Diabetic Dyslipidemia
- TG/HDL Axis Disorders -

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The triglyceride–high-density lipoprotein axis: An important target of therapy?

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Coronary heart disease is the single largest cause of morbidity and mortality in the United States. The link between elevated low-density lipoprotein cholesterol (LDL-C) levels and coronary heart disease (CHD) has been clearly established. However, triglycerides (TG) are increasingly believed to be independently associated with CHD, while high-density lipoprotein cholesterol (HDL-C) is inversely associated with CHD risk. High TG and low HDL often occur together, often with normal levels of LDL-C, and can be described as abnormalities of the TG-HDL axis. This lipid abnormality is a fundamental characteristic of patients with the metabolic syndrome, a condition strongly associated with the development of both type 2 diabetes and CHD. Patients with high TG and low HDL-C should be aggressively treated with therapeutic lifestyle changes. For high-risk patients, lipid-modifying therapy that specifically addresses the TG-HDL axis should also be considered. Current pharmacologic treatment options for such patients include statins, fibrates, niacin, fish oils, and combinations thereof. Several new pharmacologic approaches to treating the TG-HDL axis are currently being investigated. More clinical trial data is needed to test the hypothesis that pharmacologic therapy targeting the TG-HDL axis reduces atherosclerosis and cardiovascular events. (Am Heart J 2004;148:211–21.)

Coronary heart disease (CHD) is the single largest cause of morbidity and mortality in the United States. The link between elevated cholesterol and CHD has been clearly established, and clinical trials have found that a 1% reduction in serum total cholesterol (TC) reduces CHD risk by 2%. The National Cholesterol Education Program (NCEP) clinical guidelines for the treatment of hypercholesterolemia in adults identify low-density lipoprotein cholesterol (LDLC) as the primary treatment target.[1] Risk assessment limited to LDL-C, however, fails to capture a significant portion of patients at risk for CHD, and patients effectively treated for elevated LDL-C still experience a significant number of coronary events. Thus increasing attention is being focused on other lipoprotein fractions, such as high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), as additional potential targets of therapy. Elevated serum TG combined with low HDL-C, a condition often associated with smaller, dense LDL particles, is frequently referred to as atherogenic dyslipidemia or the "lipid triad" and is most often seen in the context of the metabolic syndrome. This syndrome represents a cluster of metabolic abnormalities driven by abdominal obesity and insulin resistance, leading to the development of high blood pressure, elevated TG, and depressed HDL-C levels as well as impairments of glucose tolerance.[1] The accumulating evidence suggests that metabolic syndrome is strongly associated with the development of type 2 diabetes and clinical CHD.[2] Since lipoprotein particle size is not routinely obtained in clinical practice, and since elevated TG and depressed HDL-C can occur together, we refer to this dyslipidemia as an abnormality of the TG-HDL axis. Because abnormalities of the TG-HDL often occur in the setting of a "normal" LDL-C, new approaches, not covered in detail in the recent NCEP guidelines, need to be developed in addressing this dyslipidemia. In this review, we focus on the epidemiology and treatment of disorders of the TG-HDL axis, and provide a clinical framework to address this increasingly common dyslipidemia.

Elevated TG and low HDL-C levels as CHD risk factors

There is little doubt that decreased HDL-C is a potent risk factor for CHD, independent of other known risk factors. In fact, both observational studies and controlled clinical trials suggest that each 1% increase in HDL-C is associated with a 2% to 3% reduction in risk of CHD.[3] However, there is more debate as to the independent association of TG levels with CHD risk. Although some epidemiologic studies have not found a consistent association of TG level with CHD mortality,[4] the bulk of the evidence now suggests that elevated fasting TG level is in fact an independent risk factor for CHD. For example, the Copenhagen Male Study, which followed 2906 white men over 8 years, found that fasting serum TG in the upper 2 tertiles was independently associated with incidence of CHD.[5] In this cohort, middle-aged white men with fasting TG ≥142 mg/dL had an adjusted risk ratio for CHD of 2.2 (1.4–

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doi:10.1016/j.ahj.2004.03.037

Am Heart J 2004;148:211–21

High TG, low HDL-C and normal levels of LDL-C can be described as abnormalities of the TG-HDL axis.

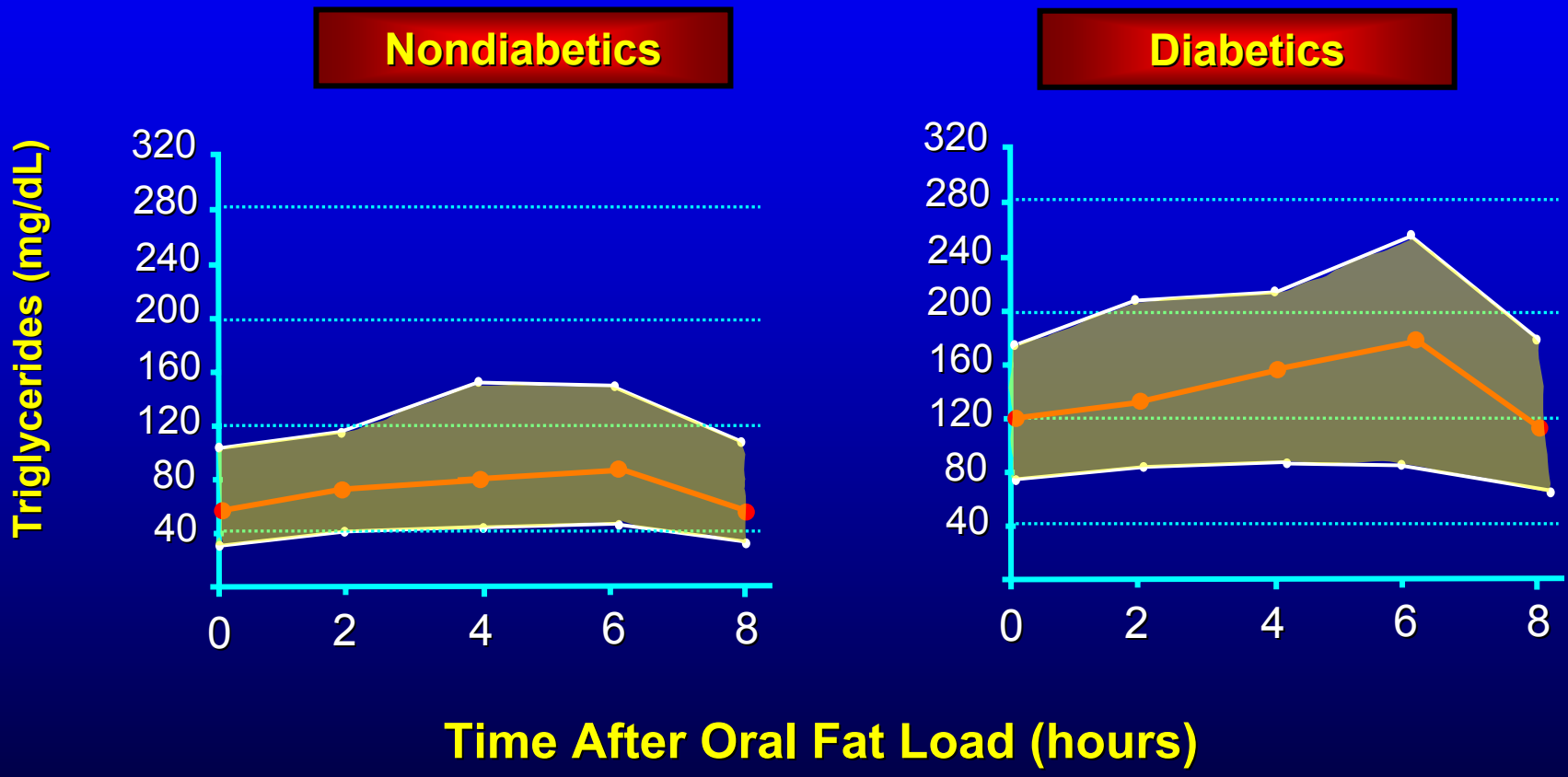
This lipid abnormality is a fundamental characteristic of patients with the metabolic syndrome, a condition strongly associated with the development of both type 2 diabetes and CHD.

Patients with high TG and low HDL-C should be aggressively treated with therapeutic lifestyle changes.

For high-risk patients, lipid-modifying therapy that specifically addresses the TG-HDL axis should also be considered.

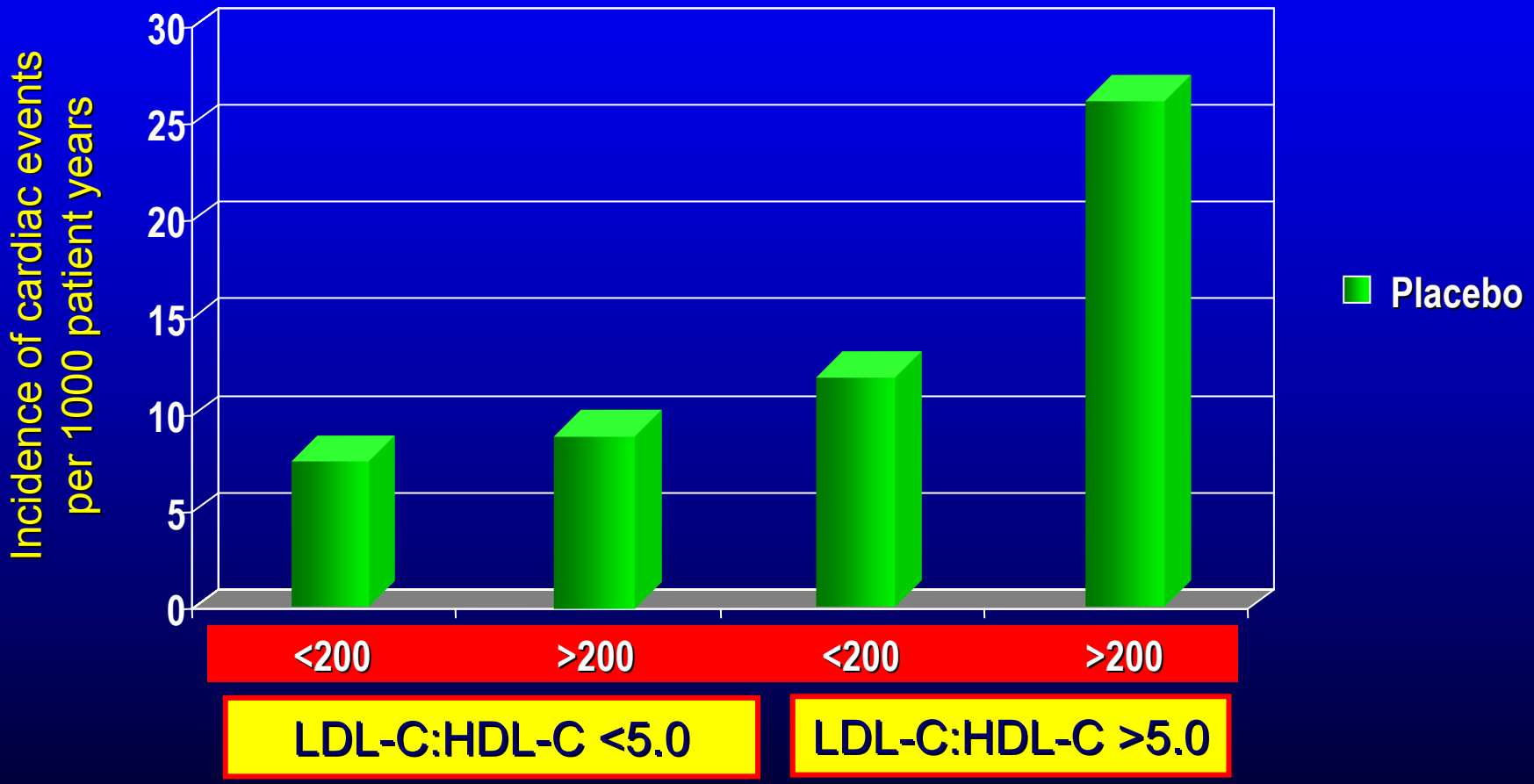
Current pharmacologic treatment options for such patients include statins, fibrates, niacin, fish oils, and combinations thereof.

Oral Triglyceride Tolerance Test



Mohanlal N & Holman R. Diabet Care 2004;27:89-94

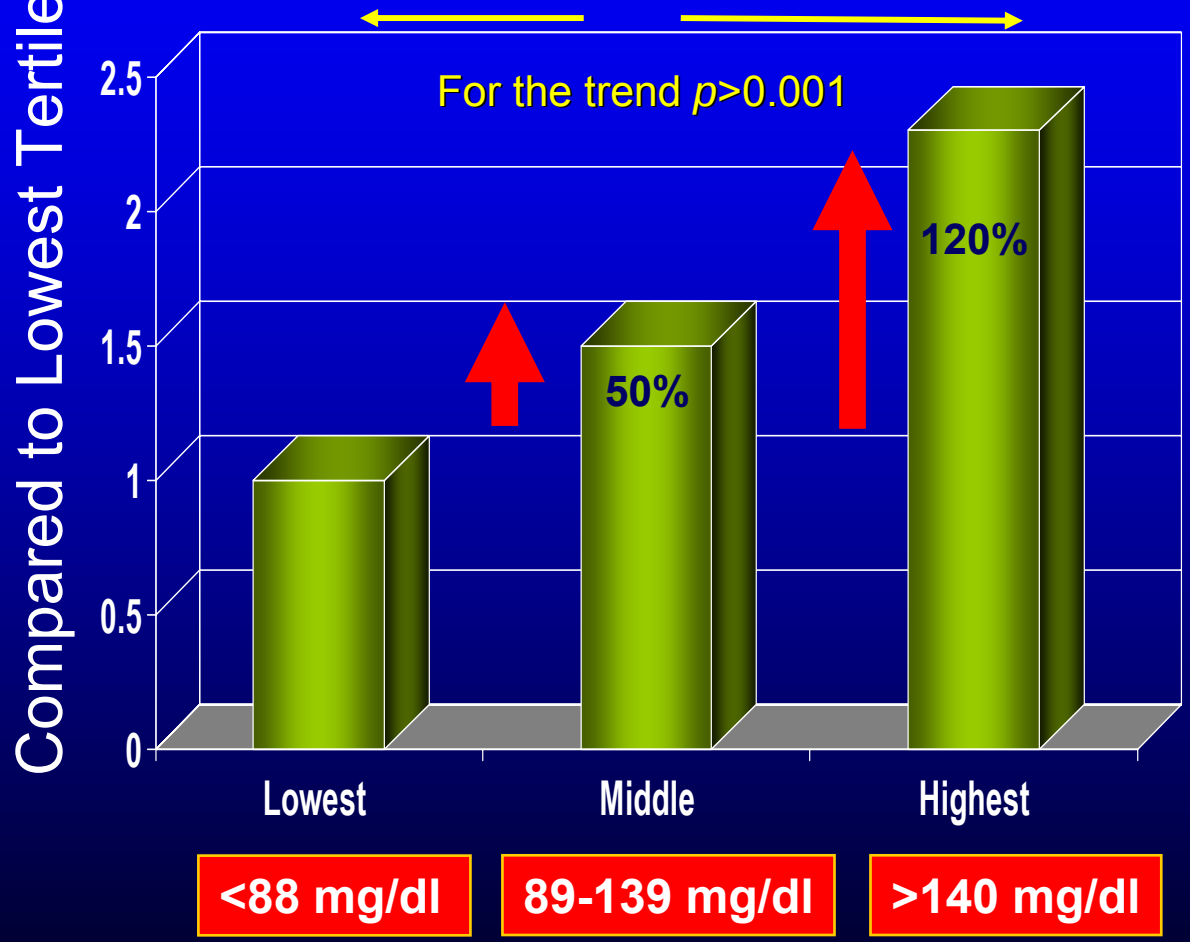
- Helsinki Heart Trial - Triglyceride, HDL-C and Risk for CAD



Circulation 1992;85:37-46

The Copenhagen Male Study

2906 men free of CVD: 8 year follow up: 229 men had first CHD event

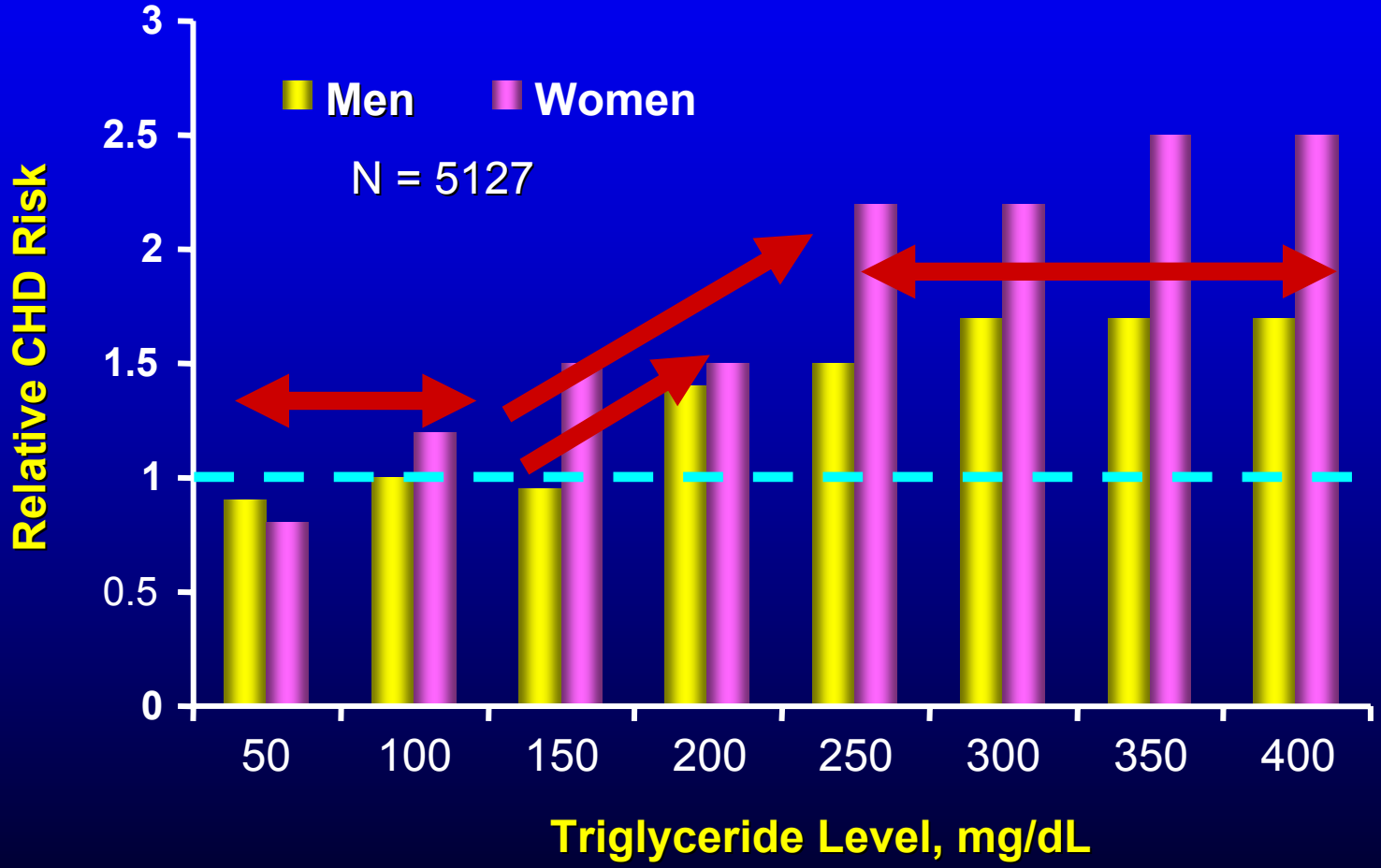


Adjusted for

- Age
- Body mass index
- Alcohol use
- Smoking
- Physical activity
- Hypertension
- Type 2 diabetes
- Social class
- LDL-C
- HDL-C

