Understanding Nicotinic Acid

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On Going Investigations

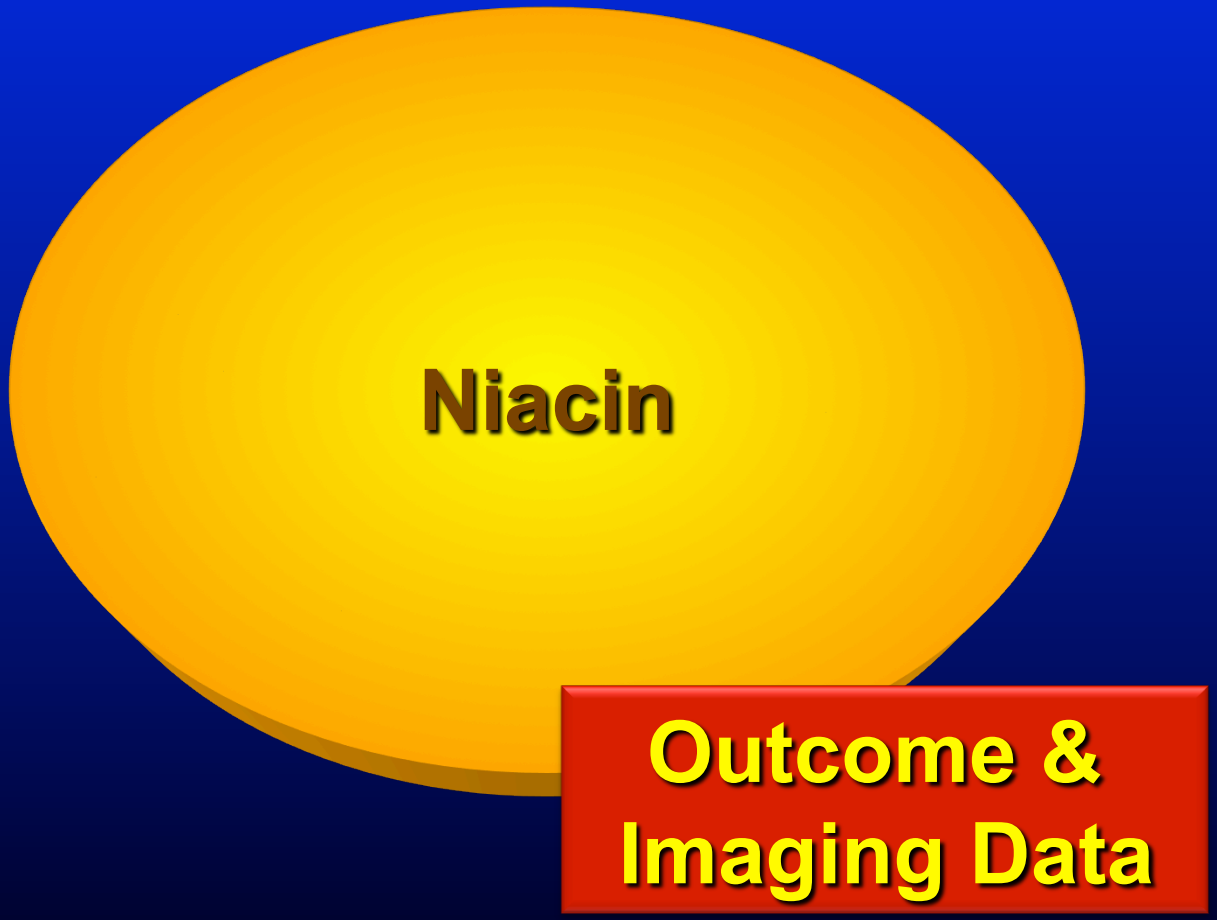
Niaspan Trials

ENCOUNTER Niaspan phase 4 studies

FAST (Flushing Tool Validation Study): ASA Study

HALTS (**ARBITER6**) HDL and LDL treatment strategies

CIMT Statin Ezetimibe vs Statin niacin


Niacin
Outcome &
Imaging Data

Niacin Clinical Trial Data

- CDP: Coronary Drug Project (#1119)
- Stockholm IHD: Ischemic Heart Disease Secondary Prevention Trial (#290)
- CLAS: Cholesterol Lowering Atherosclerosis Study (#162)
- UCSF-SCOR: University of California, San Francisco Atherosclerosis Specialized Center of Research Intervention Trial (#72)
- HARP: Harvard Atherosclerosis Reversibility Project (#79)
- FATS: Familial Atherosclerosis Treatment Study (#146)
- HATS: HDL Atherosclerosis Treatment Study (#160)
- AFREGS: Armed Forces Regression Study (#143)
- ARBITER 2 & 3 Arterial Biology for the Investigation of the Effects in Reducing Cholesterol (ARBITER 2 & 3): (#149)

Guyton JR. Current Opinion in Lipidology 2007, 18:415–420

Niacin Outcome or Angiographic Trials

Coronary Drug project (CDP): Niacin vs placebo

Stockholm IHD: Niacin + Clofibrate vs placebo

Cholesterol Lowering Atherosclerosis Study (CLAS): Niacin + Colestipol vs placebo

UCSF-Specialized Center for Atherosclerosis research (UCSF-SCOR): University of California, San Francisco Atherosclerosis Specialized Center of Research Intervention Trial: BAS, niacin, statin

Harvard Atherosclerosis Reversibility Project: Stepwise therapy with pravastatin, slow-release niacin, cholestyramine, and gemfibrozil versus placebo

Familial Atherosclerosis Treatment Study (FATS): Niacin plus colestipol versus lovastatin plus colestipol versus placebo

HDL Atherosclerosis Treatment Study: Niacin plus simvastatin versus placebo

Armed Forces Regression Study (AFREGS): Niacin, gemfibrozil, and cholestyramine versus limited use of cholestyramine alone

Arterial Biology for the Investigation of the Effects in Reducing Cholesterol (ARBITER 2 & 3): Niacin plus simvastatin on CIMT

Total # in niacin trials = 2320

Niacin Outcome or Angiographic Trials

- **CDP:** Myocardial infarction ↓ 26% (P<0.05) and total mortality ↓ 11% over 15 years (P¼0.0004 (#1119)
- **Stockholm IHD:** Total mortality ↓ 26% (P<0.05) and ischemic heart disease mortality ↓ 36% (P<0.01) (#290)
- **CLAS:** Less progression (P<0.001) and more regression (P=0.002) of coronary lesions (#162)
- **UCSF-SCOR:** Intensively treated patients had mean regression of coronary lesions versus progression in control patients (P=0.039) (#72)
- **HARP:** No effect on mean minimum coronary artery diameter; trend toward fewer clinical coronary events (14% versus 21%; P=0.19) (#79)
- **FATS:** Mean regression of coronary lesions in intensively treated groups versus progression in control group (P<0.003); clinical events reduced by 73% (P<0.05) (#146)
- **HATS:** Angiographic regression of coronary lesions with niacin–statin combination therapy (P<0.001 versus placebo); clinical events reduced by 70% (P=0.03) (#160)
- **AFREGS:** Mean regression of coronary lesions with intensive treatment versus progression in controls (P<0.05); clinical events reduced by 50% (P<0.05) (#143)
- **ARBITER 2 & 3:** Mean regression of carotid intima–medial thickness at 2 years (P0.001 versus baseline) (#149 in A2,130 of them in A3)

Total # in niacin trials = 2320

Niacin Outcome or Angiographic Trials

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AFREGS: Mean regression of coronary lesions with intensive treatment versus progression in controls (P<0.05); clinical events reduced by 50% (P<0.05)

ARBITER 2 & 3: Mean regression of carotid intima–medial thickness at 2 years (P0.001 versus baseline)

