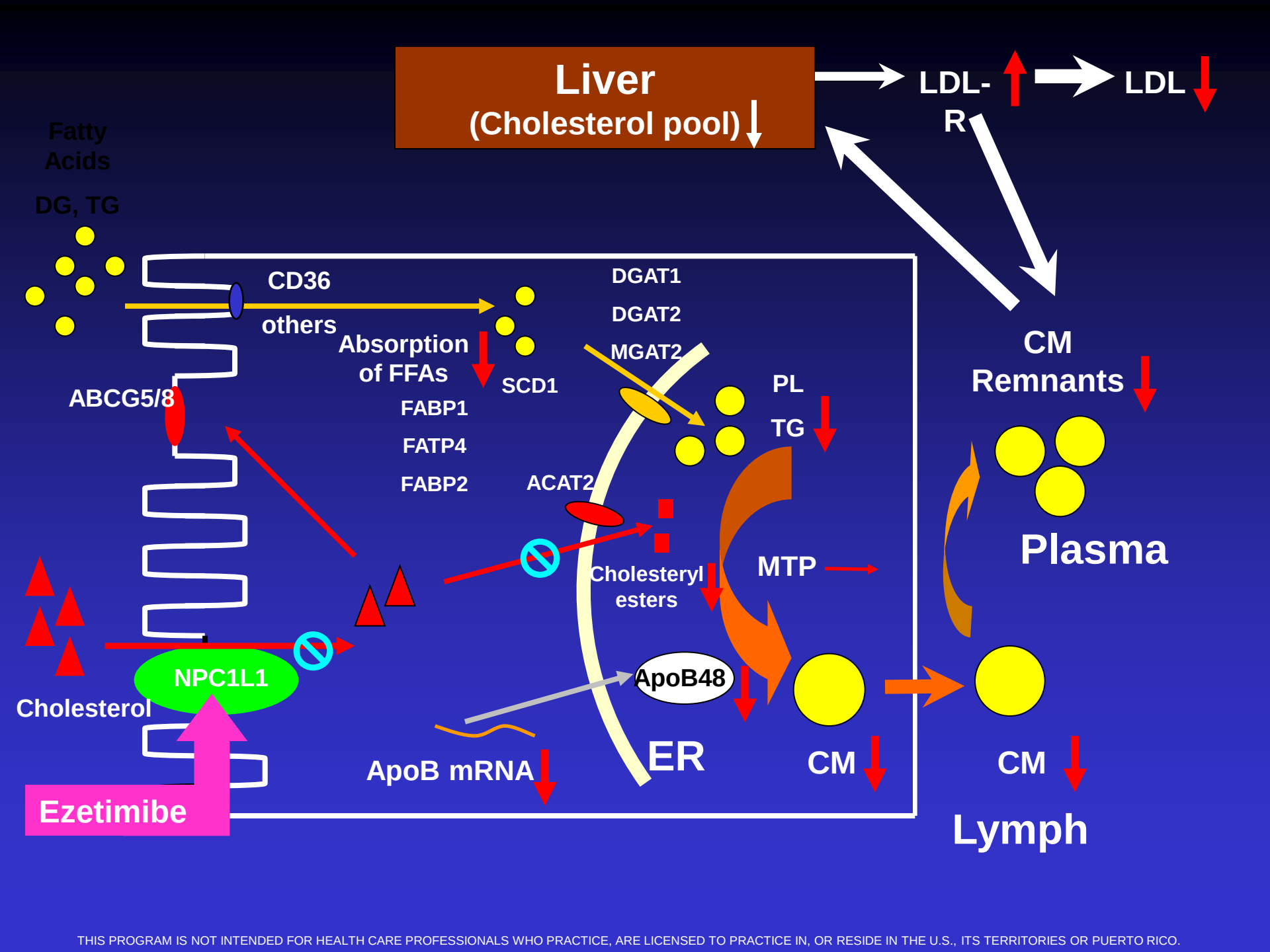


Ezetimibe Reduces Intestinal Absorption of ^{3}H-labeled Trioleate in Both CD36KO and WT Mice