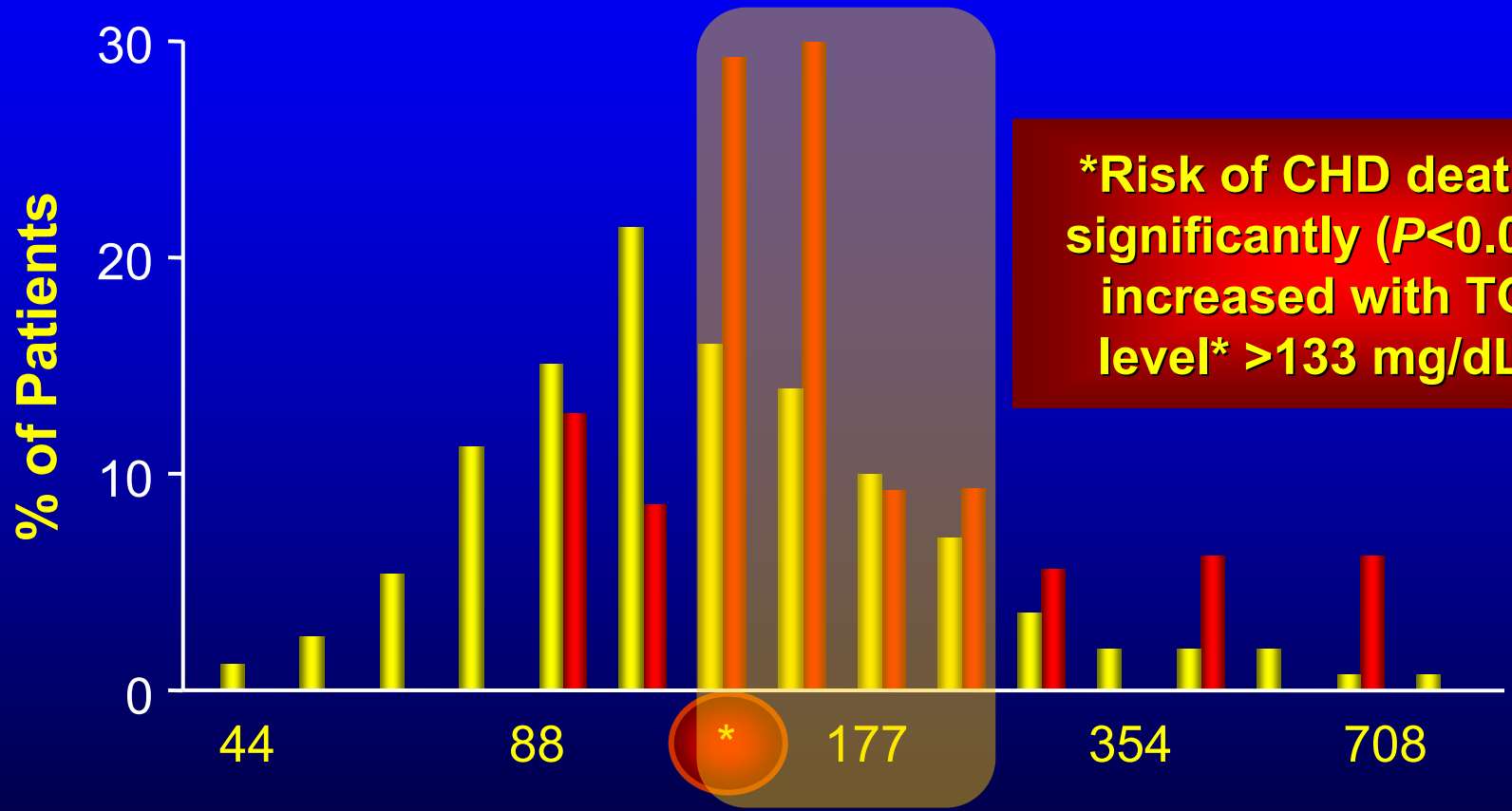
Circulation 1998;97:1029-36

Risk of CHD by Triglyceride Level
The Framingham Heart Study



Castelli WP. *Am J Cardiol.* 1992;70:3H-9H.

Paris Prospective Study: 11 Year Follow-up Hypertriglyceridemia as a Risk Factor for CHD in Male Patients with Diabetes or IFG



*Risk of CHD death significantly (*P*<0.01) increased with TG level* >133 mg/dL.

Fontbonne et al. *Diabetologia.* 1989;32:300.

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III

Risk of Triglycerides

Risk Classification of Serum Triglycerides

Normal <150 mg/dL

Borderline high 150–199 mg/dL

High 200–499 mg/dL

Very high ≥500 mg/dL

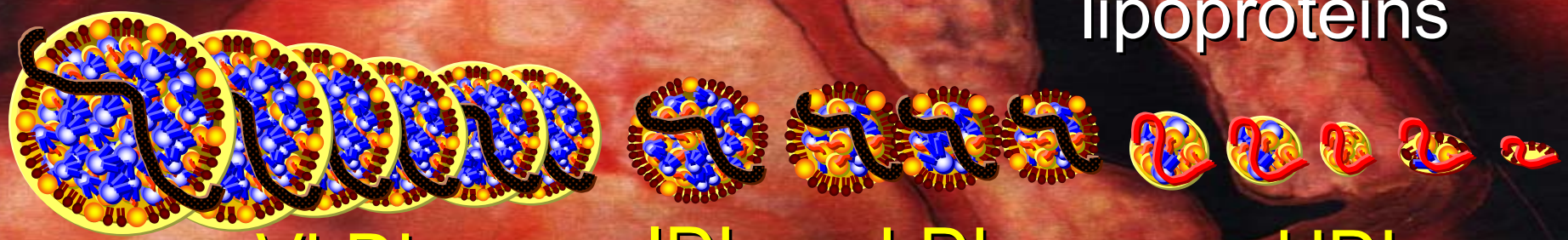
NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

Atherosclerosis is due to an abnormality of sterol trafficking

How did the cholesterol get into the intimal layer ?

How do triglycerides influence lipoproteins trafficking sterols ?

Lipids are trafficked in lipoproteins



Journal of Internal Medicine 2006; 259: 247–258 doi:10.1111/j.1365-2796.2006.01616.x

REVIEW

Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

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Abstract. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, John Chapman M, Couture P, de Graaf J, Durrington PN, Faergeman O, Frohlich J, Furberg CD, Gagne C, Haffner SM, Humphries SE, Jungner I, Krauss RM, Kwiterovich P, Marcovina S, Packard CJ, Pearson TA, Srinath Reddy K, Rosenson R, Sarrafzadegan N, Sniderman AD, Stalenhoef AF, Stein E, Talmud PJ, Tonkin AM, Walldius G, Williams KMS (Heart Research Institute, Sydney, NSW, Australia; Baylor College of Medicine, Houston, TX, USA; Hospital Clinico Universitario, Valencia, Spain; St Franciscus Gasthuis, Rotterdam, the Netherlands; Hôpital de la Pitié, Paris, France; Centre Hospitalier Universitaire de Québec, Québec, Canada; Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; University of Manchester, Manchester, UK; Aarhus Amtssygehus University Hospital, Aarhus C, Denmark; University of British Columbia, St Paul's Hospital, Vancouver, BC, Canada; Wake Forest University School of Medicine, Winston-Salem, NC, USA; Université de Laval, Laval, Québec, Canada; University of Texas Health Science Center, San Antonio, TX, USA; Royal Free and University College Medical School, London, UK; Karolinska Institute, Stockholm; CALAB Research, Stockholm, Sweden; Children's Hospital Oakland Research Institute, Oakland, CA; The Johns Hopkins Medication Institutions, Baltimore, MD; University of Washington, Seattle, WA, USA; Glasgow Royal Infirmary, Glasgow, UK; University of Rochester,

All of the national and transnational screening and therapeutic guidelines are based on total or LDL cholesterol.

This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable.

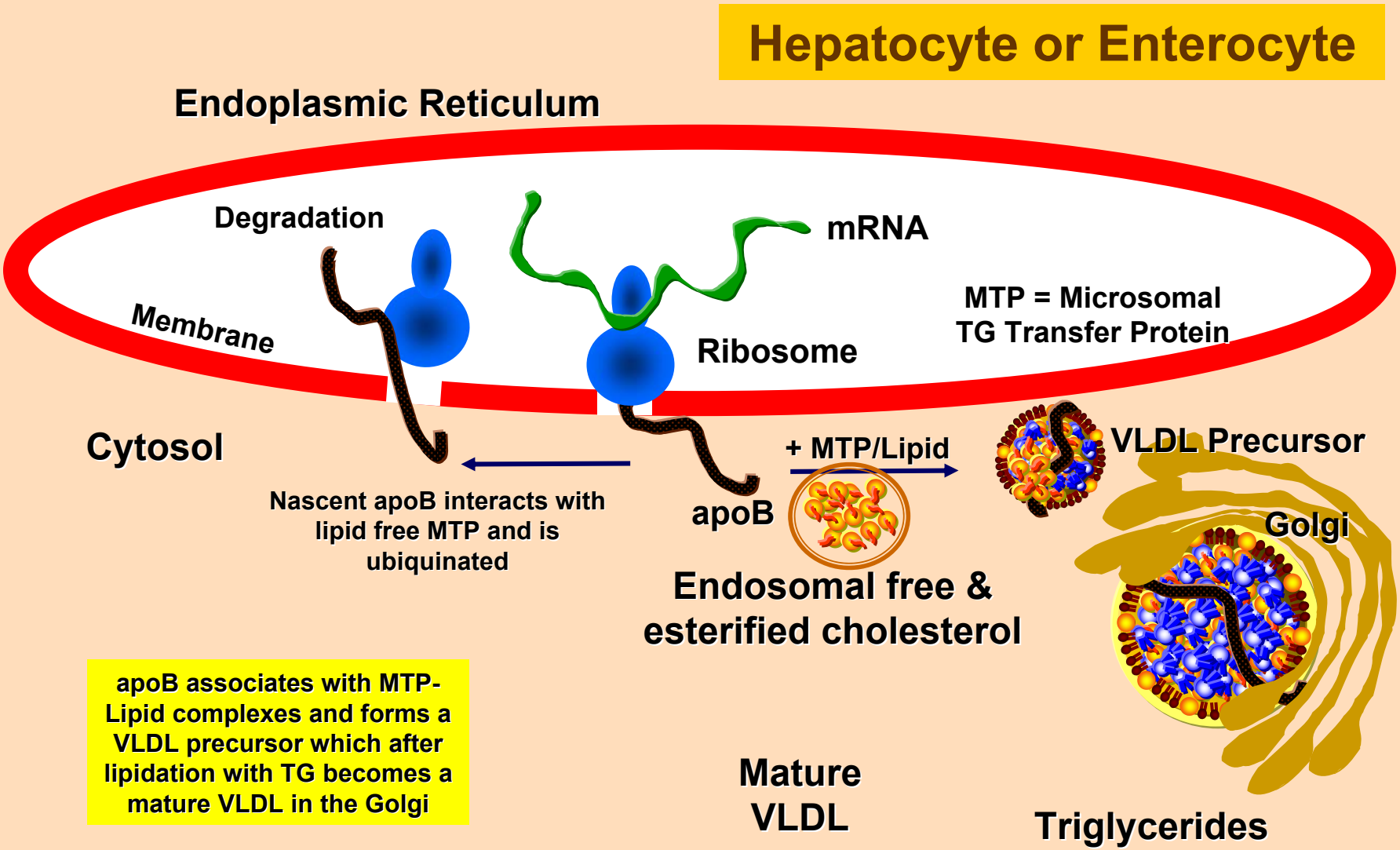
On the contrary, risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall than to the measured concentration of cholesterol in these lipoprotein fractions.

Each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein (apo) B and therefore the concentration of apo B provides a direct measure of the number of circulating atherogenic lipoproteins.

Evidence from fundamental, epidemiological and clinical trial studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy.

Barter PJ et al. J Intern Med 2006;249:247-258

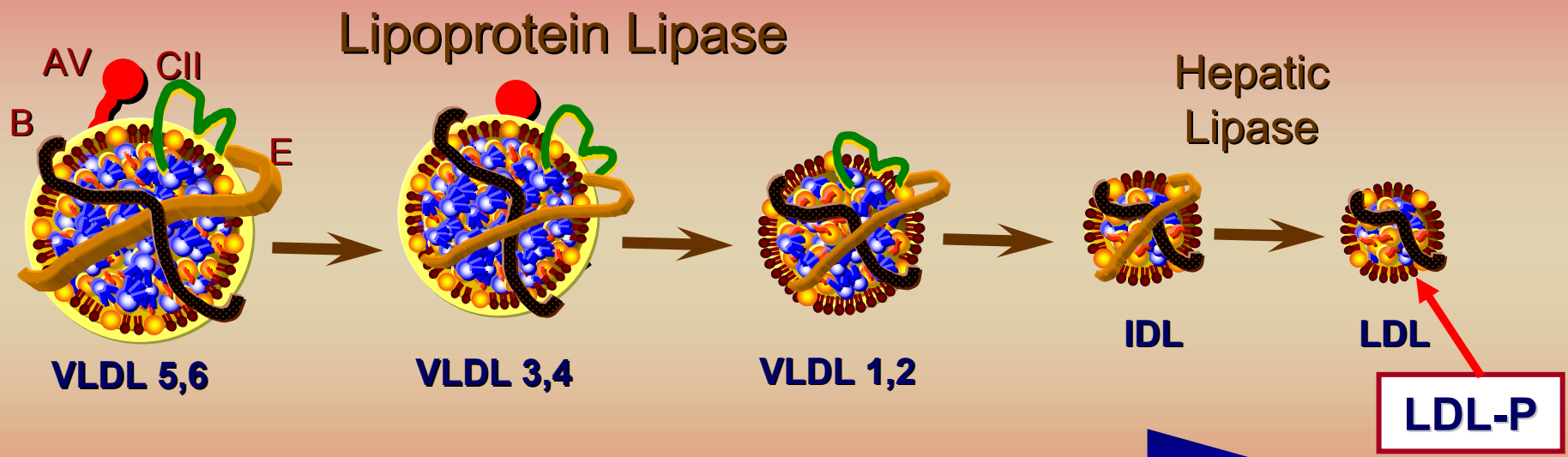
Lipidation of Apolipoprotein B



Whitfield AJ et al. Clin Chem 2004;50:1725-1732

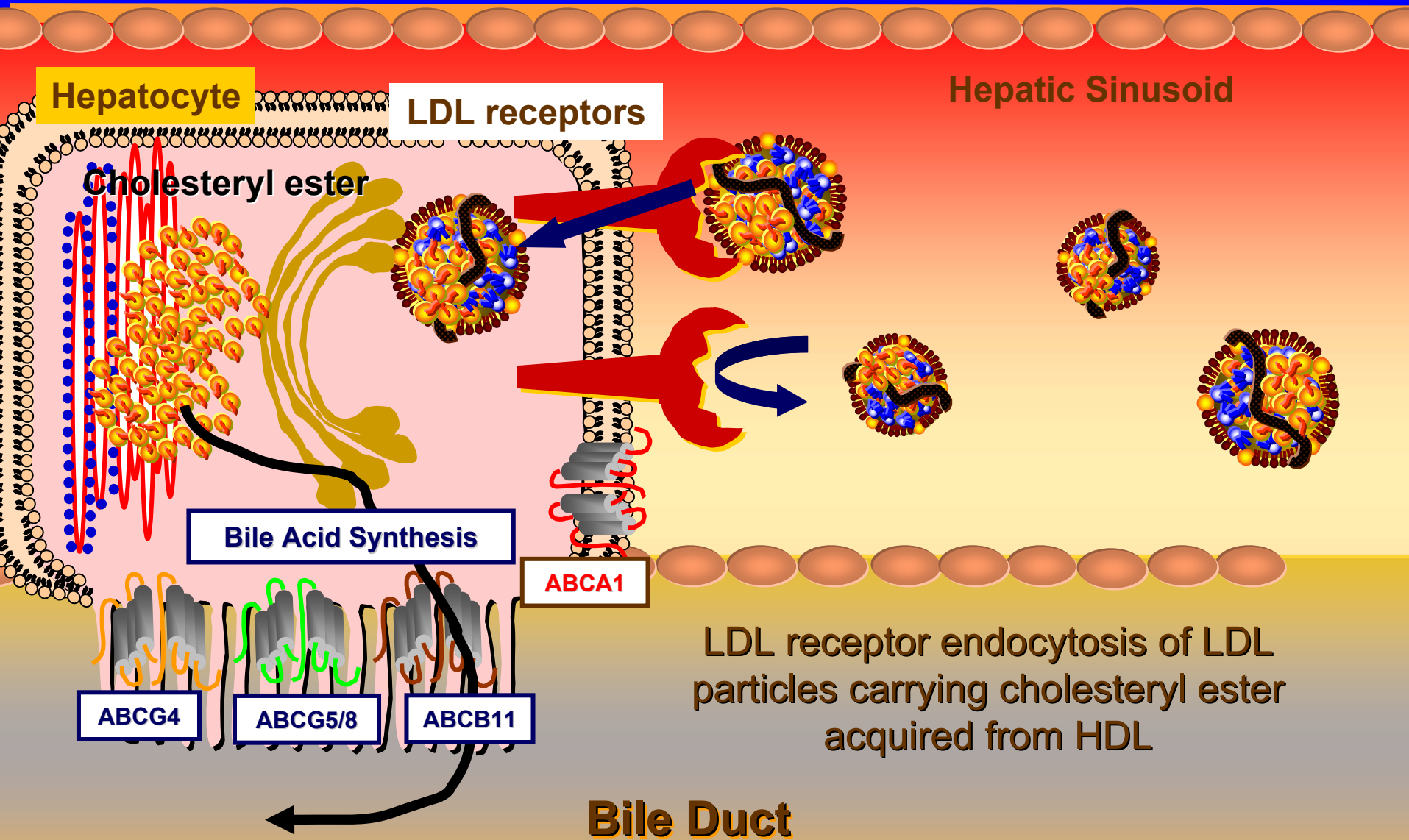
Normal VLDL Lipolysis

In patients with normal triglycerides, VLDL lipolysis (hydrolysis of TG) is rapid