Outcome Trials in Patients With Type 2 Diabetes

Niacin Therapy	# diabetics
CDP: #1119 patients on niacin Insulin dependent diabetes excluded #61 were diabetics taking oral agents	61
CLAS: #162 patients on colestipol & niacin Diabetes excluded	0
FATS: #146 on Niacin, colestipol, lovastatin Diabetics excluded	0
HATS #146 The Simva- Niacin group was #33 Diabetes #25 in all arms of the study	< 25
ARBITER-2 #87 patients: 24 were diabetics	24

~ 100

Clinical Trials Enrolling Diabetics

- **Niacin**
  - No prospective outcome data from any clinical outcome trials enrolling diabetics
  - HATS
    - (n = 160: 16% with diabetes)
  - ARBITER 2, 3
    - (n = 167: 28% with diabetes)

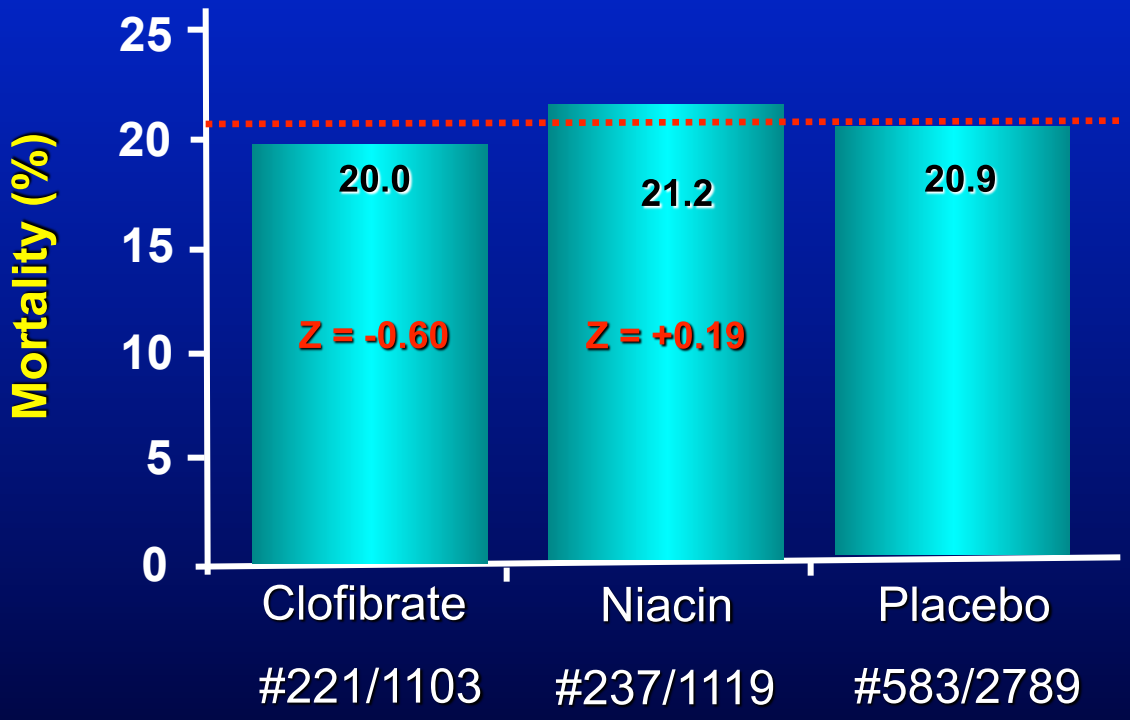
Coronary Drug Project (CDP)

- Men aged 30-64 with at one or more MI (at least 3 months post and not unstable)
- Treatment allocated 1966-1969
- Primary endpoint was total mortality
  - Coronary mortality, sudden death, nonfatal coronary events (MI)
- Compliance rate was 82%

JAMA 1975;231:360-381

Coronary Drug Project (CDP)

All Cause Mortality at 5 Years



Result is not statistically significant unless it achieves a

$z > 2.58$ or < 2.58

A negative z value denotes an event rate in the drug group that is lower than that in placebo group

T2DM on oral agents

Clofibrate #65 Niacin #61

JAMA 1975;231:360-381

Coronary Drug Project
Five Year Data

On the basis of data from the CDP, there is no specific efficacy of niacin with respect to total mortality and cause specific mortality.

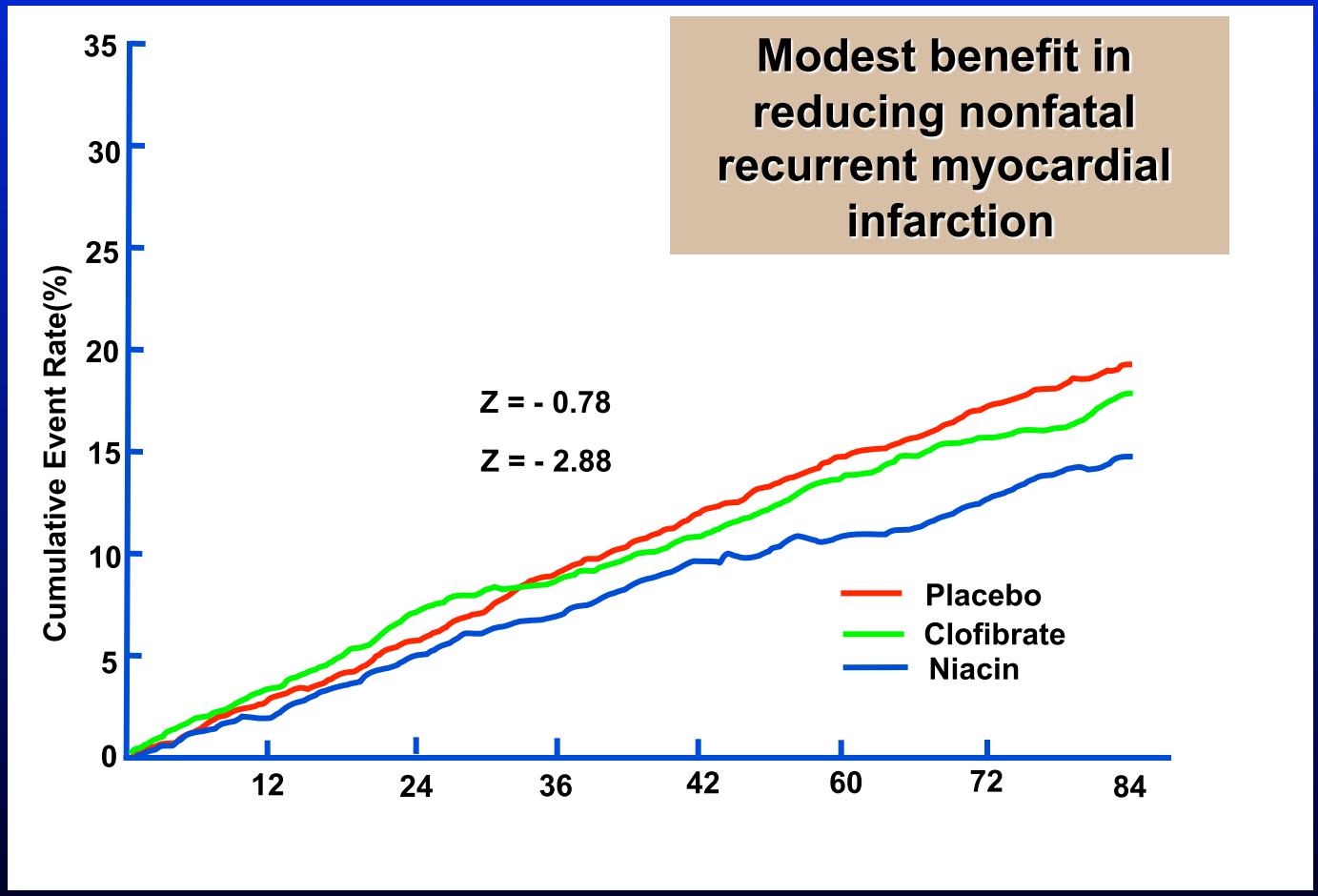
The five year total mortality for niacin was slightly higher than that for the placebo group (21.2% vs 20.9%).