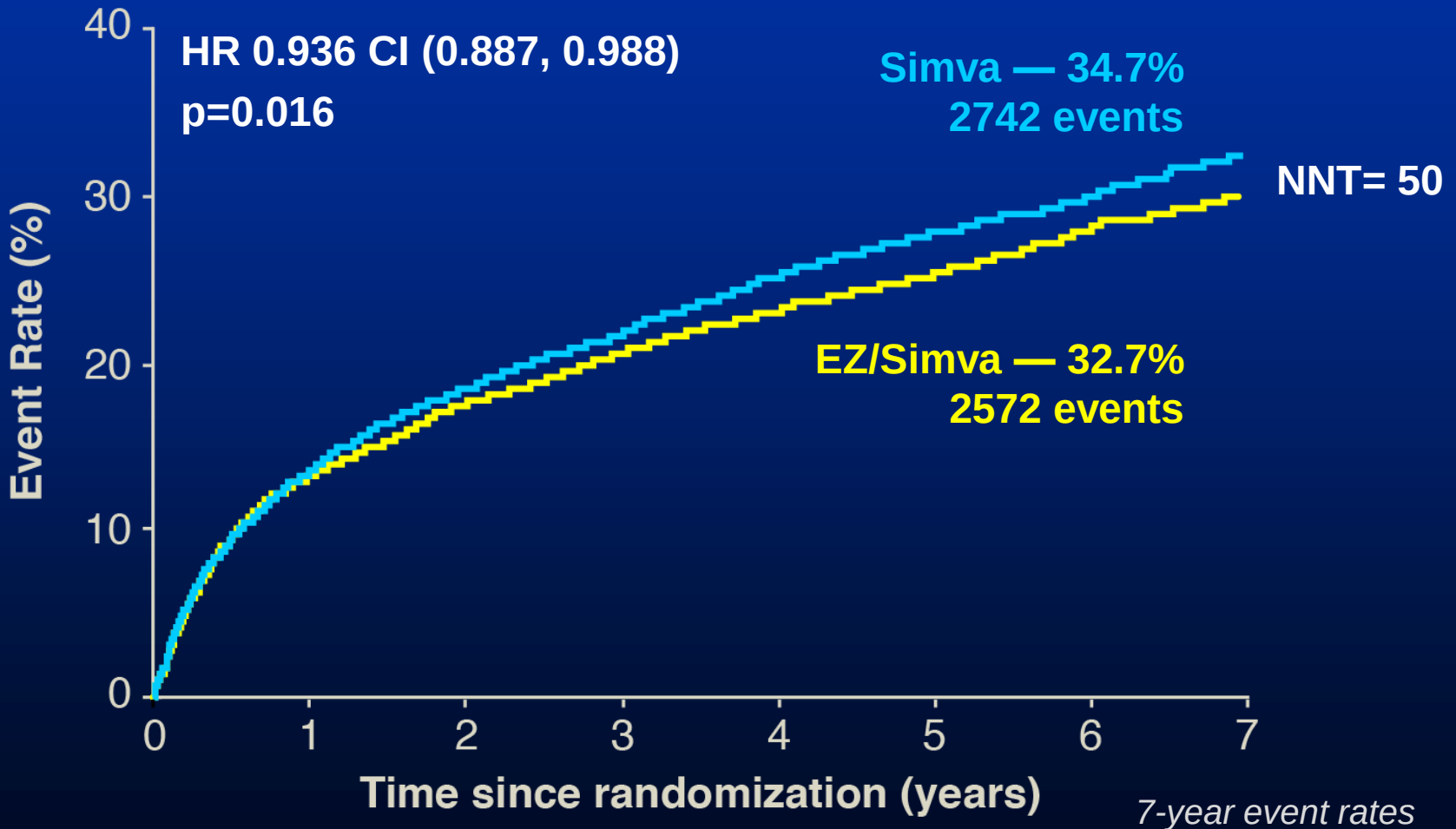


$p<0.05$



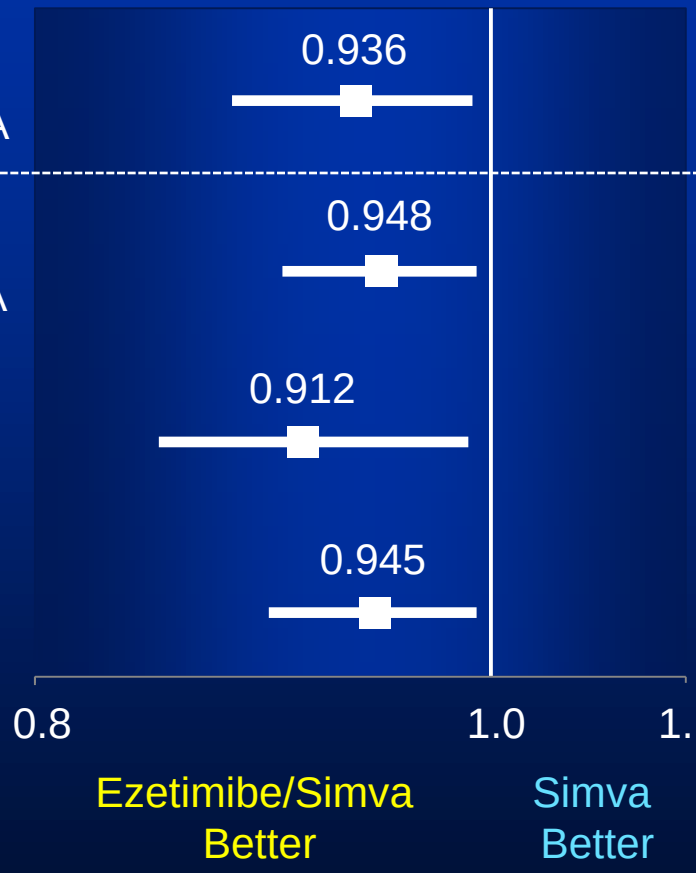
IMPROVE-IT
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

IMPROVE-IT
Primary and 3 Prespecified Secondary Endpoints — ITT



	Simva*	EZ/Simva*	p-value
Primary CVD/MI/UA/Cor Revasc/CVA	34.7	32.7	0.016
Secondary #1 All D/MI/UA/Cor Revasc/CVA	40.3	38.7	0.034
Secondary #2 CHD/MI/Urgent Cor Revasc	18.9	17.5	0.016
Secondary #3 CVD/MI/UA/All Revasc/CVA	36.2	34.5	0.035

**7-year event rates (%)*

UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)

Take home messages

- Postprandial hyperlipidemia is a strong risk factor for CHD due to increases in chylomicron remnants
- Postprandial hyperlipidemia is often observed in patients with diabetes, metabolic syndrome and CHD
- Postprandial hyperlipidemia can be treated with diet/exercise and anti-hyperlipidemic drugs such as statins, fibrates and intestinal cholesterol transporter inhibitor (ezetimibe)
- Inhibition of cholesterol absorption by ezetimibe on top of statin even at very low LDL-C levels prevented CV events in patients with ACS