Caslake M & Packard C Curr Opin Lipidol 2004;15:387-392

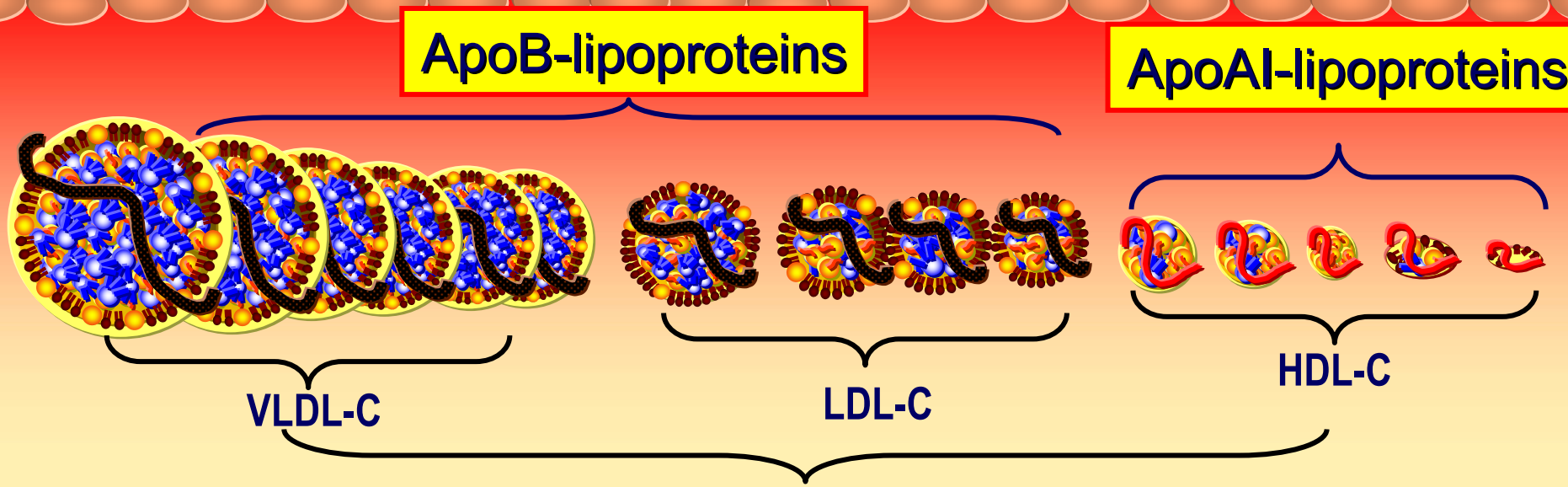
Indirect RCT at the Hepatocyte



Barter, Philip et al. Atherosclerosis 2003;168:195-211

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III: ApoB Surrogate



Total Cholesterol

ApoB-Cholesterol

Non HDL-C

Non HDL-C = TC – HDL-C

National Cholesterol Education Program

Adult Treatment Panel III NCEP-ATP III 2004 Addendum

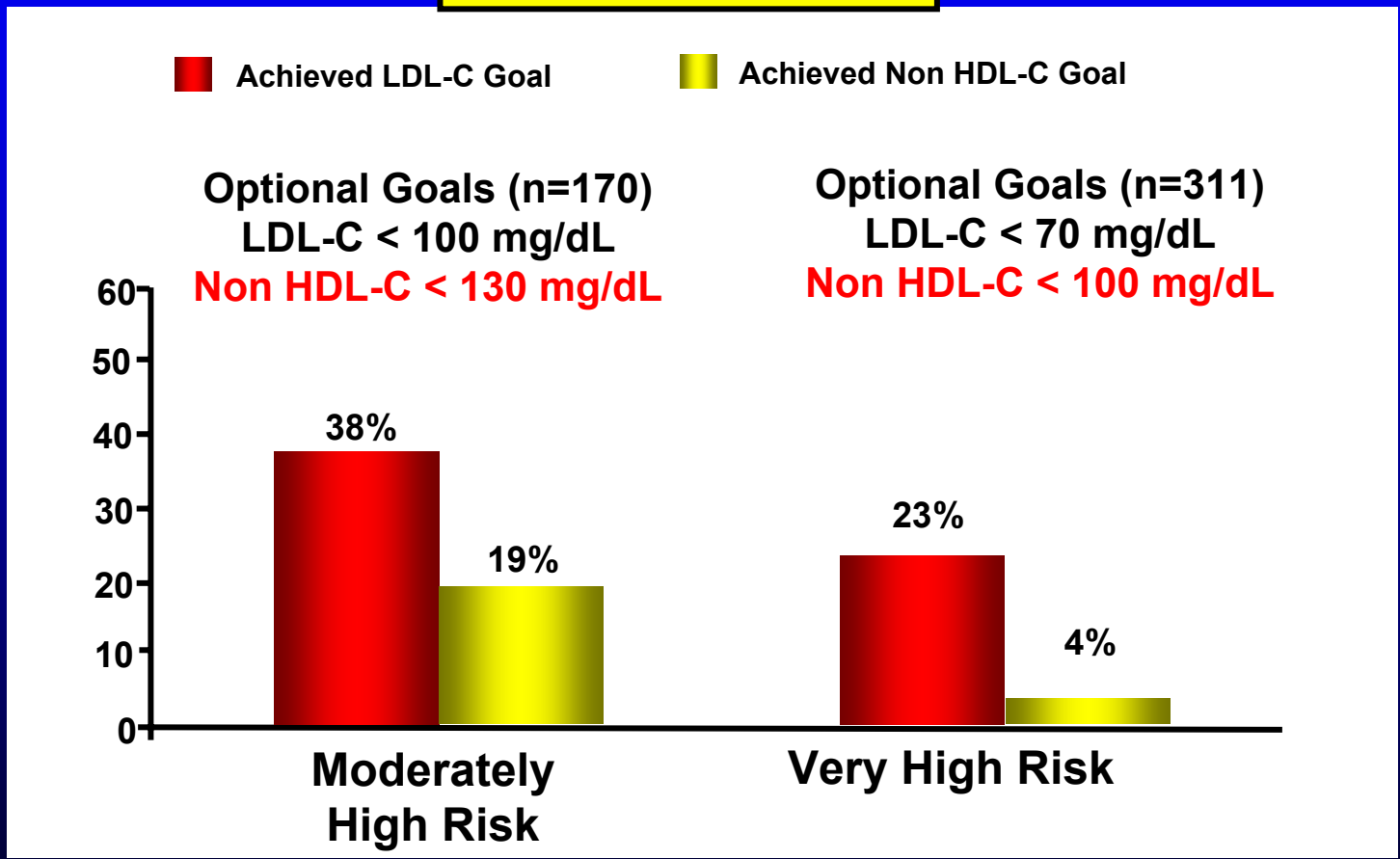
Risk Category	If LDL-C is:	LDL-C	Non HDL-C
Very High: CVD + ACS, diabetes, MS, ↑BP, smoking,	≥ 100, initiate TLC & consider drugs	< 70 (optional)	< 100
High: CVD or diabetes or CHD equivalent	≥ 100, initiate TLC & consider drugs	< 100	< 130
Moderately High: ≥2 risk factors with 10-20% MI risk	≥ 130, initiate TLC & consider drugs 100-129	< 130 (<100 optional)	160 (<130 option)
Moderate: 2 or more risk factors with <10% MI risk	≥ 130, initiate TLC & ≥ 160 consider drugs	< 130	160
Low: Zero or 1 risk factor	≥ 160, initiate TLC & ≥ 190 consider drugs	< 160	190

Circulation 2004;110:227-239

NEPTUNE II Survey Non HDL-C Goal

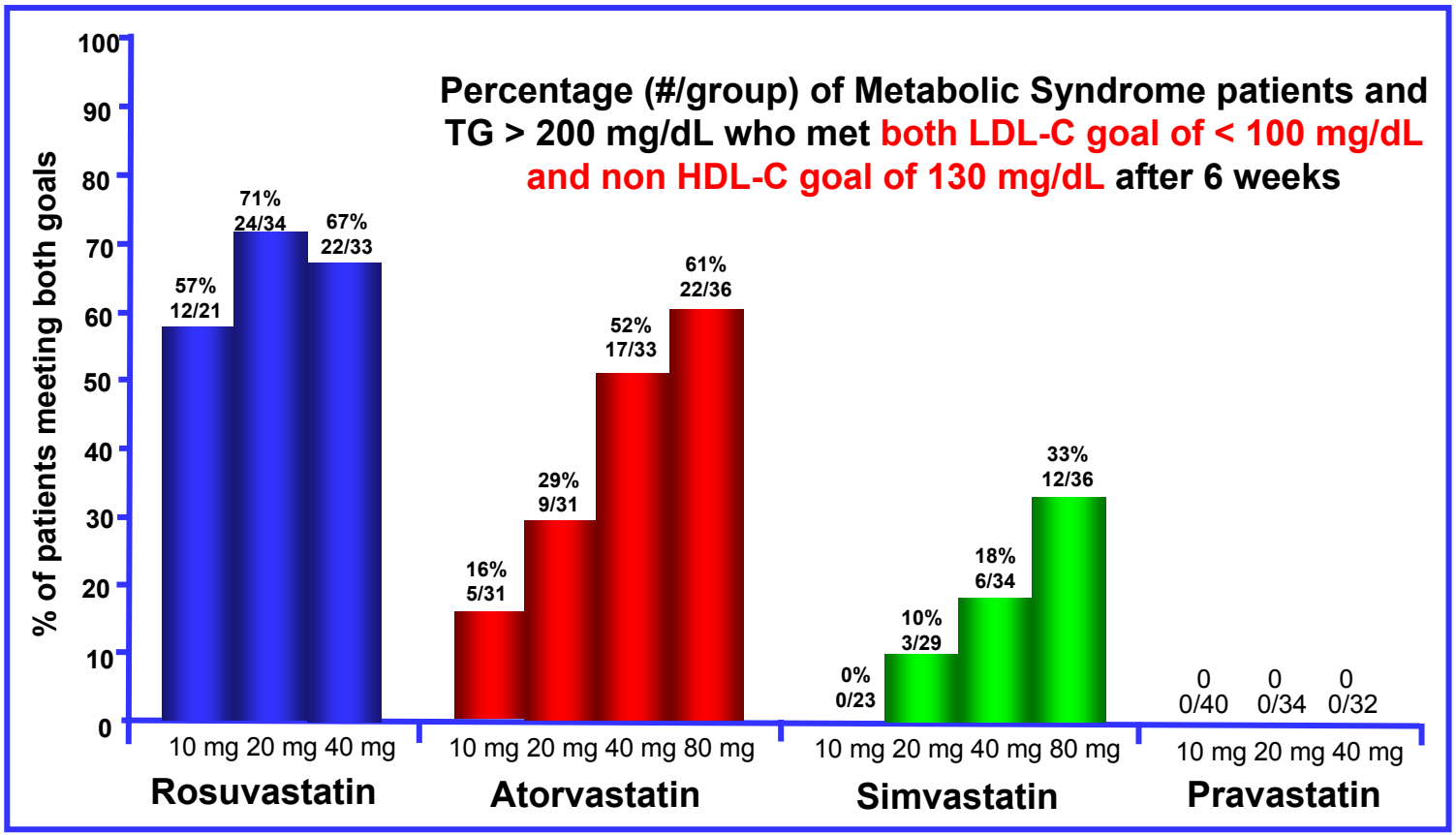
NCEP Evaluation ProjecT Utilizing Novel E-technology

TG > 200 mg/dL

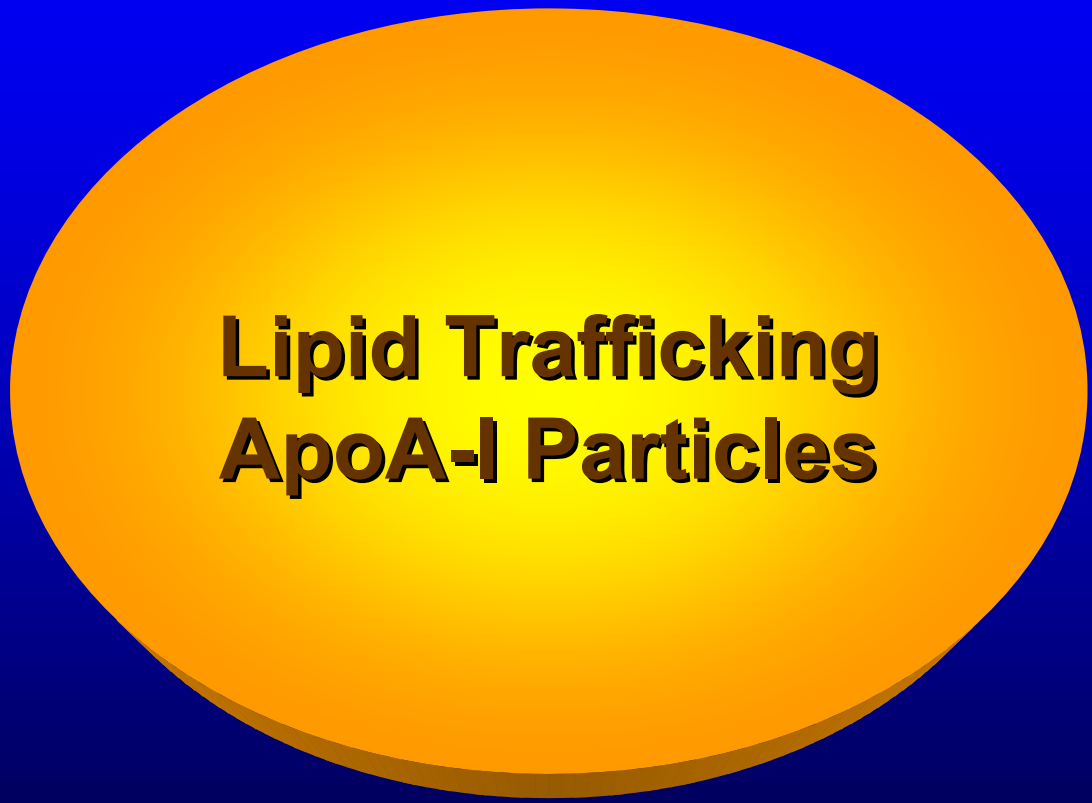


Am J Cardiol 2005;96:556-563

Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR)

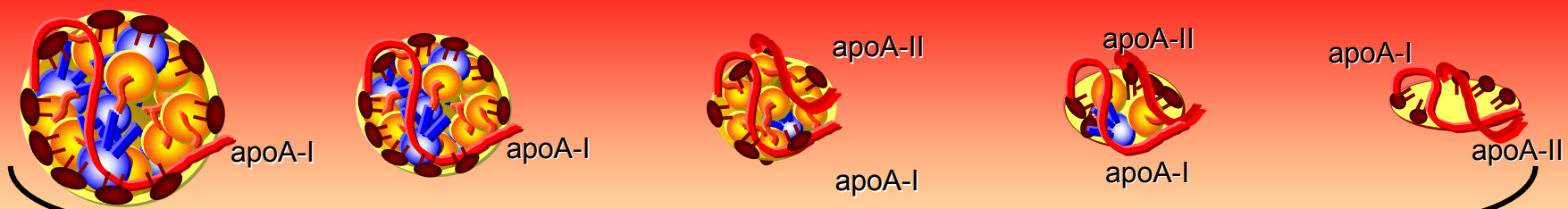


Deedwania PC. Amer J Cardiol 2005;95:360-366


Lipid Trafficking
ApoA-I Particles

HDL-cholesterol Concentration

HDL5	HDL4	HDL3	HDL2	HDL1
HDL_{2b}	HDL_{2a}	HDL_{3a}	HDL_{3b}	HDL_{3c}

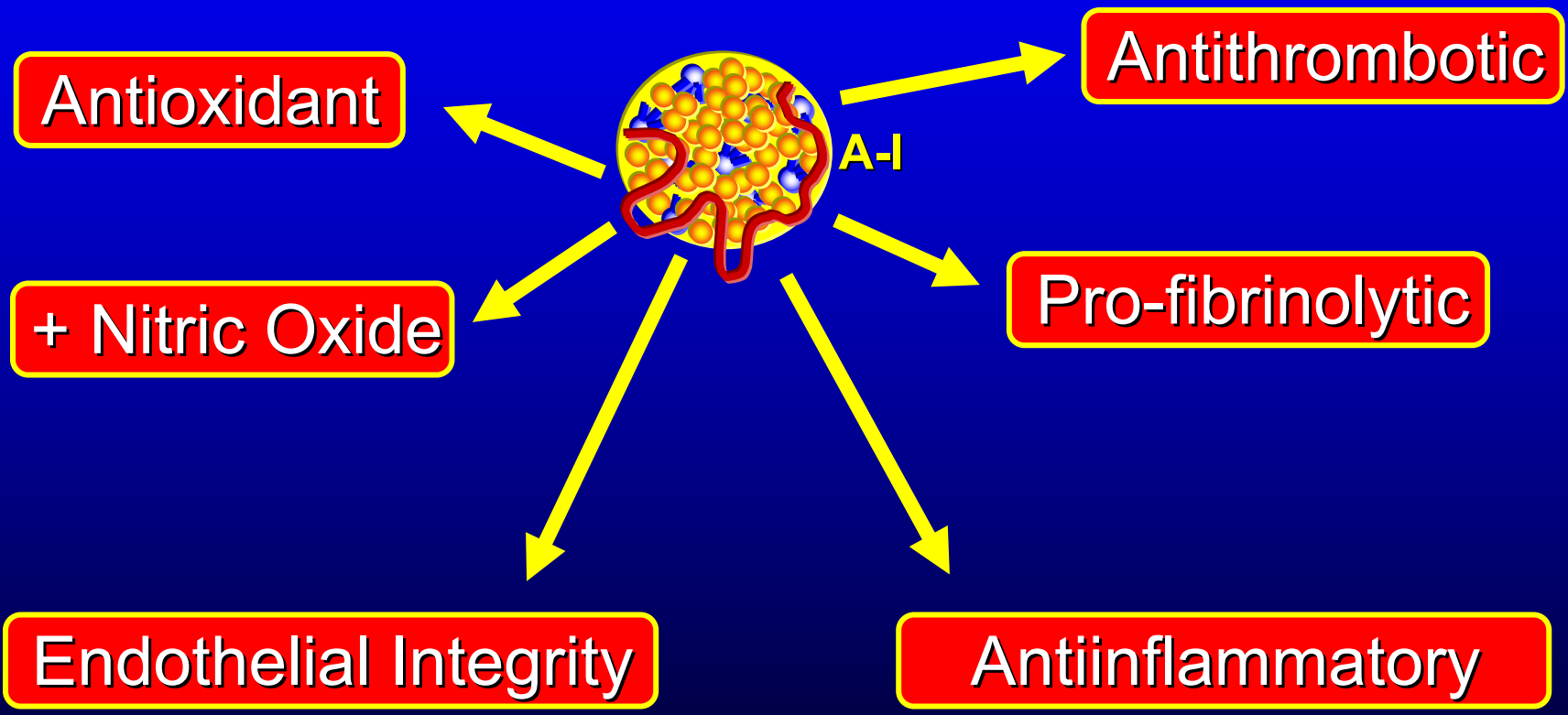


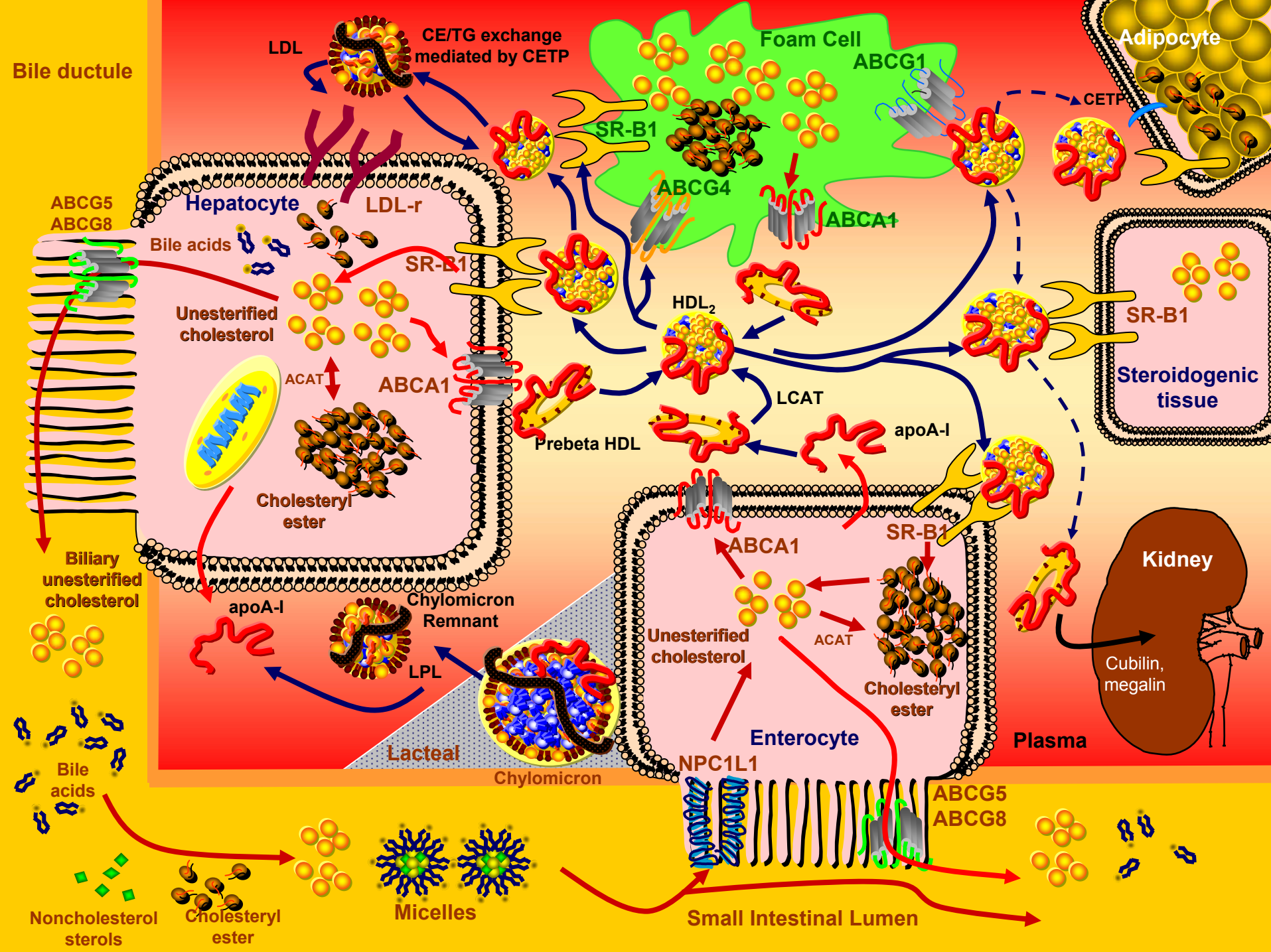
HDL-P reflects the number of HDL particles