Niacin patients = 1119 Placebo 2789
Clofibrate 1103

JAMA 1975;231:360-381

Coronary Drug Project (CDP)

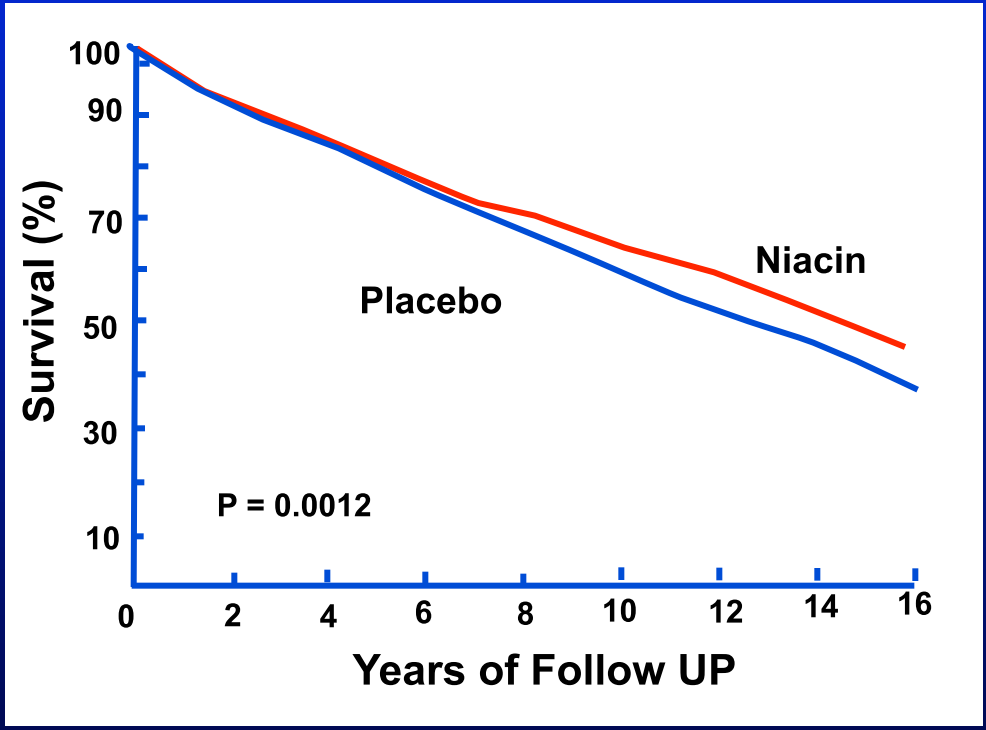
Nonfatal Myocardial Infarction



JAMA 1975;231:360-381

Coronary Drug Project (CDP)

Survival Curves for Niacin and Placebo Groups



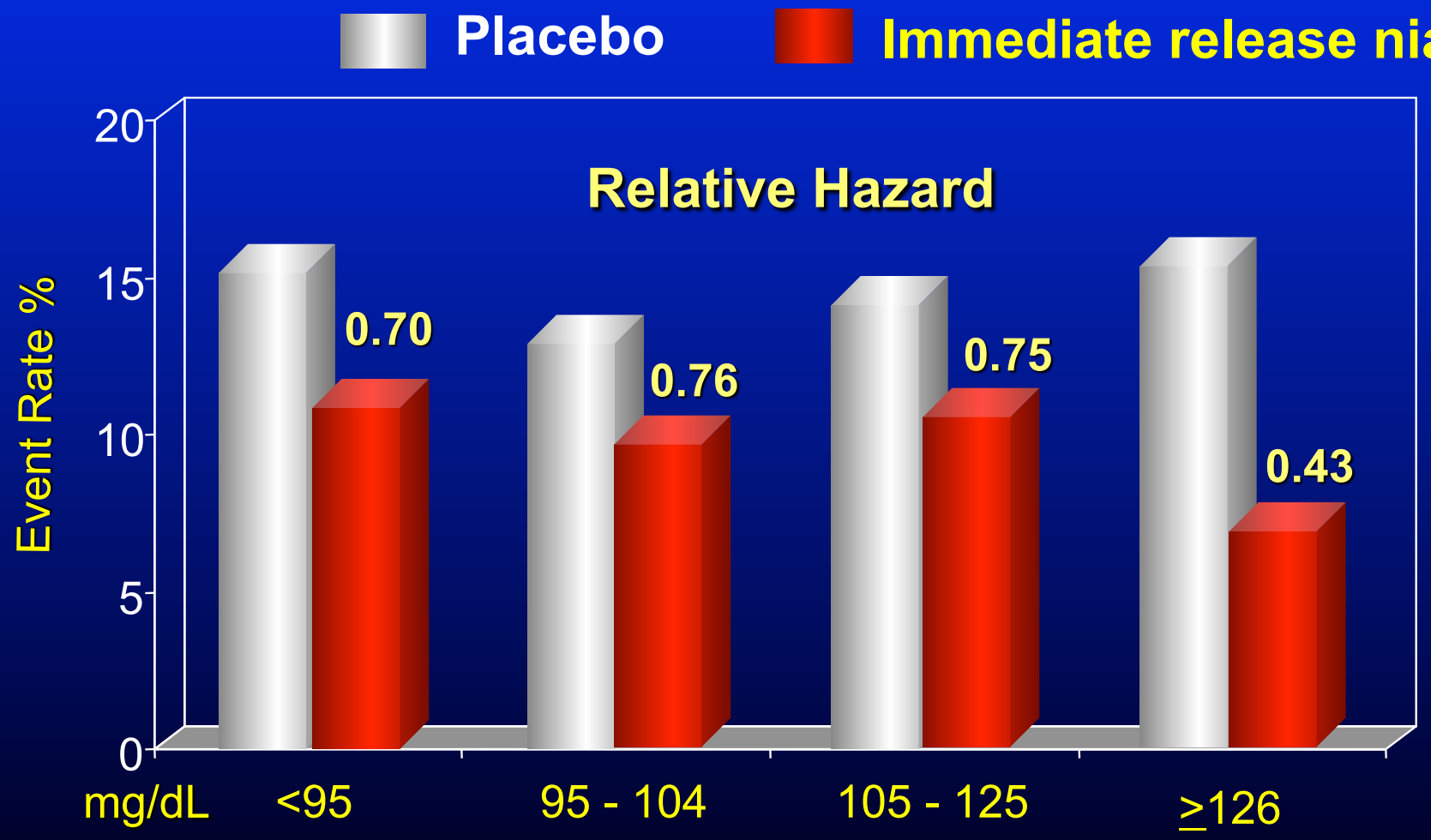
With a mean follow-up of 15 years, nearly 9 years after trial termination mortality from all causes was 11% lower in the niacin group compared to placebo group (52-58%; p = 0.0004).

This late benefit of niacin (off medication) may be a result of translation into a mortality benefit over subsequent years of the early favorable effect

Vital status follow up was by letters, telephone calls to patients or relatives or neighbors, physicians and employees as well as Social Security Administration, VA File system & National Search Agency

JACC 1986;8:1245-55

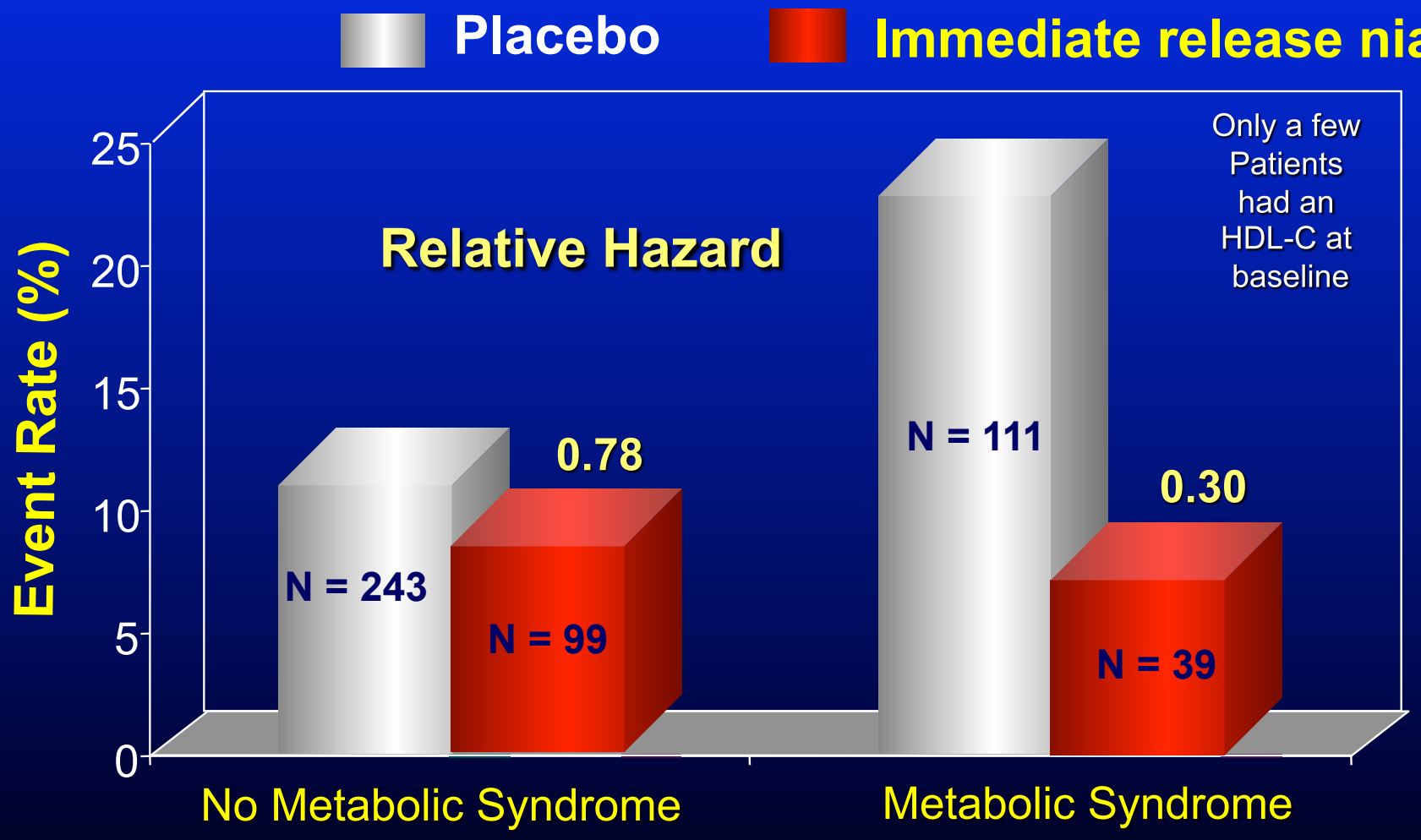
Coronary Drug Project at 6 Years: Nonfatal MI by Baseline FBG*



*Z for interaction = -0.35. Indicates homogeneity

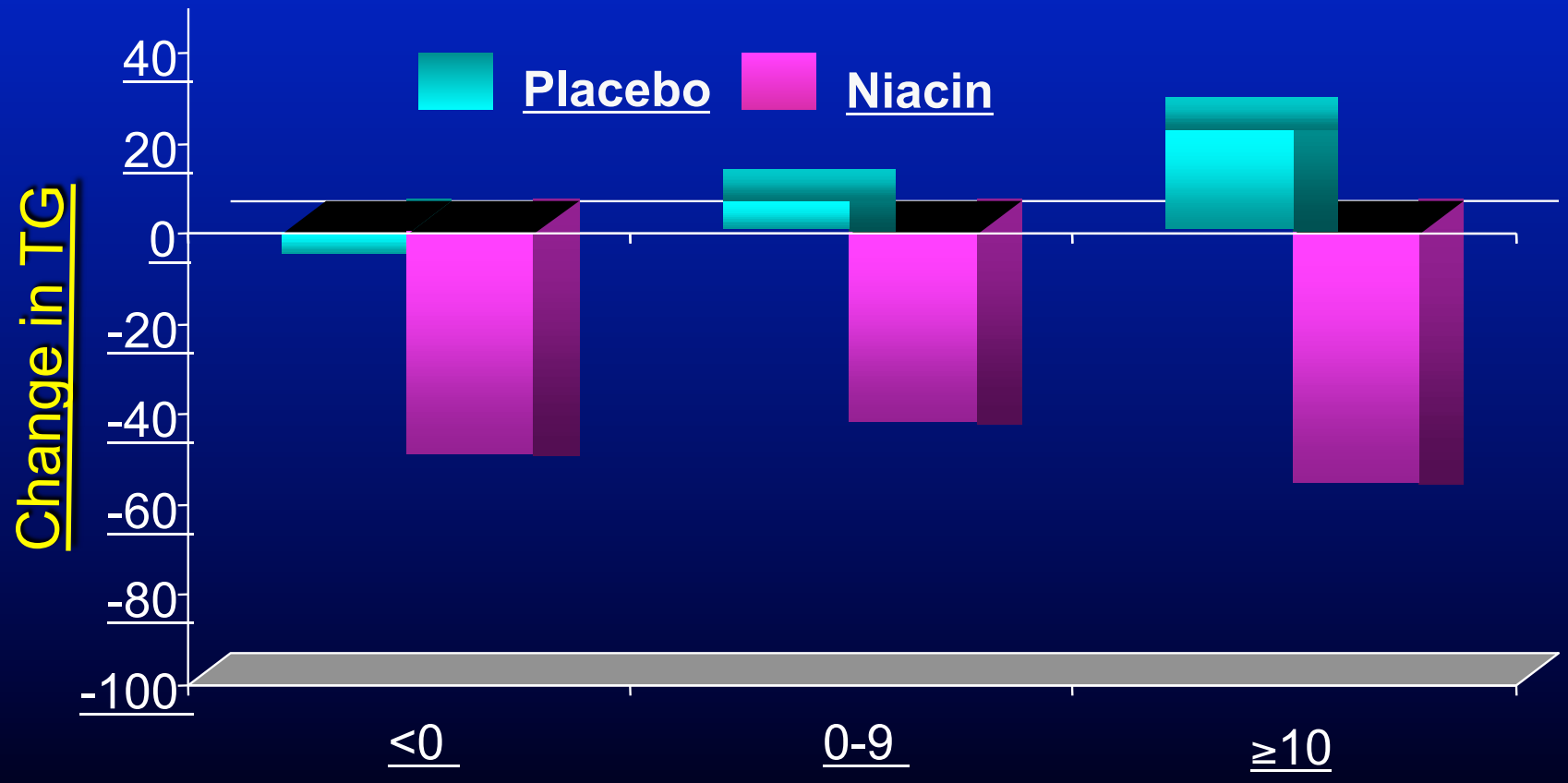
Canner PL et al. Am J Cardiol 2005;95:254–257)