HDL-C primarily reflects cholesterol levels within large, cholesterol-rich particles and lacks sensitivity to detect small cholesterol-poor particles

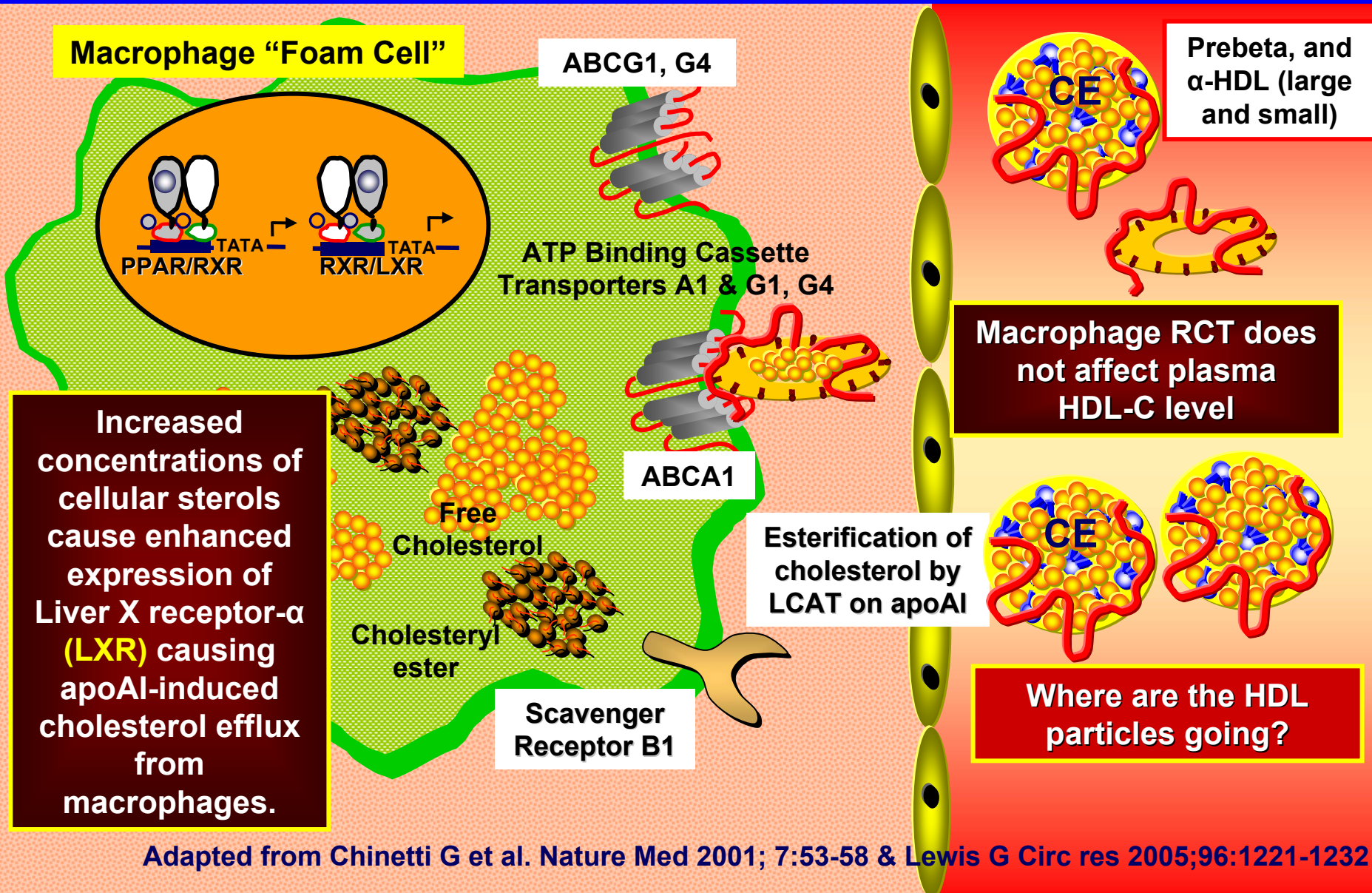
Kontush A & Chapman J. Pharm Rev. 2006;58:342-374

HDL Functionality and Vascular Protection




Bile ductule
LDL
CE/TG exchange mediated by CETP
Foam Cell
ABCG1
Adipocyte
CETP
SR-B1
ABCG4
ABCA1
ABCG5
ABCG8
Hepatocyte
LDL-r
Bile acids
SR-B1
Unesterified cholesterol
ACAT
ABCA1
Cholesteryl ester
HDL2
Prebeta HDL
LCAT
apoA-I
SR-B1
Steroidogenic tissue
Biliary unesterified cholesterol
apoA-I
Chylomicron Remnant
LPL
ABCA1
SR-B1
Kidney
Cubilin, megalin
Unesterified cholesterol
ACAT
Cholesteryl ester
Lacteal
Chylomicron
Enterocyte
NPC1L1
Plasma
ABCG5
ABCG8
Bile acids
Micelles
Small Intestinal Lumen
Noncholesterol sterols
Cholesteryl ester

Macrophage Reverse Cholesterol Transport



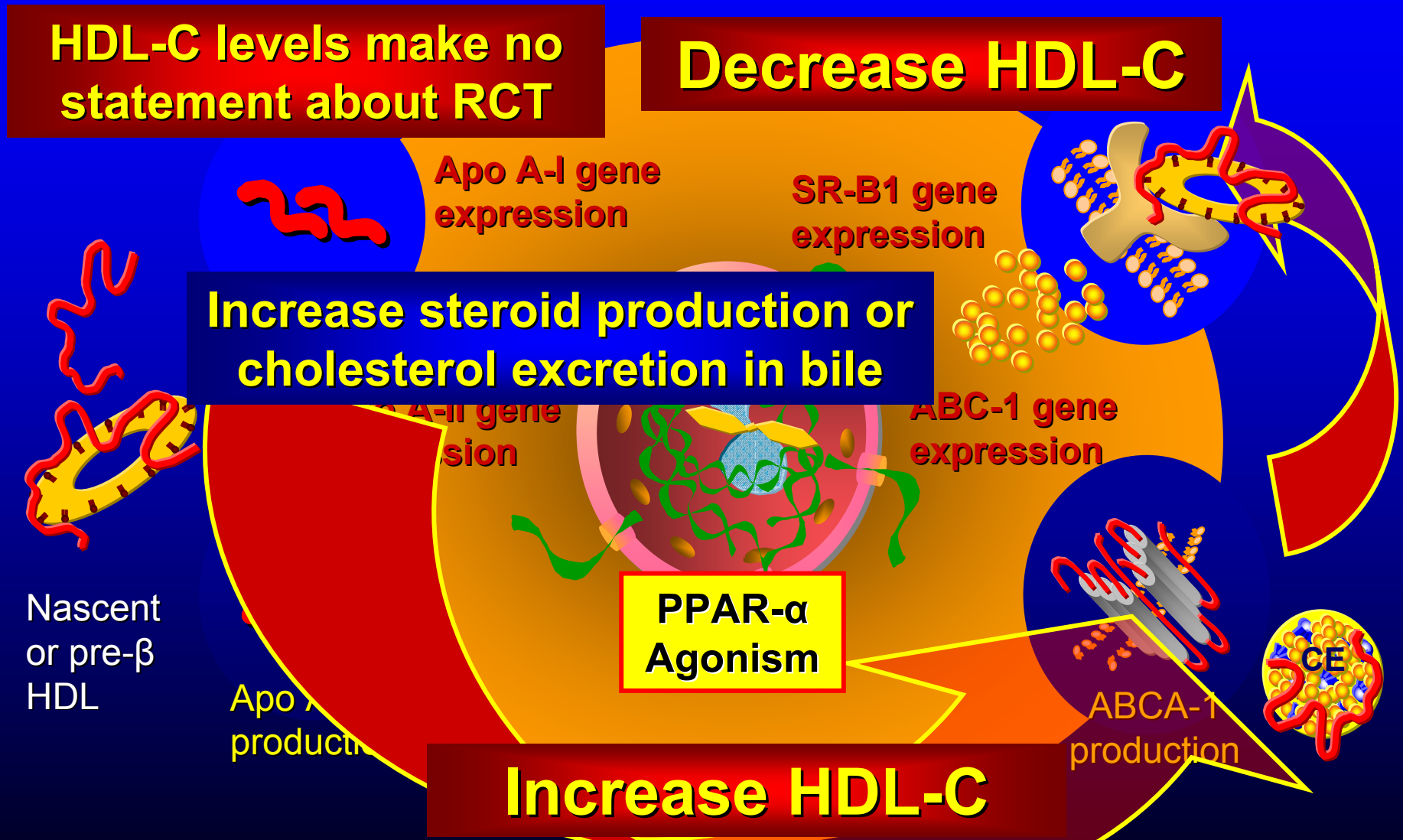
Adapted from Chinetti G et al. Nature Med 2001; 7:53-58 & Lewis G Circ res 2005;96:1221-1232

ApoA-I Cholesterol Transport

The major determinant of serum HDL-C is the cellular ABCA1 transporter

The vast majority of the cholesterol in HDL originates in hepatocytes or enterocytes

High Density Lipoprotein Flux
– Changing HDL Composition & HDL-C -



HDL Therapies

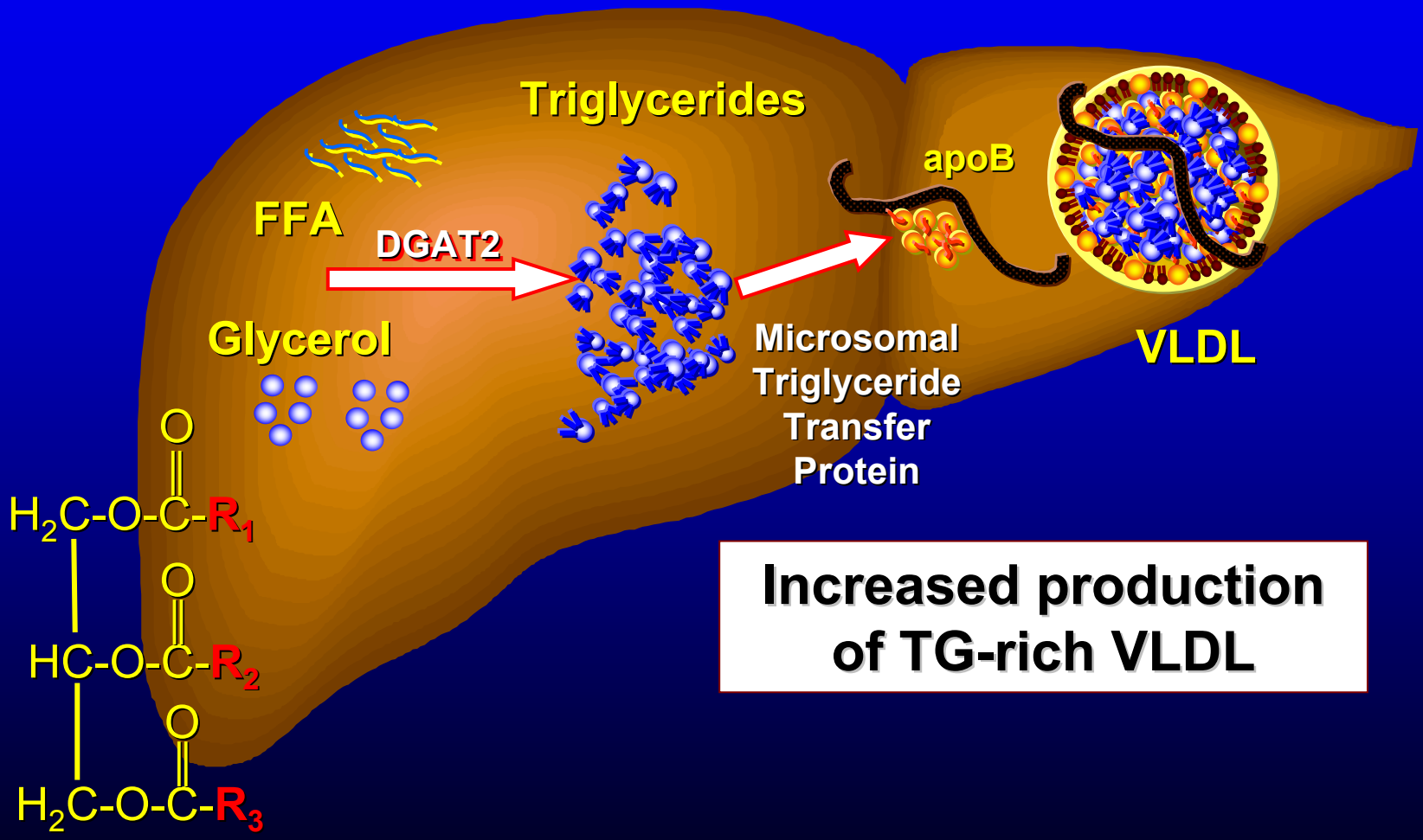
Plasma steady state **HDL-C levels are not an assay of the rate of RCT**, which is a dynamic process that can only be assessed through kinetic measures of cholesterol flux.

An important concept is that simply raising HDL-C levels may not necessarily be the optimal target for the development of new therapies targeted toward HDL.

Duffy D & Rader D. Circulation 2006;113:1140-1150

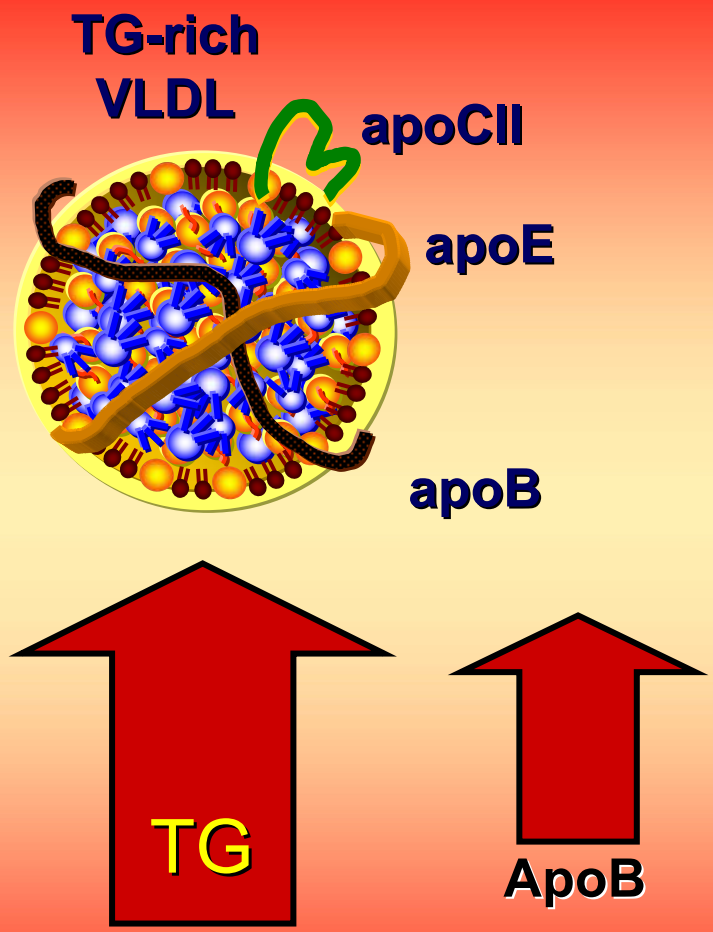
Understanding Triglycerides

↑ VLDL Synthesis in Diabetics



Increased production of TG-rich VLDL

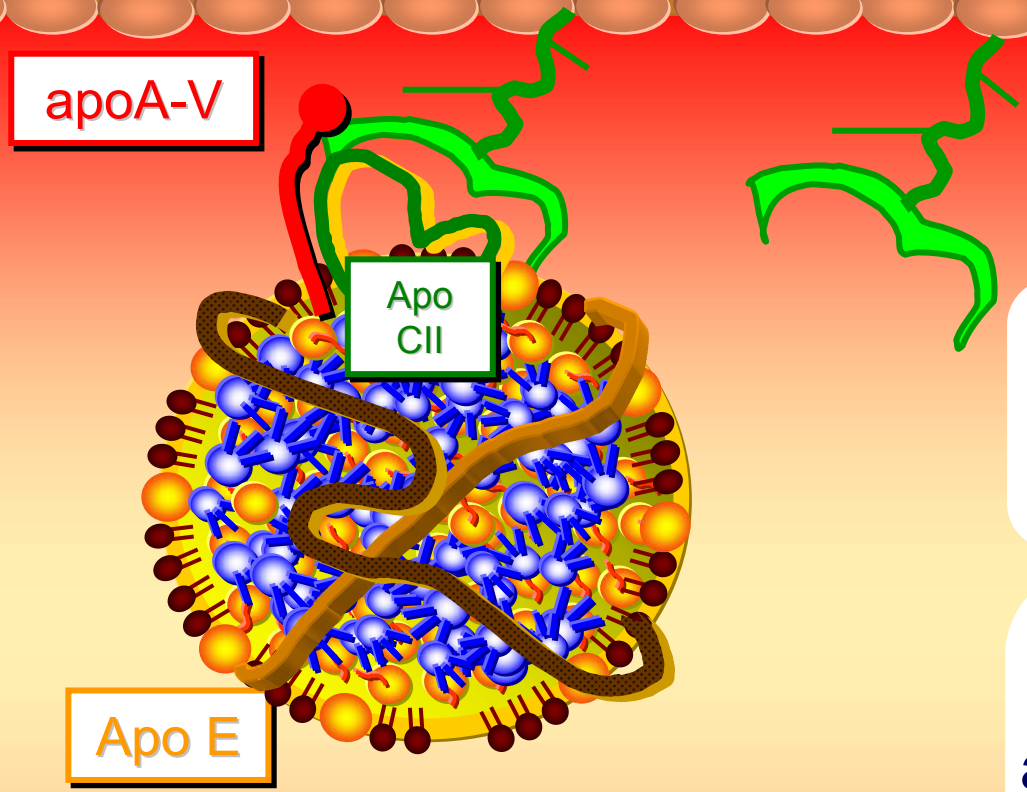
Lipoprotein Abnormalities in TG/HDL Axis Disorders