Coronary Drug Project: Nonfatal MI at 6 Years by Baseline Metabolic Syndrome

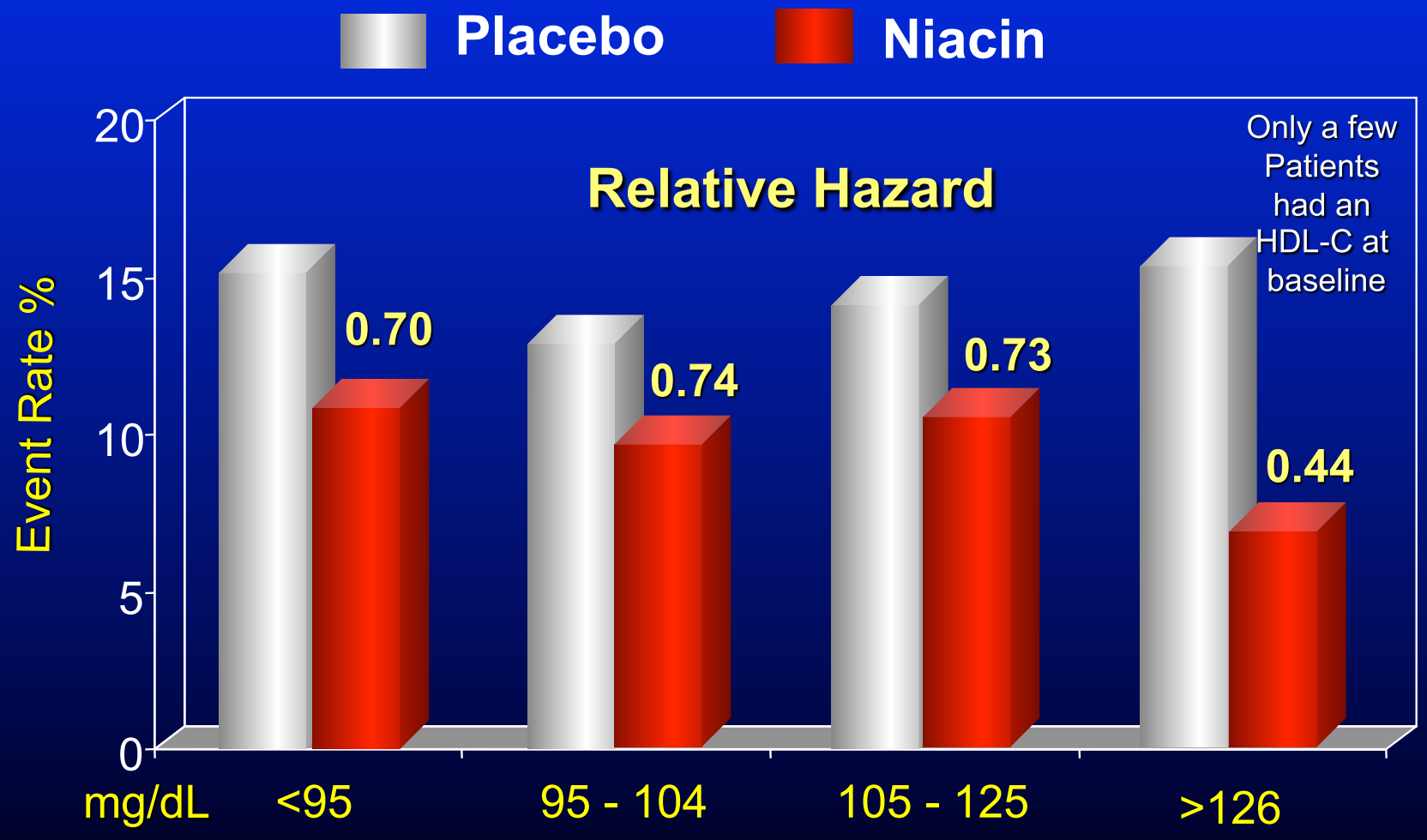


Canner PL et al. Am J Cardiol 2005;95:254–257)

Coronary Drug Project: Yr 1 Change in Triglycerides by Yr 1 Change in FBG



Coronary Drug Project at 6 Years: Nonfatal MI by Baseline FBG*



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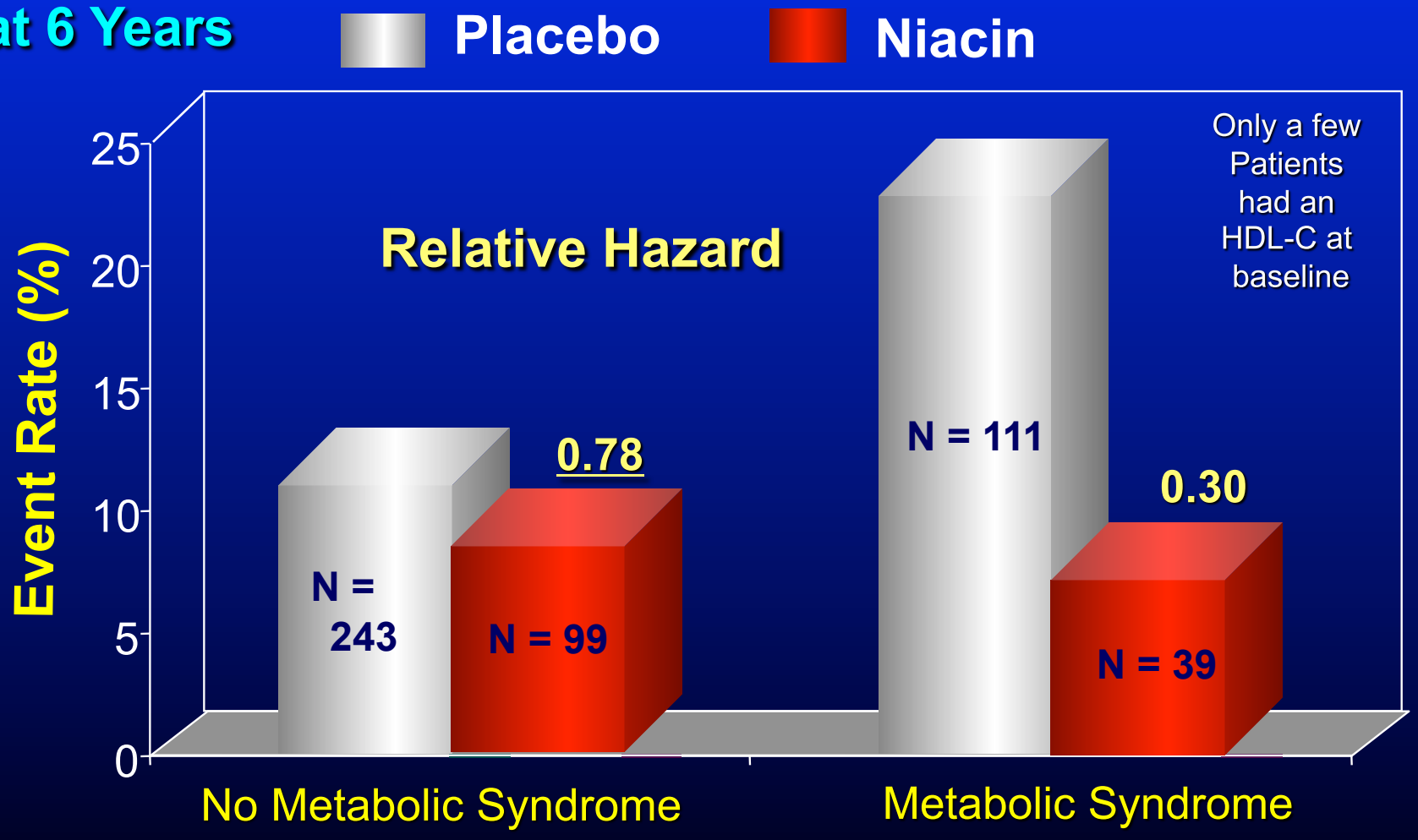
Canner PL et al. Circulation 2002;106(suppl) 3138

Coronary Drug Project
Nonfatal MI by Baseline Metabolic Syndrome

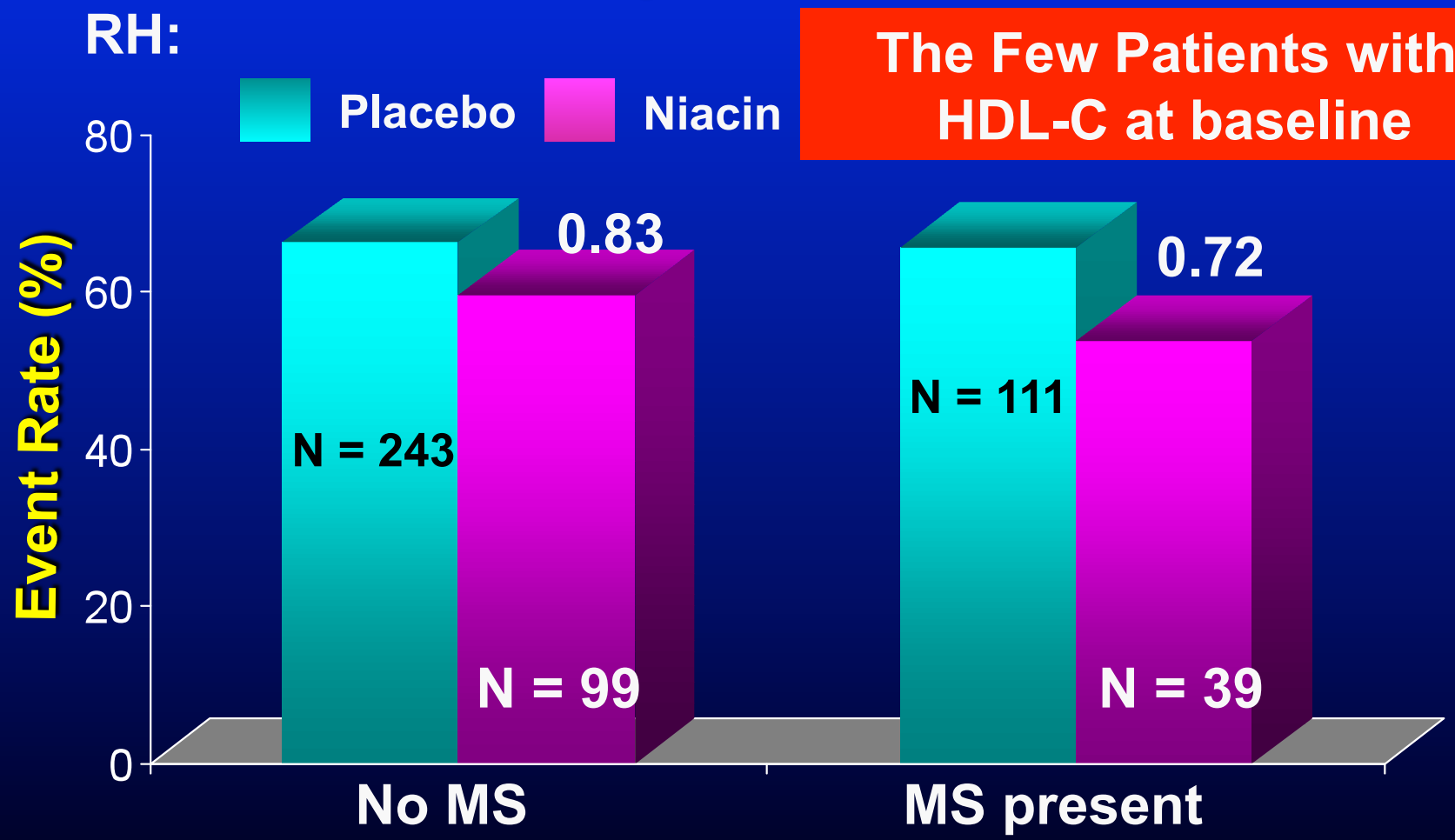


Z (int) = - 1.78

Canner PL et al. Circulation 2002;106(suppl) 3138

Coronary Drug Project

Total Mortality by Baseline Metabolic Syndrome at 6 Years



Z (int) = - 0.49

MS = metabolic syndrome

HDL Atherosclerosis Treatment Study (HATS)

- DBPCT 3 year angiographic & clinical endpoint trial n=160 with CAD and average LDL-C =125
  - Niacin (2-4 gm) – simvastatin (10-20 mg)
  - Vitamins E, C, B, β carotene, selenium
  - Niacin – simvastatin plus vitamins
  - placebo

HDL-C increased 30% LDL dropped 39%

B Greg Brown NEJM 2001;345:1583-92

HDL Atherosclerosis Treatment Study (HATS)

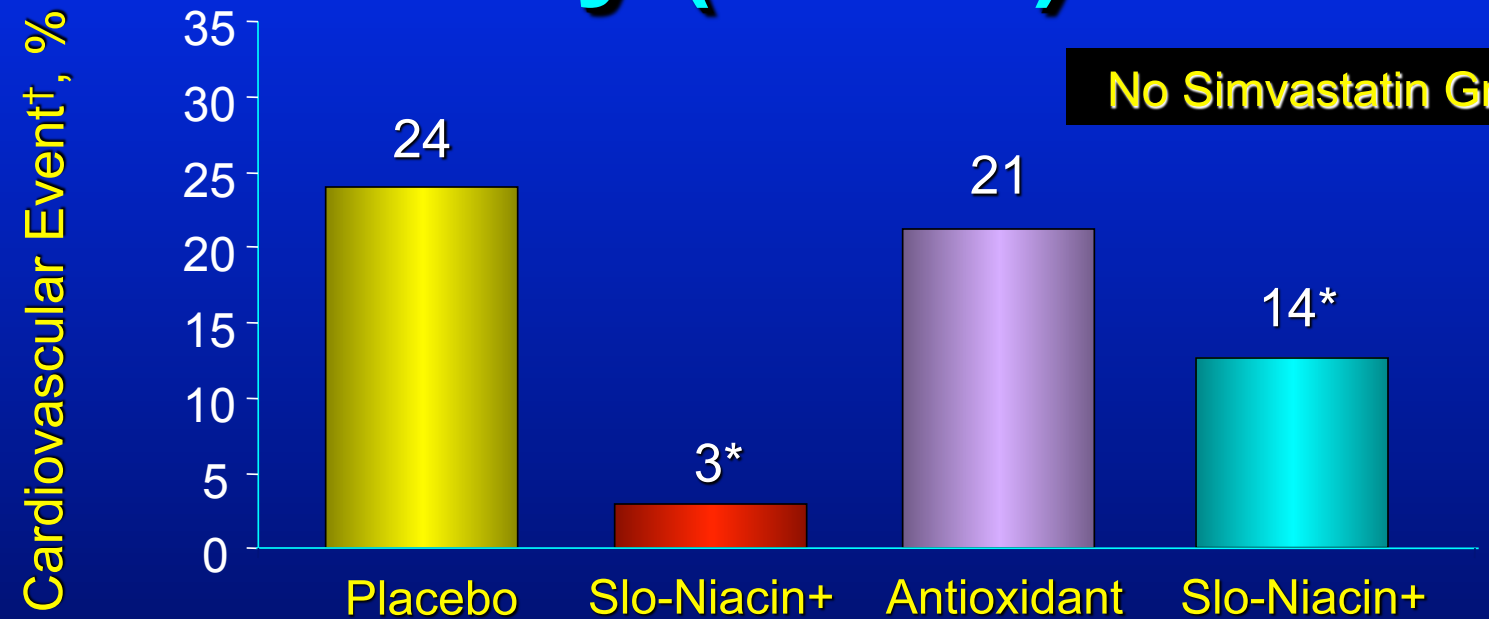
Niacin plus simvastatin have strikingly favorable effects. Atherosclerosis progression is virtually halted and clinical events reduced by 70%.