- Increased hepatic production of large apoB enwrapped TG-rich VLDL particles
- The more VLDL that is produced, the higher the apoB will be

Triglyceride Cholesteryl ester

ApoAV and TG-rich VLDL Lipolysis



Lipoprotein Lipase (LPL)

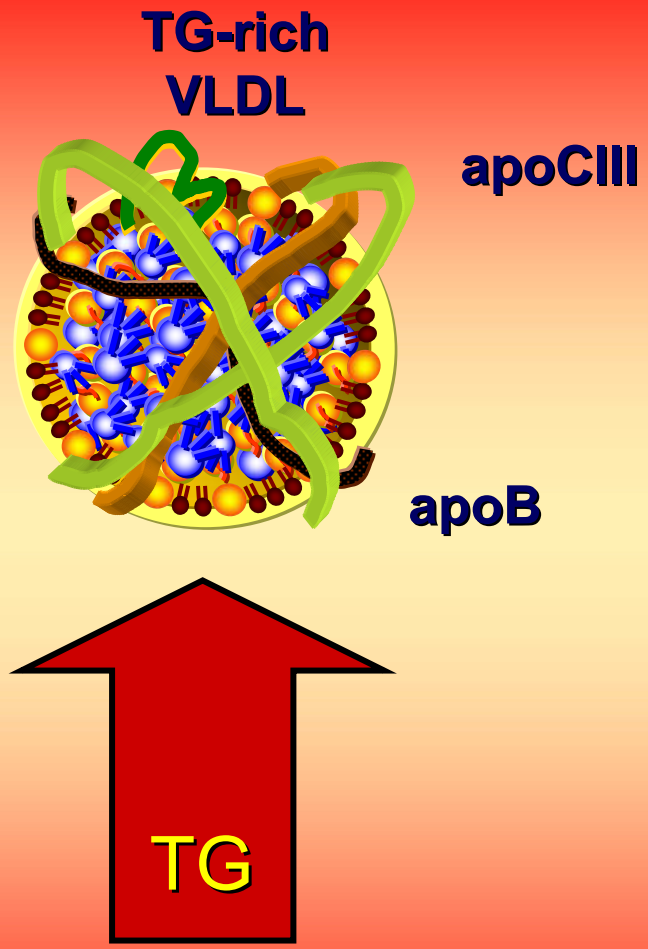
ApoA-V targets VLDL to proteoglycans placing VLDL in close proximity to LPL

After hydrolysis, VLDL remnants are released and apoA-V can be transferred to HDL and reused.

AV deficiency leads to hypertriglyceridemia

Merkel M et al. JCI 2006;115:2694-6

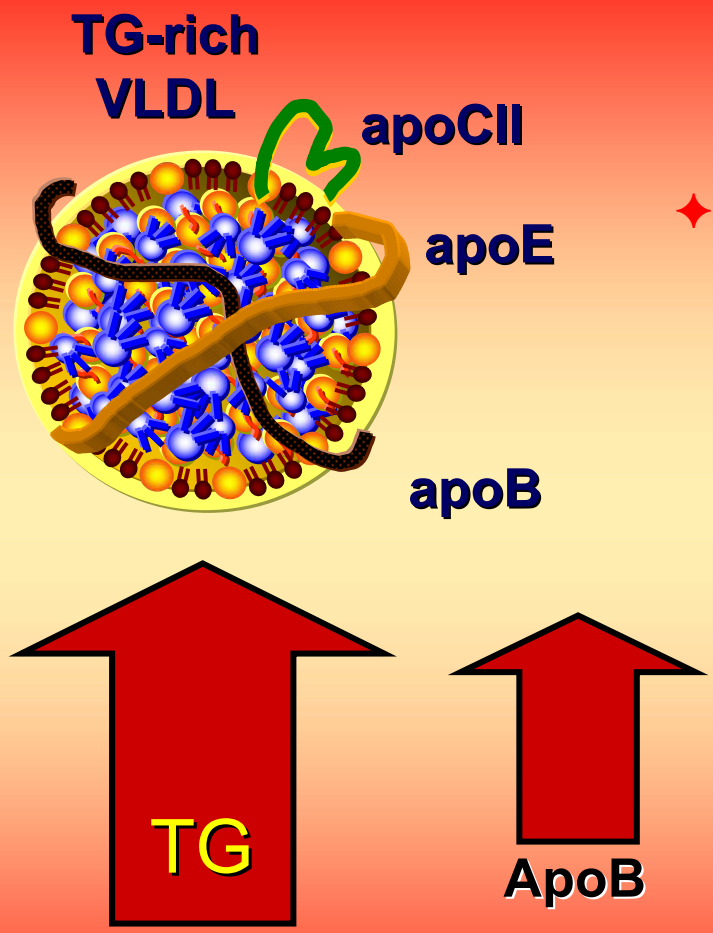
Lipoprotein Abnormalities in TG/HDL Axis Disorders



- ↑apoCIII is an independent risk factor for CHD
- ↑ apoCIII blocks or displaces apoCII and apoE, which delays VLDL lipolysis
- ↑apoCIII is associated with fasting and postprandial hypertriglyceridemia
- ↑apoCIII is common in insulin resistant patients

Triglyceride Cholesteryl ester

Rheological Abnormalities in TG/HDL Axis Disorders



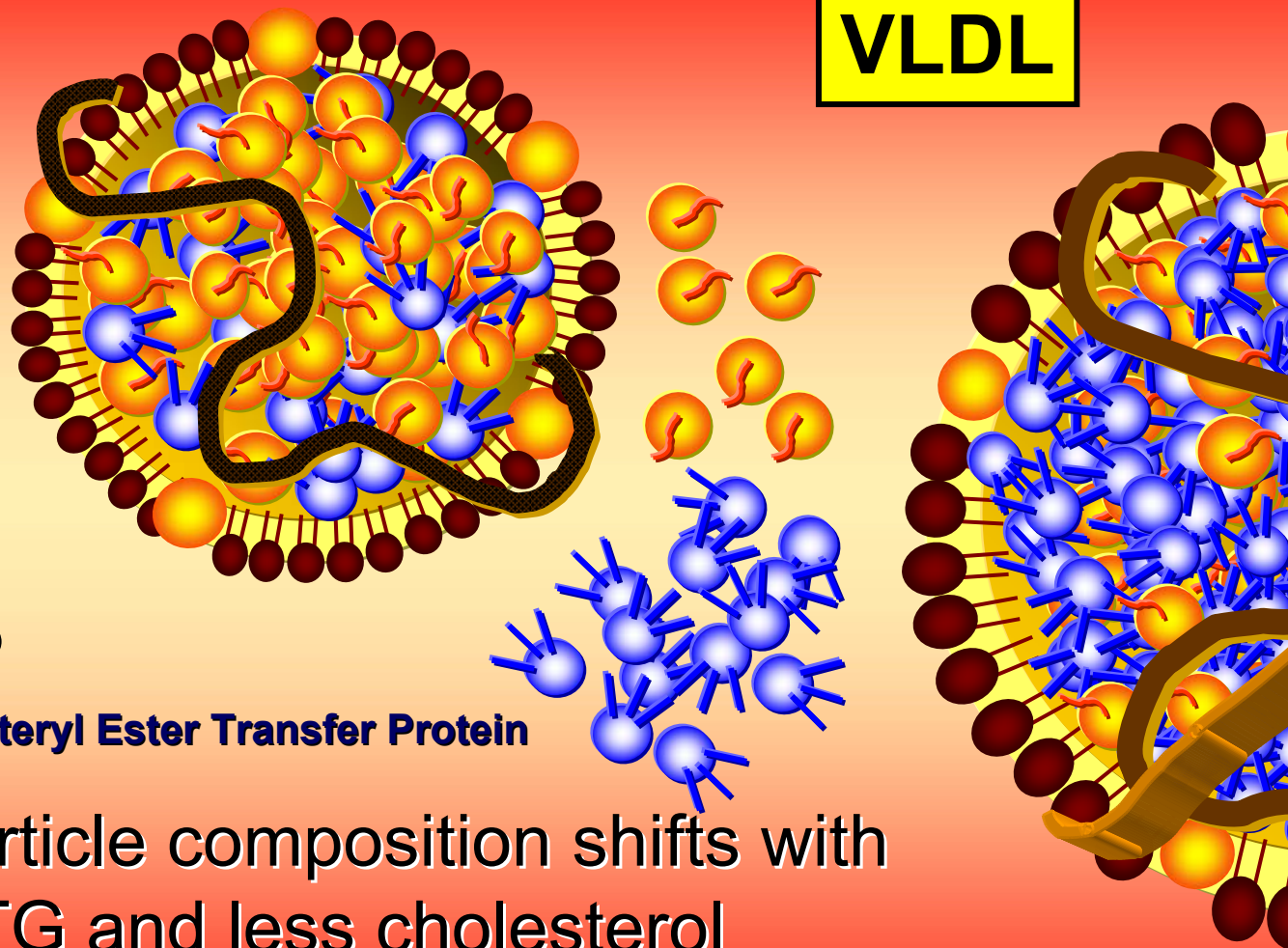
- **Increased hepatic production of large TG-rich VLDL particles is also associated with**
  - **Increased blood viscosity**
  - **Decreased arterial flow-mediated dilation (endothelial dysfunction)**
  - **Increased hypercoagulability**

Triglyceride Cholesteryl ester

LDL Particles in Patients with Elevated TG

LDL

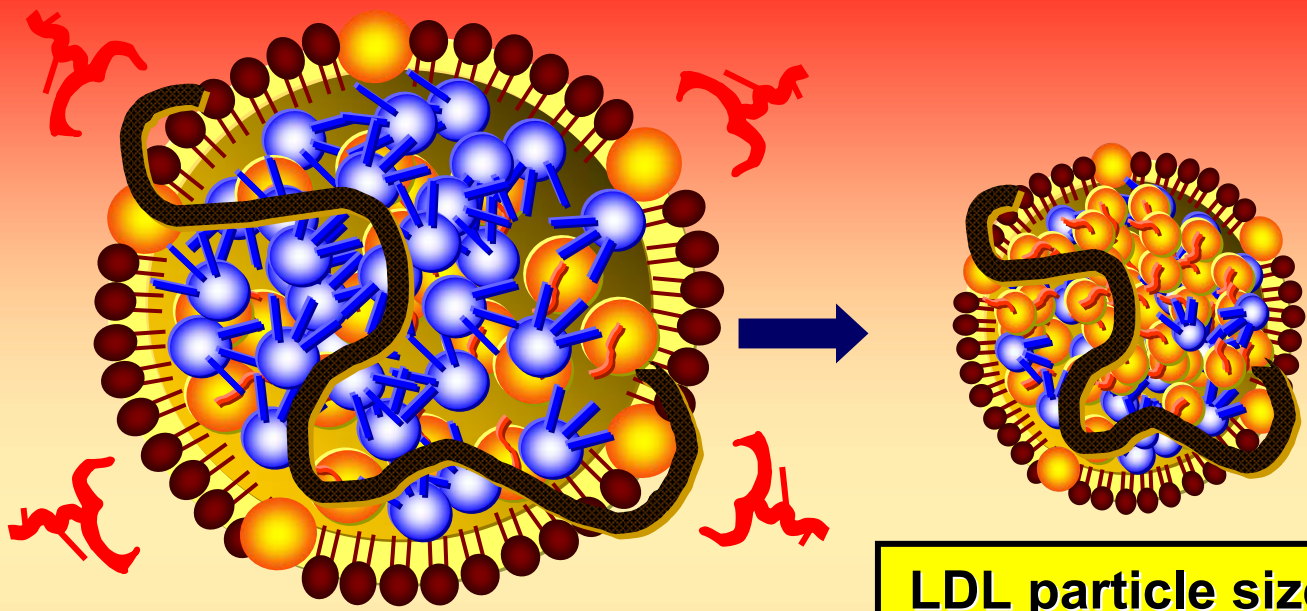
LDL-C is reduced



The LDL particle composition shifts with more TG and less cholesterol

Fate of TG-rich LDL Particles

LDL–C is reduced

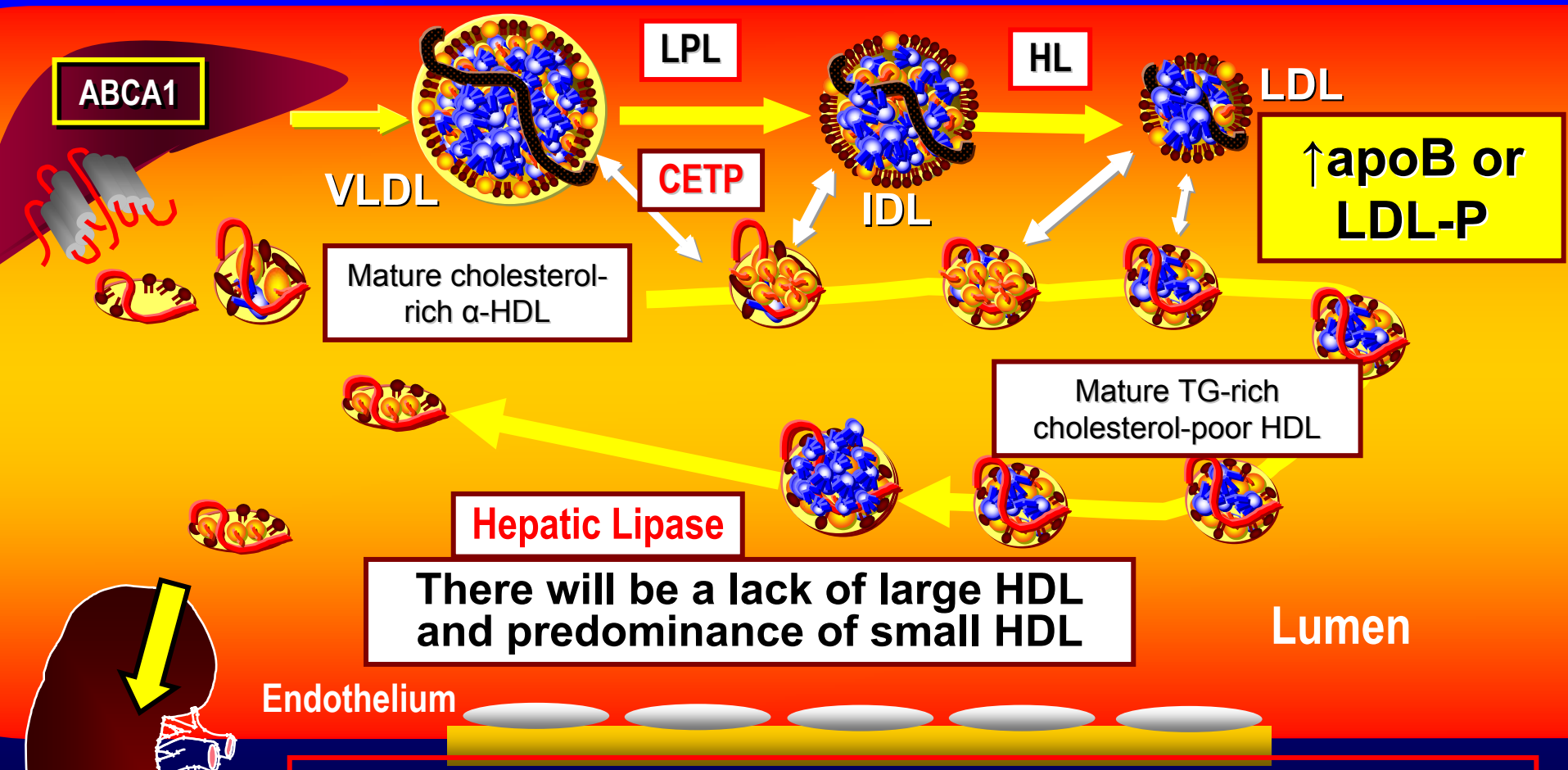


↑ LDL-P

LDL particle size is reduced

Hepatic Lipase causes further lipolysis (hydrolysis of TG & phospholipids) which reduces the size of the LDL particle

Triglyceride HDL Axis



HDL_3, facilitated by CETP, gathers TG, becomes a larger, TG rich HDL_2 which is subject to lipolytic action of hepatic lipase

With TG removal the large HDL_2 becomes a small HDL_3 which is is then subject to renal elimination or relipidation at ABCA1

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Adult Treatment Panel III NCEP-ATP III

Treatment of Triglycerides

What is the NCEP ATP III **goal for TG therapy,** if baseline TG is 200-500 mg/dL?