- The antioxidants negated the rise in beneficial HDL_2 particles and Apo A1.

B Greg Brown NEJM 2001;345:1583-92

Arterioscler Thromb Vasc Biol. 2001;21:1320 –1326.

HDL Atherosclerosis Treatment Study (HATS)



Patients = 160
Diabetics = 26

Baseline Lipids				
LDL-C	127	132	117	124
HDL-C	32	31	32	30
TG	203	202	207	236

*p<0.01

†death, MI, stroke, or revascularization

Brown BG, et al. *N Engl J Med.* 2001;345:1583-1592.

HATS: Changes in Lipids and Lipoproteins

	Baseline	Simva + Niacin	Change (%)
TC	197 ± 41	140 ± 31	-27 ± 19
LDL-C	130 ± 34	80 ± 28	-36 ± 23
HDL-C	34 ± 7	41 ± 11	
VLDL-C	34 ± 23	19 ± 12	-35 ± 49
RLP-C	12 ± 11	7 ± 4	-15 ± 74
TG	199 ± 130	124 ± 65	-27 ± 43
ApoAI	111 ± 16	118 ± 17	7 ± 10
ApoAII	29 ± 4	27 ± 4	-7 ± 14
$preβ_1$	15.1 ± 5.7	8.2 ± 2.8	-39 ± 29
$preβ_2$	1.3 ± 0.6	1.5 ± 0.5	31 ± 67
$α_1$	9.2 ± 4.8	17.6 ± 10	115 ± 123
$α_2$	29.7 ± 6.6	37.2 ± 8.5	27 ± 25
$α_3$	44.7 ± 5.8	36.9 ± 9.9	-17 ± 23
pre $α_1$	2.8 ± 2.3	6.0 ± 4.0	311 ± 555
pre $α_2$	4.4 ± 2.0	6.7 ± 2.4	77 ± 85
pre $α_3$	4.0 ± 1.2	4.3 ± 1.8	20 ± 69
$Preβ_1/α_1$	2.6 ±2.6	0.7 ± 0.6	-58 ± 43

Asztalos BF et al. Arterioscler Thromb Vasc Bio 2003;23:847-852

HDL Atherosclerosis Treatment Study (HATS)
Change in α_1 HDL Concentration and Coronary Stenosis Progression

- Treatment with simvastatin plus niacin normalized the HDL subpopulation of CHD patients
  - Increased α_1 and preα_1
  - Decreased preβ_1 HDL subpopulation
- The preβ_1/α_1 ratio are significantly correlated with the mean change in coronary artery stenosis

Asztalos BF et al. Arterioscler Thromb Vasc Bio 2003;23:847-852

HDL Atherosclerosis Treatment Study (HATS)
Change in α_1 HDL Concentration and Coronary Stenosis Progression

- Increasing α_1 HDL decreases progression of CAD
- The **preβ1/α1 ratio** is a measure of the efficiency of reverse cholesterol transport and a significant decrease indicates enhanced RCT
- It is assumed that increased RCT accompanied by decreased cholesterol in LDL, VLDL and remnants plus decreased TG represents a decreased risk for atherosclerosis

Asztalos BF et al. Arterioscler Thromb Vasc Bio 2003;23:847-852

HDL Atherosclerosis Treatment Study (HATS)

- It should be noted that 1) 65% of the eligible cohort declined to enroll in HATS
- The placebo tablets were active, containing 50 mg of crystalline niacin, an amount known to cause flushing but no effects on lipid levels
- 20 minutes of counseling was provided at each of approximately 20 study visits, addressing both lifestyle and medication issues.

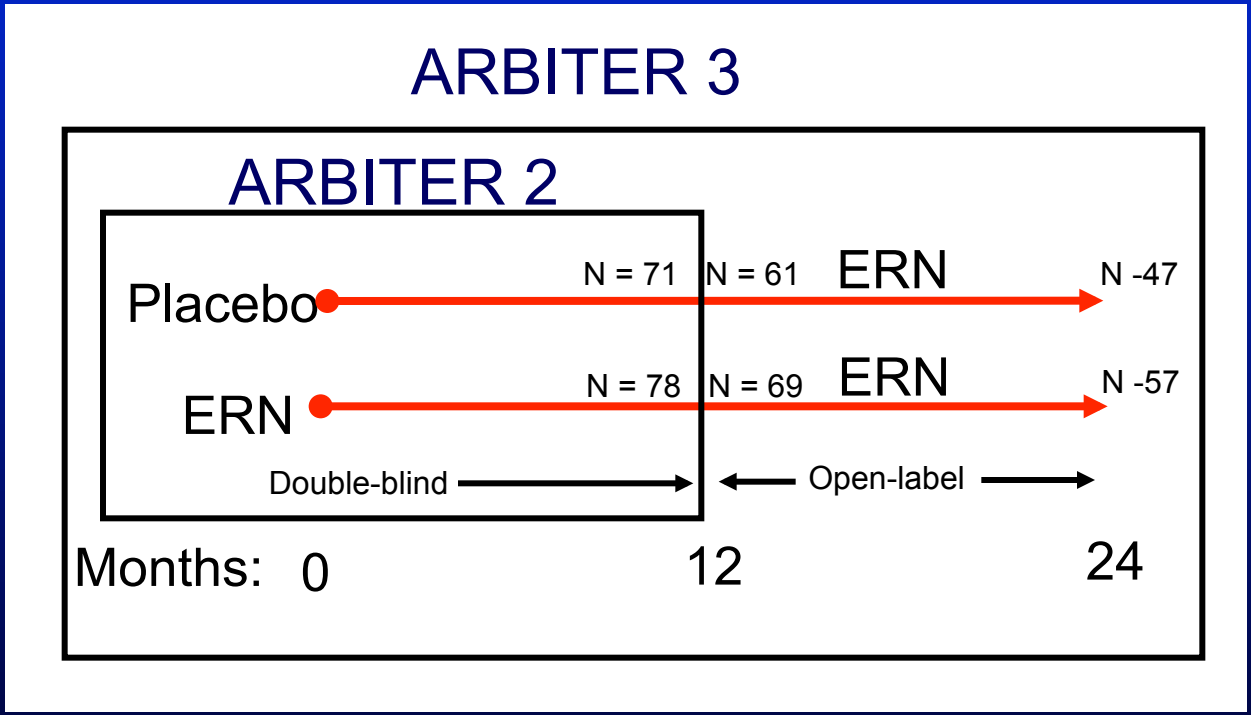
Ansell B Current Atherosclerosis Reports 2005, **7:**29–33

HDL Atherosclerosis Treatment Study (HATS)

- Those patients receiving niacin/simvastatin also experienced a significant increase in fasting glucose levels in the setting of diabetes (mean, 163 mg/dL vs 124 mg/dL for placebo) or no diabetes (mean, 93 mg/dL vs 80 mg/dL for placebo), although these disparities were no longer evident by the conclusion of the study.
- Fasting insulin levels also remained modestly higher throughout the study in those receiving the combination regimen.
- However, trends toward increased rates of side effects and mild glycemic changes must be considered in the context of the superlative event reductions in the study.