1) Normalize LDL-C
2) Normalize the non HDL-C value

} ↓ **ApoB**

TG are surrogates for apoB

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

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Adult Treatment Panel III NCEP-ATP III

Treatment of Low HDL-C

- **Low HDL-C: is defined as <40 mg/dL**

  No specific goal defined for raising HDL-C

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

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Treatment of Low HDL-C

- **Low HDL-C: is defined as <40 mg/dL**

  No specific goal defined for raising HDL-C

If HDL-C is low, the TC/HDL-C and Non HDL-C will likely be high

Low HDL-C is often a surrogate of elevated apoB

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

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Treatment of Low HDL-C

- **Low HDL-C: is defined as <40 mg/dL**
  No specific goal defined for raising HDL-C

- Targets of therapy:
  - Normalize LDL-C in all
  - Those with TG 200–499 mg/dL: achieve **non–HDL-C goal** as secondary priority

↓ **ApoB**

JAMA 2001;285 :2331-2338

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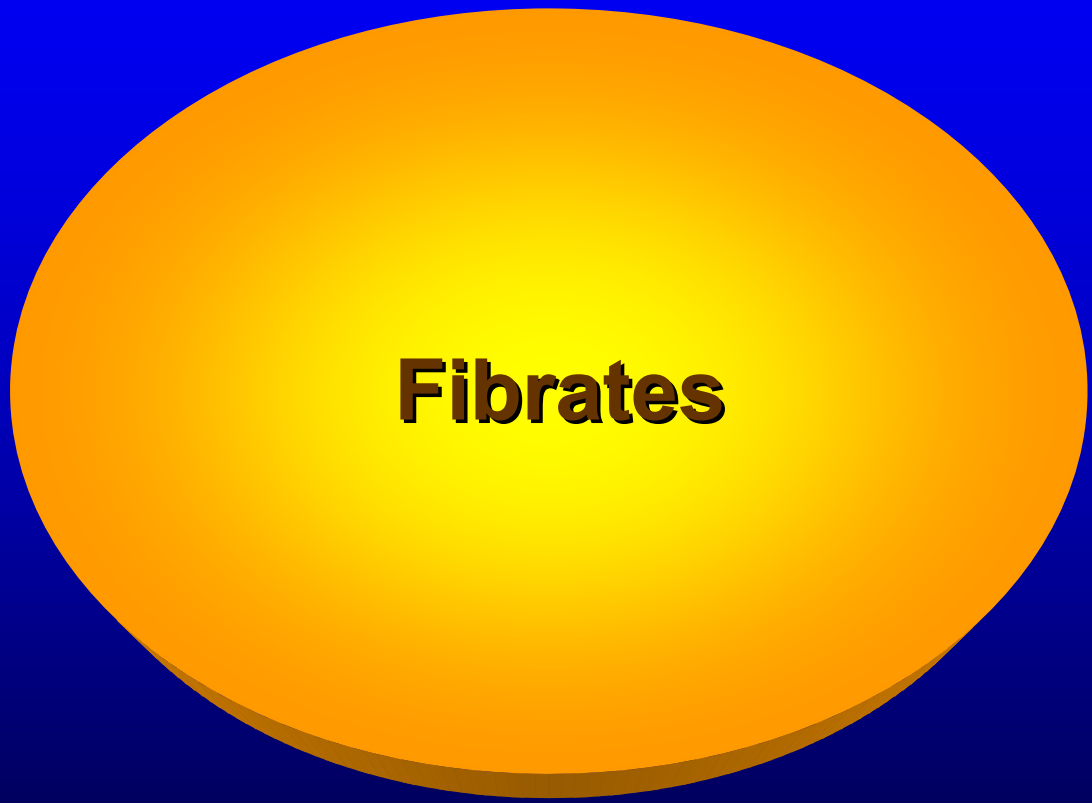
Adult Treatment Panel III NCEP-ATP III

Non HDL-C: Treatment

If the non HDL-C is elevated on a statin, it should be normalized with the use of a fibrate or niacin.

COMBINATION THERAPY

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421


Fibrates

Lipid-Modification Trials in Patients With Type 2 Diabetes

	Therapy	DM (n)
Secondary Prevention		
4S	simvastatin	202
CARE	pravastatin	586
Post-CABG	lovastatin	122
LIPID	pravastatin	1077
GISSI-Prevenzione	pravastatin	582
GREACE	atorvastatin	313
Primary Prevention		
WOSCOPS	pravastatin	76
AFCAPS/TexCAPS	lovasatin	155
CARDS	atorvastatin	2838
Mixed		
PROSPER	pravastatin	623
ALLHAT-LLT	pravastatin	3638
HPS	simvastatin	5963
ASCOT-LLA	atorvastatin	2532

All Statin = 18,707

	Therapy	DM (n)
Secondary Prevention		
VA-HIT	gemfibrozil	769
BIP	bezafibrate	309
Primary Prevention		
SENDCAP	bezafibrate	164
HHS	gemfibrozil	135
Mixed		
DAIS	fenofibrate	418
LEADER	bezafibrate	268

All Fibrate = 11,858

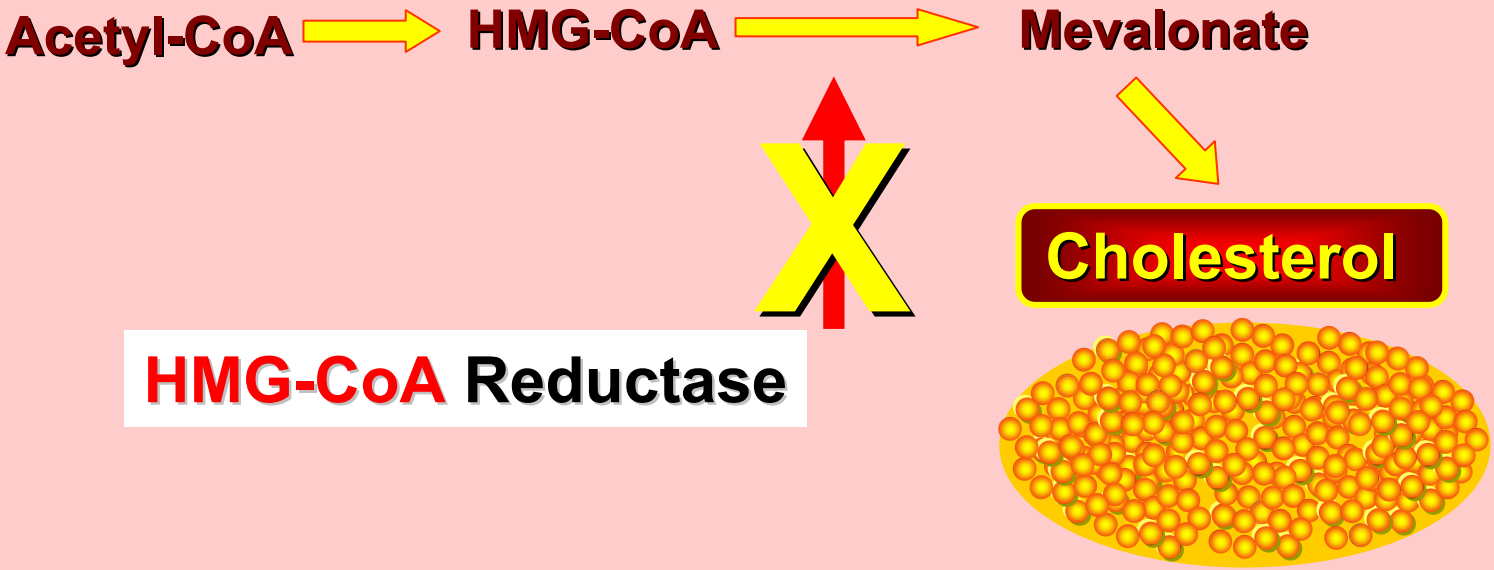
The FIELD Study

Primary and Secondary Prevention

N = 9795

FIELD Study Investigators. *Cardiovasc Diabetol*. 2004;3:9-24.

Statins: Mechanism of Action

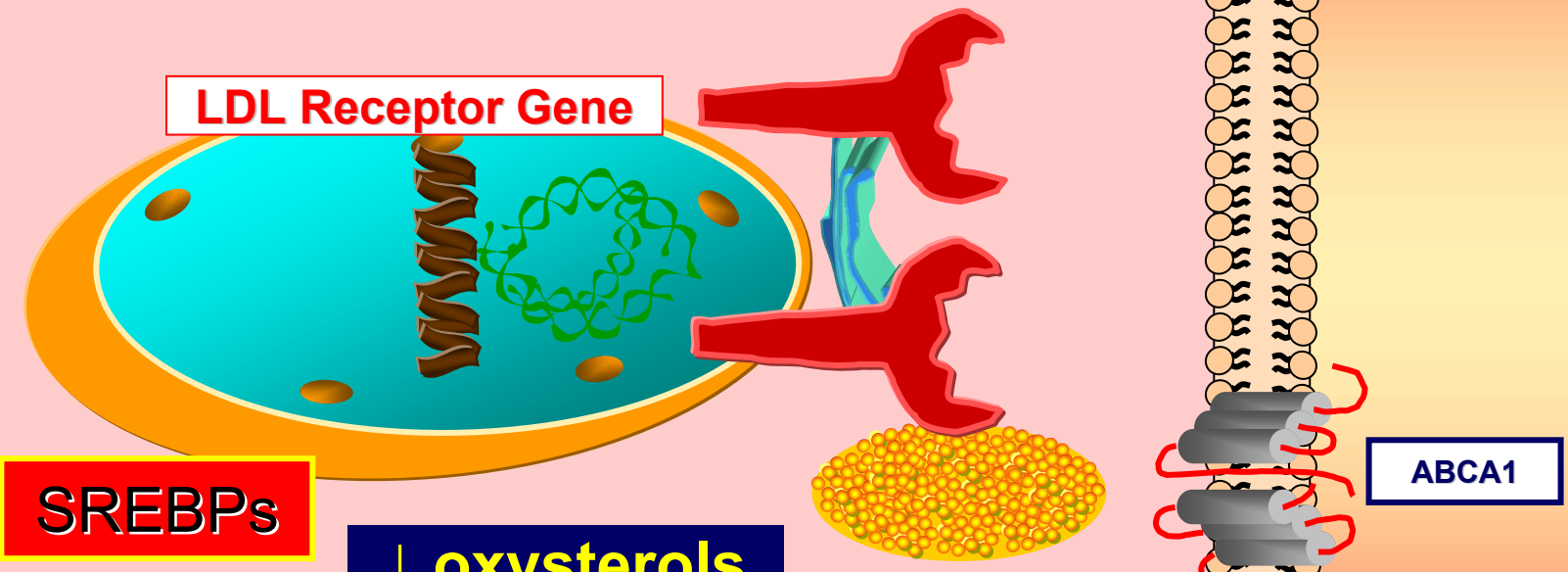


- Statins competitively inhibit HMG-CoA reductase, reducing cholesterol formation

Honda A et al. *J Lipid Res*. 1998;39:44–50.

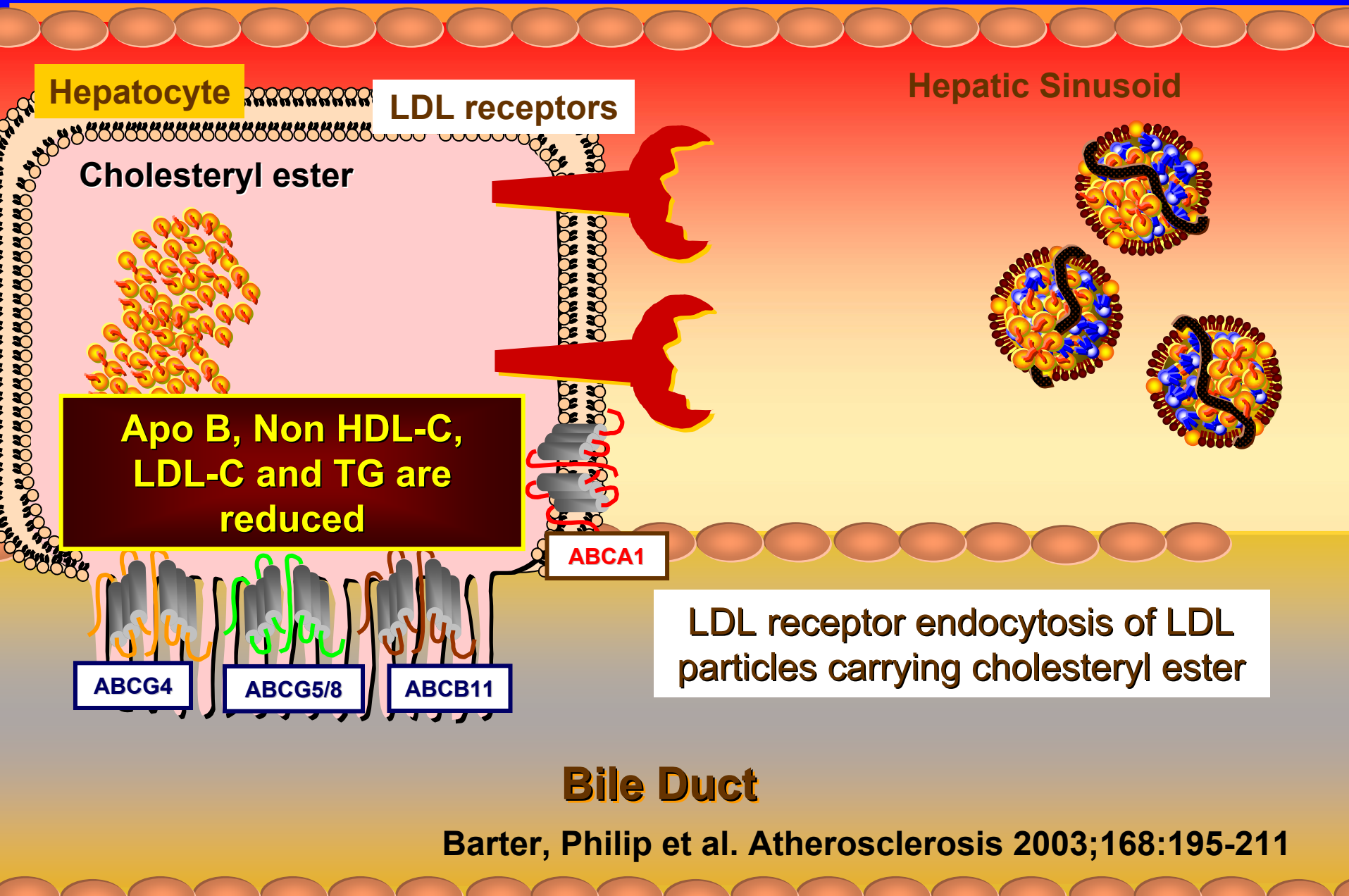
LDL Receptor Upregulation

Upon hepatocyte cholesterol depletion, SREBPs are upregulated



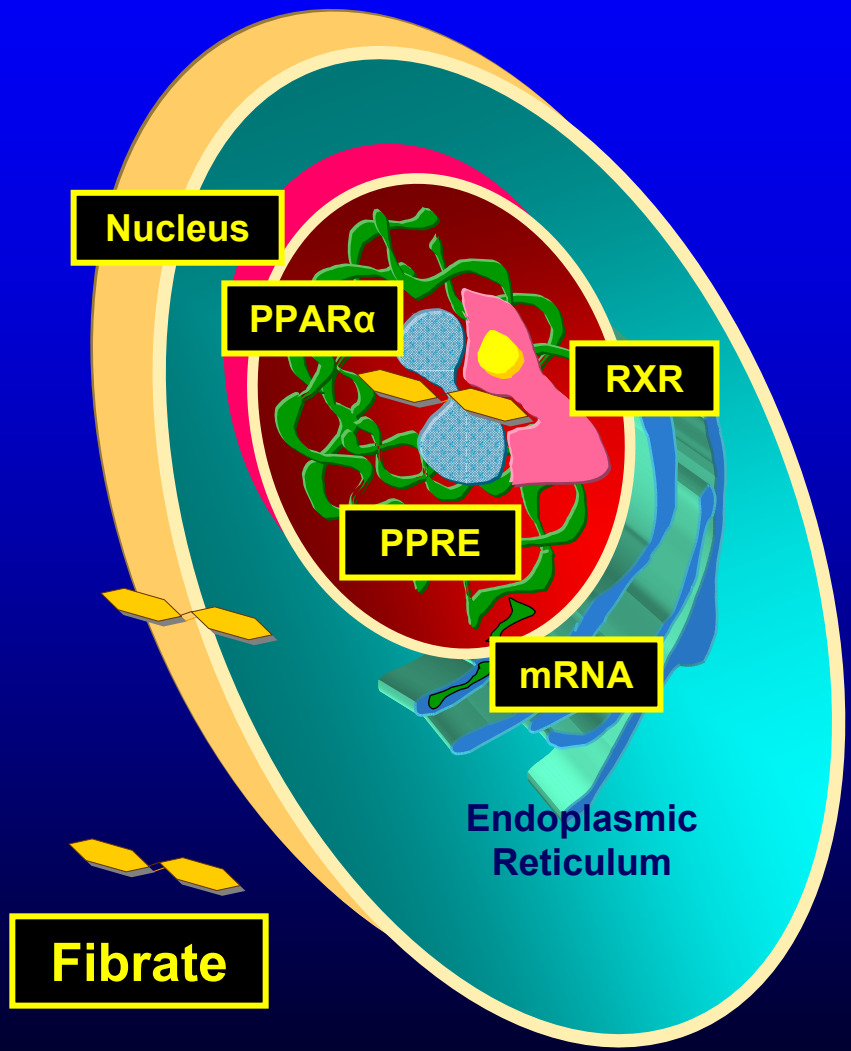
Sterol regulatory binding element proteins (SREBPs) are nuclear transcription factors regulating LDL receptors

Indirect RCT at the Hepatocyte



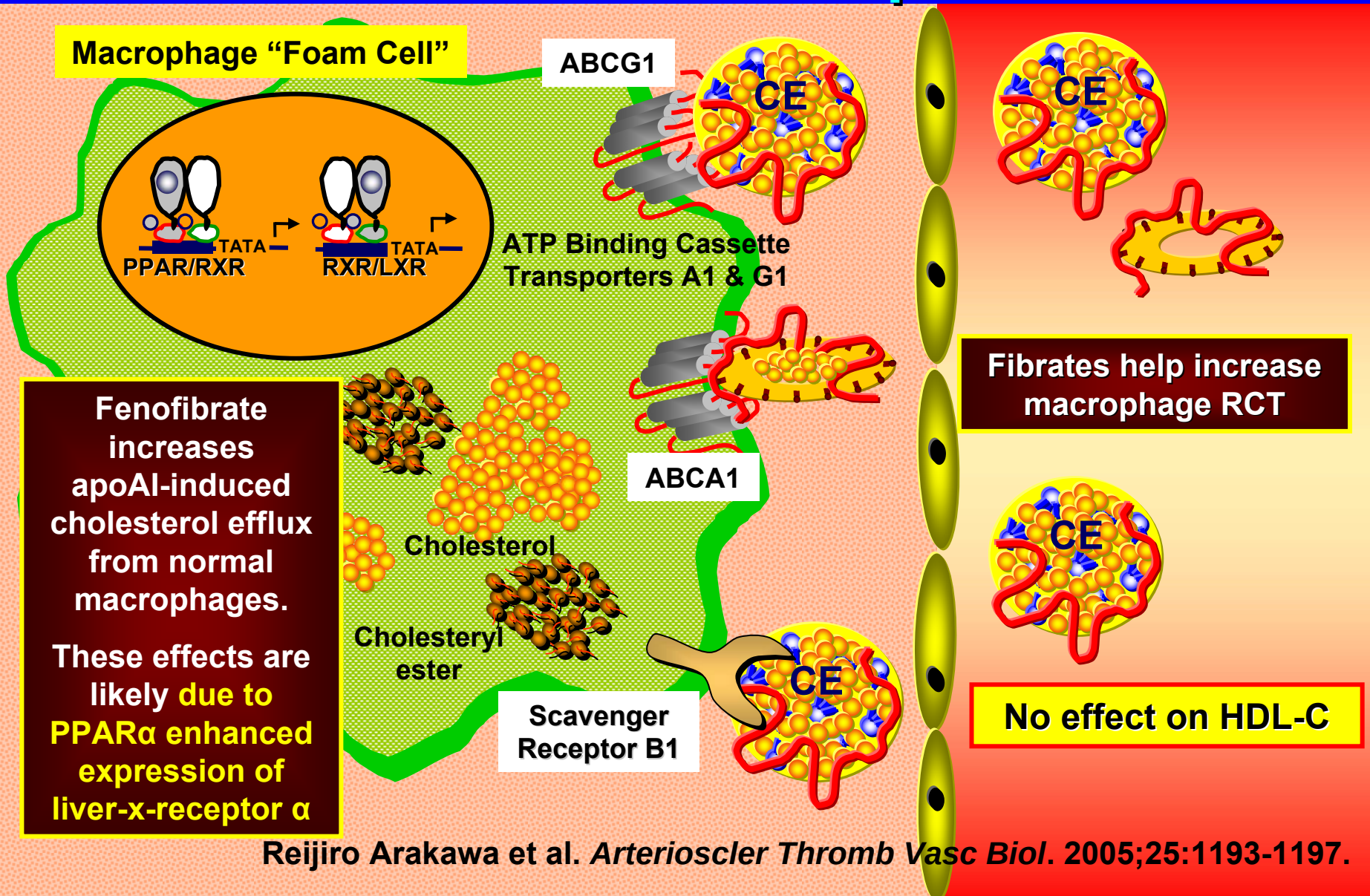
Barter, Philip et al. Atherosclerosis 2003;168:195-211

Fibrate agonism of PPARα and heterodimerization with Retinoid X Receptor



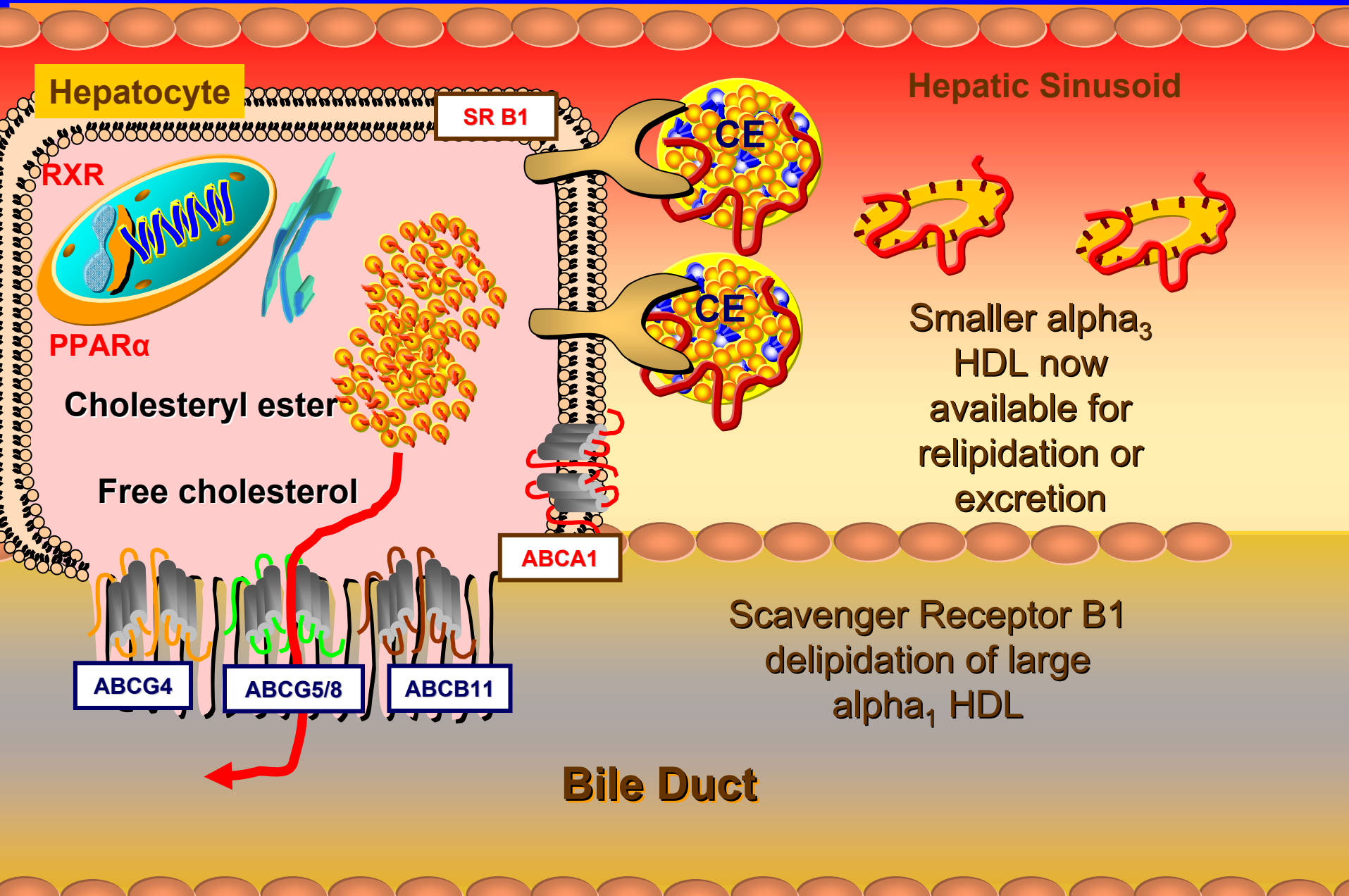
- ↑ Fatty acid catabolism
- ↓ TG synthesis
- ↑ insulin sensitivity
- ↑ production of lipoprotein lipase
- ↑ production of apoAI, apoAII and apoA-V
- ↓ production of apoCIII
- ↑ lipidation of HDL via ABCA1 upregulation
- ↑ hepatic delipidation of mature HDL via SR B1 upregulation
- ↑ macrophage reverse cholesterol transport and HDL functionality
- Beneficial modification of multiple inflammatory markers via transrepression of NFκB
- ↓ levels of hs-CRP & Lp-PLA2

Fibrates and Macrophage Reverse Cholesterol Transport



Reijiro Arakawa et al. *Arterioscler Thromb Vasc Biol*. 2005;25:1193-1197.

Direct RCT at the Hepatocyte



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Adult Treatment Panel III NCEP-ATP III Addendum

Use of Fibrates

One class of drugs that modestly raises HDL-C is the fibrates.

Post-hoc analysis of several clinical trials with fibrates indicates that they reduce risk for CHD events in patients with high triglycerides and low HDL-C, especially when the patients have diabetes or characteristics of the metabolic syndrome.

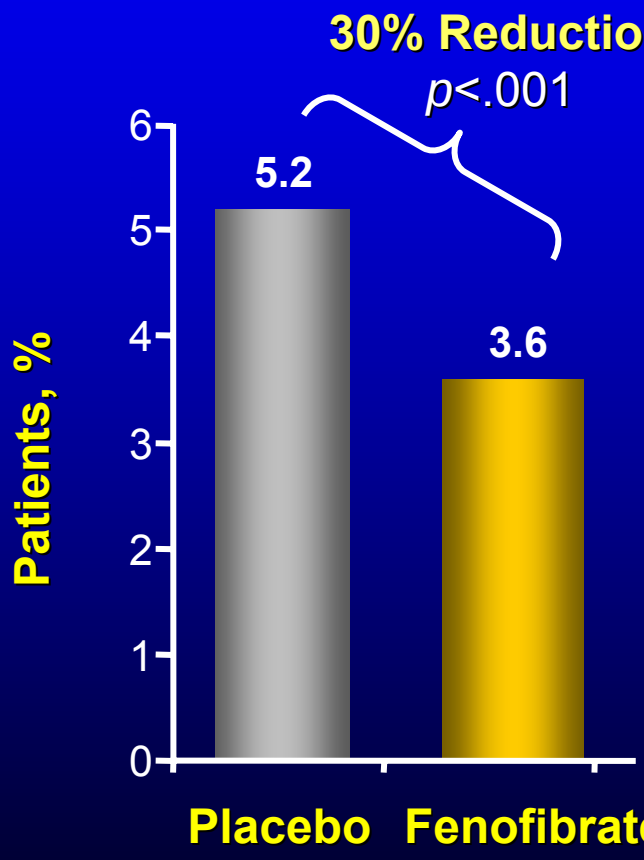
Although the evidence base to support fibrate therapy is not as strong as that for statins, fibrates may have an adjunctive role in the treatment of patients with high triglycerides/low HDL-C,

especially in combination with statins.

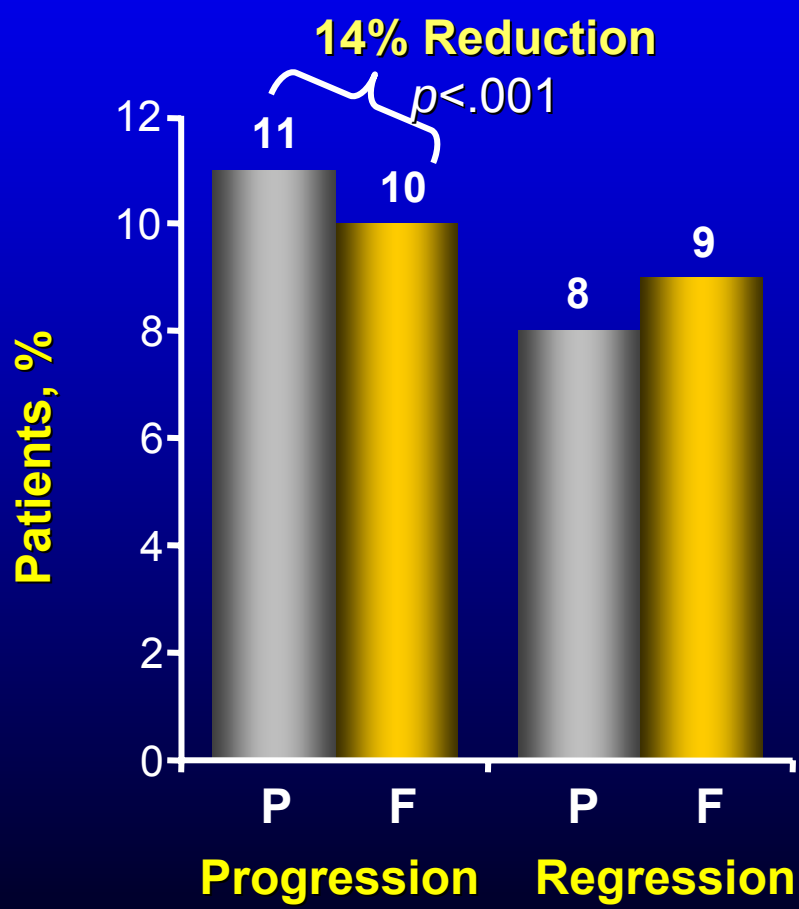
Circulation 2004;110:227-239

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

Laser Treatment for Retinopathy



Progression and Regression of Albuminuria*



*Progression of albuminuria was defined as the proportion of patients who progressed either from normoalbuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria

Keech A, et al. *Lancet.* 2005;366:1849-1861.

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

- **Amputations**
  - Placebo 74 (1.5%)
  - Fenofibrate 51 (1.0%)
  - RR = 0.69 (95% CI = 0.48-0.99) p = 0.04

31%

- **Hospitalizations for Angina Pectoris**
  - Placebo 252 (5.1%)
  - Fenofibrate 209 (4.3%)
  - RR = 0.82 (95% CI = 0.69-1.00) p = 0.04

18%

Tertiary Endpoint

The FIELD Study Investigators.

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Adult Treatment Panel III NCEP-ATP III Addendum

Use of Fibrates

Concern about development of myopathy with this combination has been lessened somewhat by the recent finding that one fibrate, **fenofibrate**, does not interfere with catabolism of statins

and thus likely does not substantially increase the risk for clinical myopathy in patients treated with moderate doses of statins.

Circulation 2004;110:227-239

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Adult Treatment Panel III NCEP-ATP III

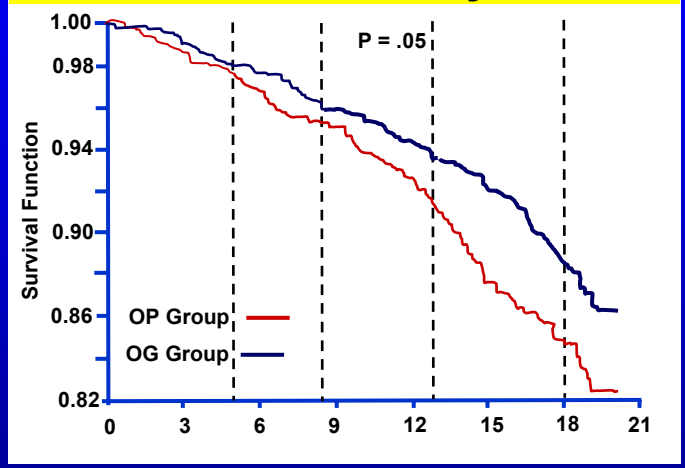
Mortality and Fibrates

- Worldwide clinical experience with various fibrates is vast
- No evidence of specific toxicity that enhances non-CHD mortality has emerged
- This experience, taken in the light of all the clinical trials, provides little support for the concern that fibrates carry significant short-term toxicity that precludes their use for appropriately selected persons.

NCEP JAMA 2001;285:2486 Final Report Circulation 2002;106:3143-3421

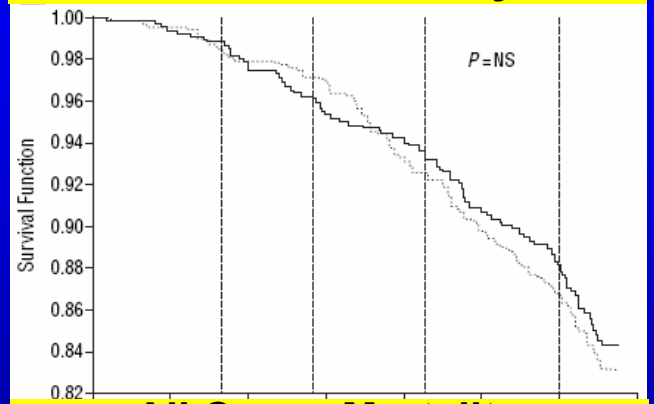
Helsinki Heart Study (HHS): 18 Year Follow UP of Mortality

CHD Mortality

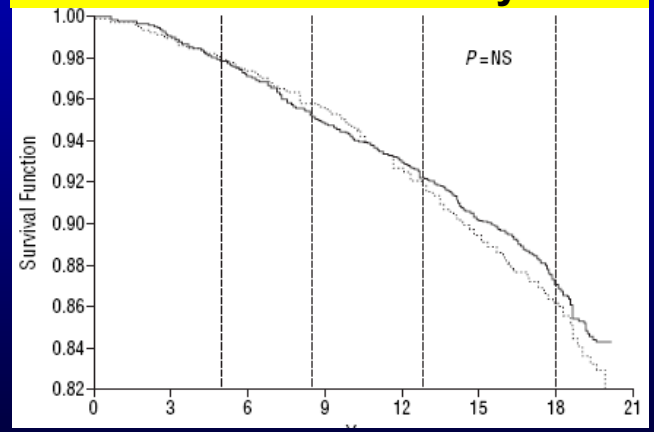


Those in the OG group **with both body mass index and triglyceride level in the highest tertiles** had a 71% lower RR of CHD mortality (*P*.001), a 33% lower RR of all cause mortality (*P*=.03), and a 36% lower RR of cancer mortality (*P*=.22) compared with those in the OP group.

Cancer Mortality

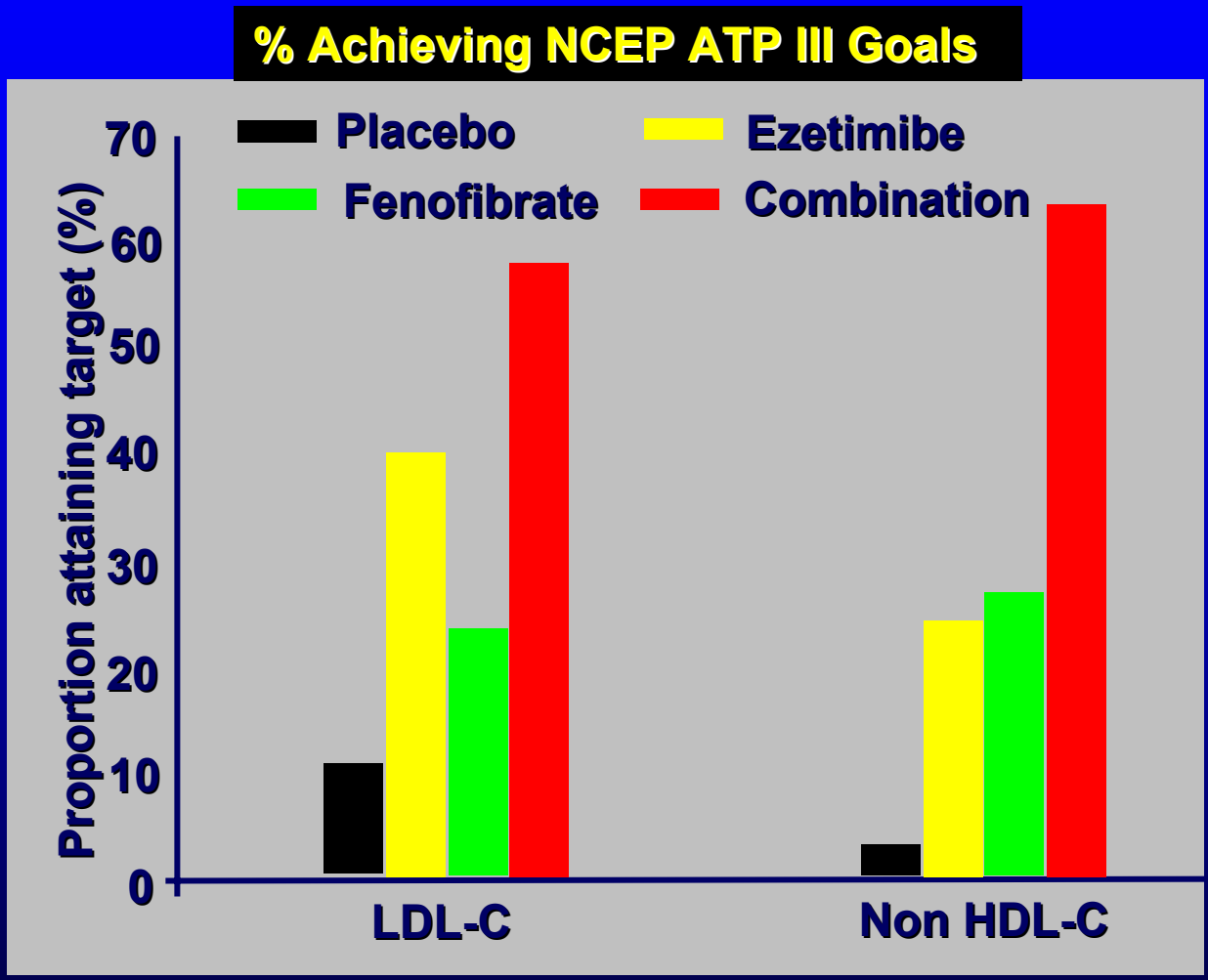


All Cause Mortality



Tenkanen L. et al. Arch Int Med 2006;166:743-748

Ezetimibe – Fenofibrate Study



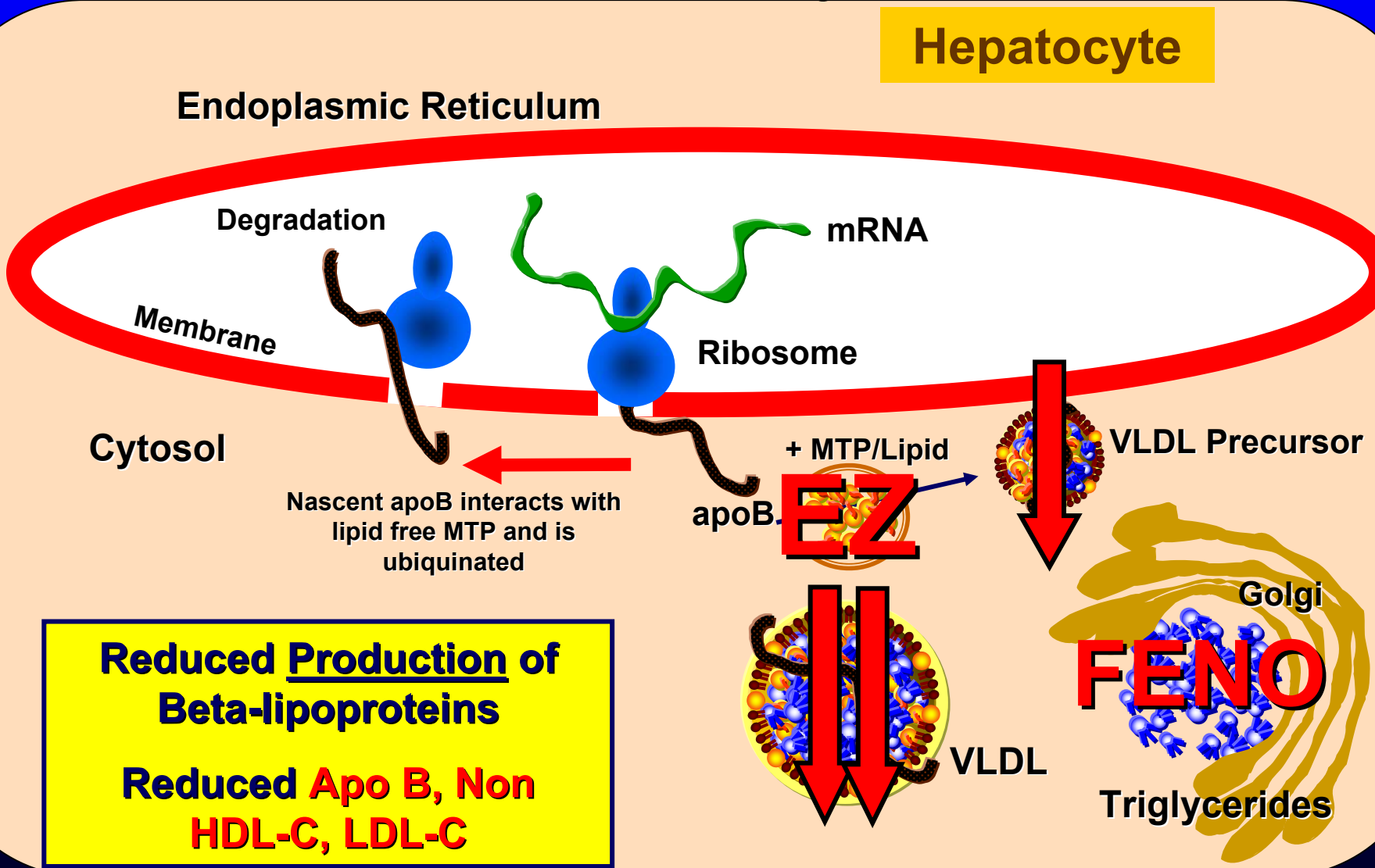
More than 62% of patients shifted to the larger, more buoyant LDL pattern from the smaller, more dense pattern with coadministration, and FENO alone treatments.

The Non HDL-C goal attainment was comparable across baseline TG values

Baseline: LDL-C ~ 140
HDL-C ~ 40 TG ~ 240

Farnier M, et al. *Eur Heart J.* 2005;26:897-905.

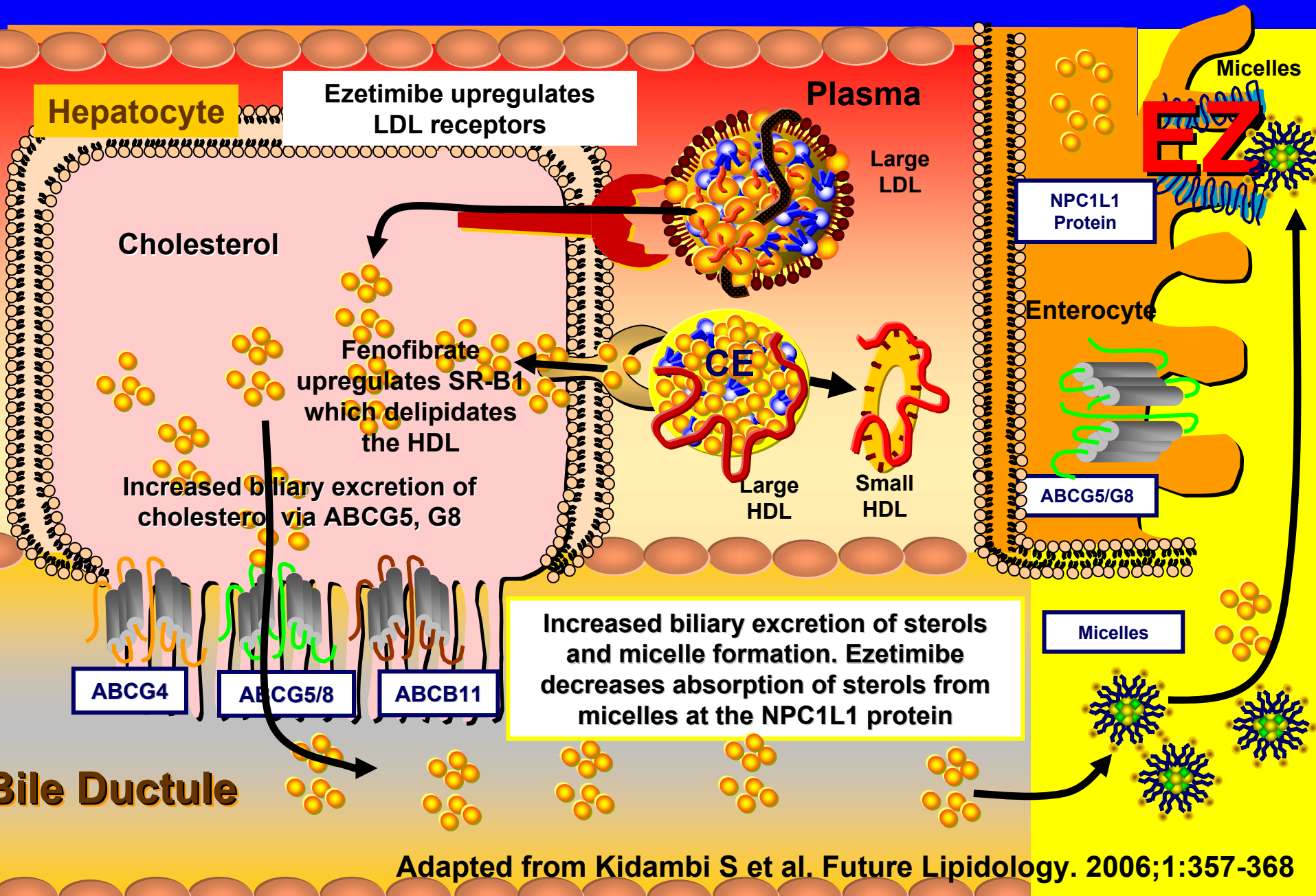
Ezetimibe & Fenofibrate Decrease Beta-lipoprotein Synthesis



Reduced Production of Beta-lipoproteins

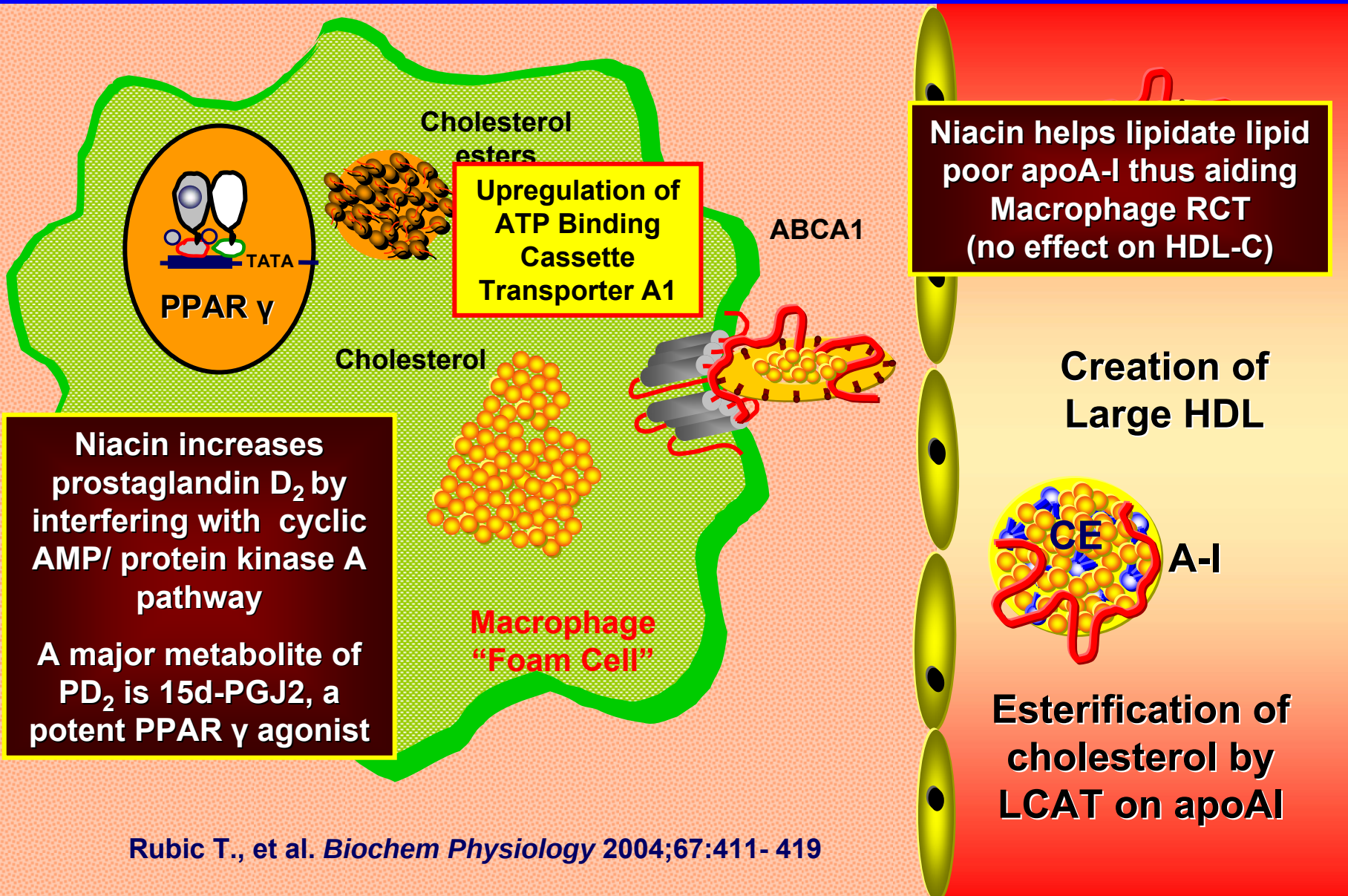
Reduced Apo B, Non HDL-C, LDL-C

Ezetimibe and Fenofibrate Increase Stool Cholesterol Excretion



Adapted from Kidambi S et al. Future Lipidology. 2006;1:357-368

Niacin and Monocyte ABCA1 Transporters



Rubic T., et al. *Biochem Physiology* 2004;67:411- 419

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Adult Treatment Panel III NCEP-ATP III Addendum

Use of Niacin

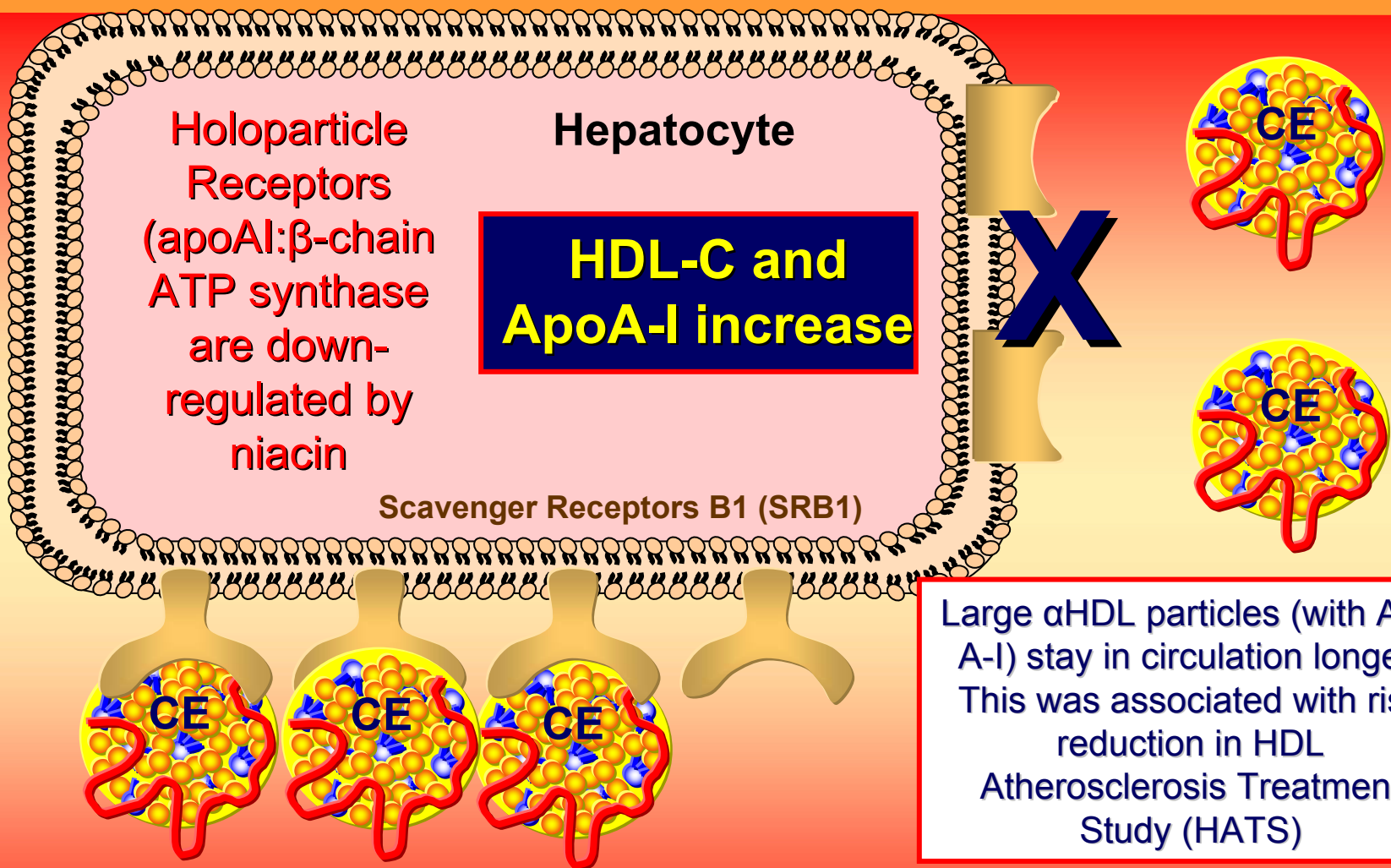
Another drug that raises HDL-C is **nicotinic acid**. Several clinical trials support the efficacy of nicotinic acid for reduction of CHD risk, both when used alone and in combination with statins.

The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. statin/nicotinic acid combination.

Although the majority of patients can tolerate nicotinic acid therapy, a sizable minority are intolerant because of a variety of side effects.

Circulation 2004;110:227-239

Niacin & Reverse Cholesterol Transport

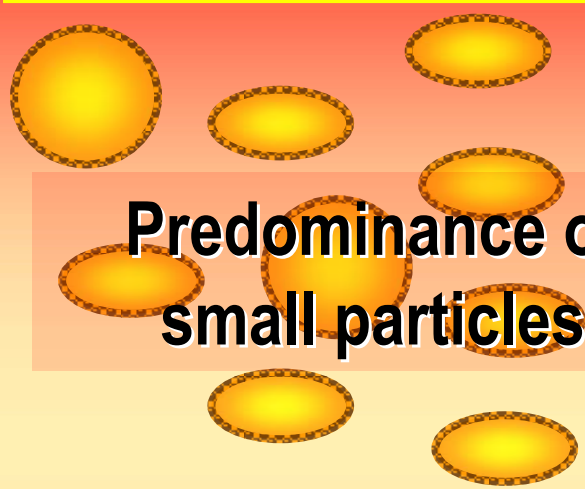


Large αHDL particles (with Apo A-I) stay in circulation longer. This was associated with risk reduction in HDL Atherosclerosis Treatment Study (HATS)

Kashyap M. Am J Cardiol 1998;82:42U-48U)
Curr Opin Card 2004;19:366-373

Drug Effect on HDL-C vs HDL-P

Patient on Fenofibrate



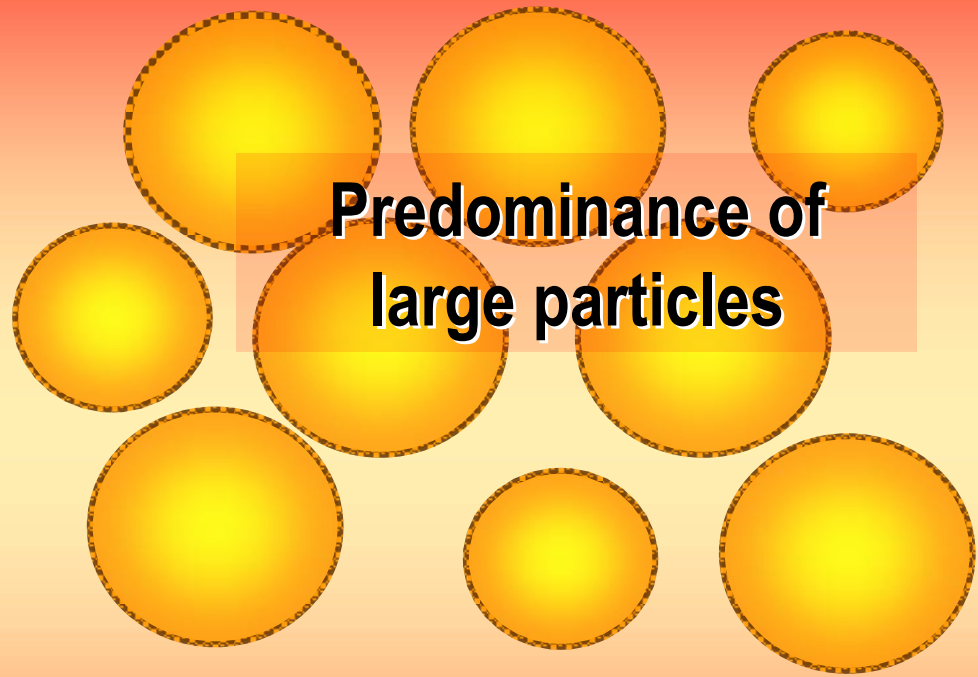
Predominance of small particles

HDL-P = X

HDL-C = Y

↑ Biliary Cholesterol

Patient on Niacin



Predominance of large particles

HDL-P = X

HDL-C > Y

Targeting HDL Metabolism and RCT

HDL metabolism is exceedingly complex, and because the protective ability of HDL may relate to the flux of cholesterol through the RCT pathway and to other aspects of HDL functionality, the plasma level of HDL-C alone **is almost certainly not** an adequate predictor of the potential clinical benefit of an HDL-targeted therapy.

Some interventions that raise HDL-C may not reduce atherosclerosis or cardiovascular events; conversely, other interventions may not raise HDL-C but through effects on RCT or HDL function may have major effects on atherosclerosis or cardiovascular events.

There is a great need for the development of novel biomarkers and kinetic methods to assess the effects of novel interventions on RCT and HDL function.

Duffy D & Rader D. Circulation 2006;113:1140-1150