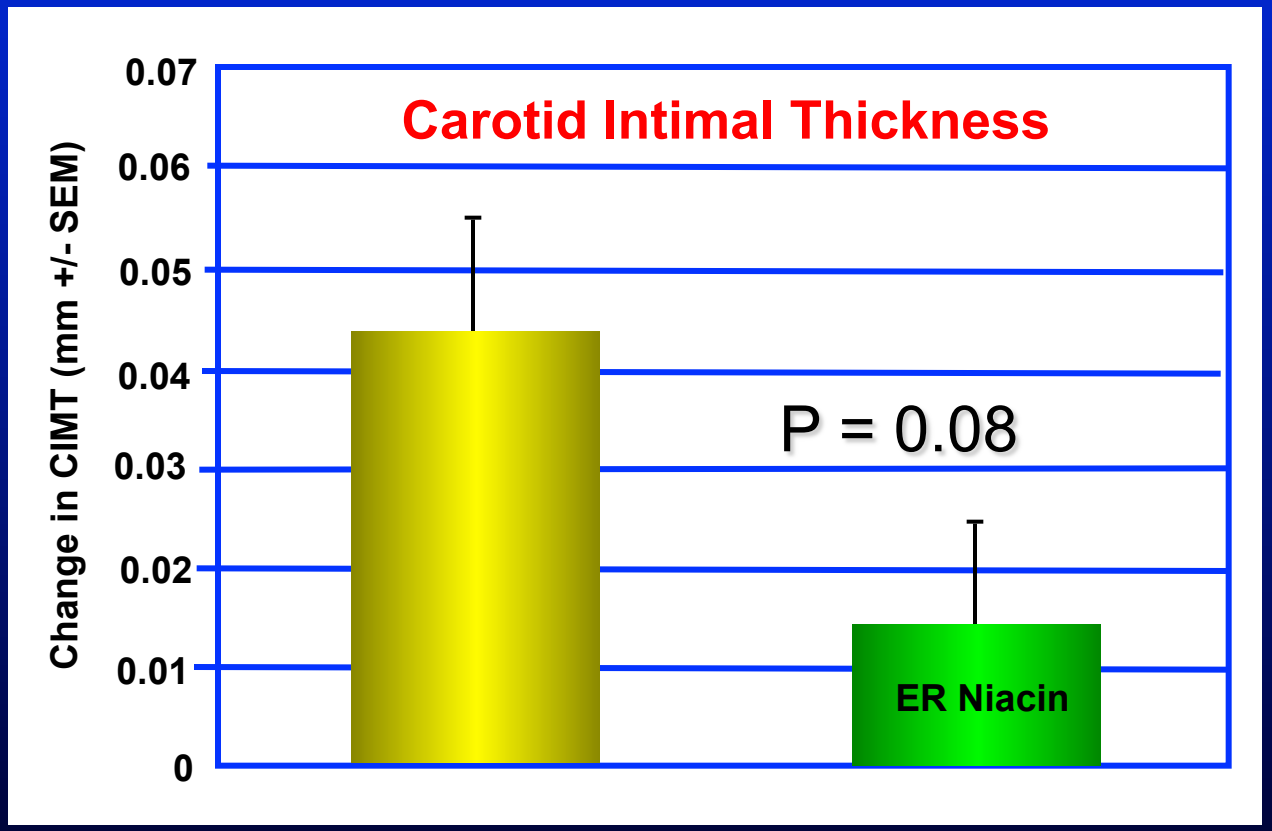
Ansell B. Current Atherosclerosis Reports 2005, 7:29–33

ARterial Biology for the Investigation of The Effects of Reducing Cholesterol (ARBITER) 3



Taylor, AJ. Et al. Current Medical Research and Opinion 2006;22: 2243–2250

ARterial Biology for the Investigation of The Effects of Reducing Cholesterol (ARBITER) 2

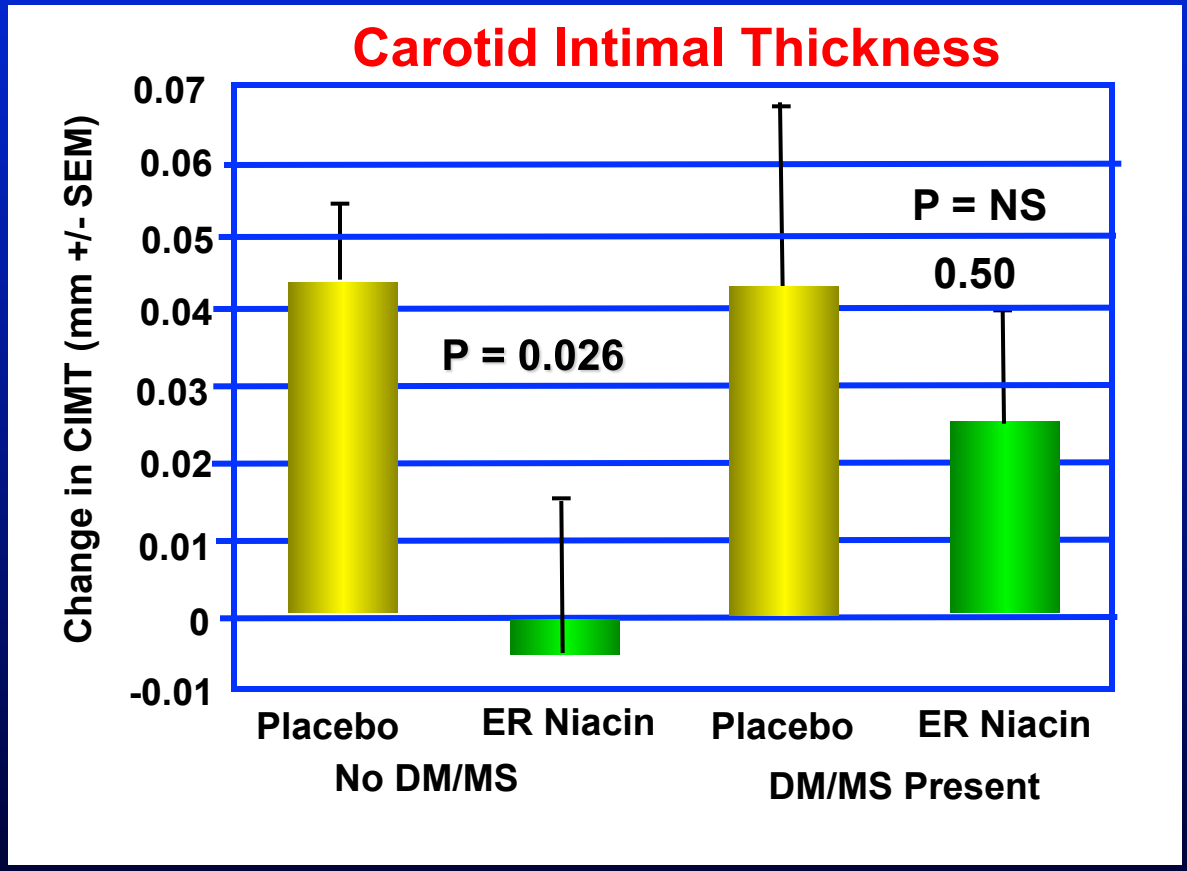


1000 mg extended release niacin added to the statin

The overall difference in IMT progression between niacin and placebo groups was not significant

Taylor, AJ. Et al. Circulation 2004;110: December 7

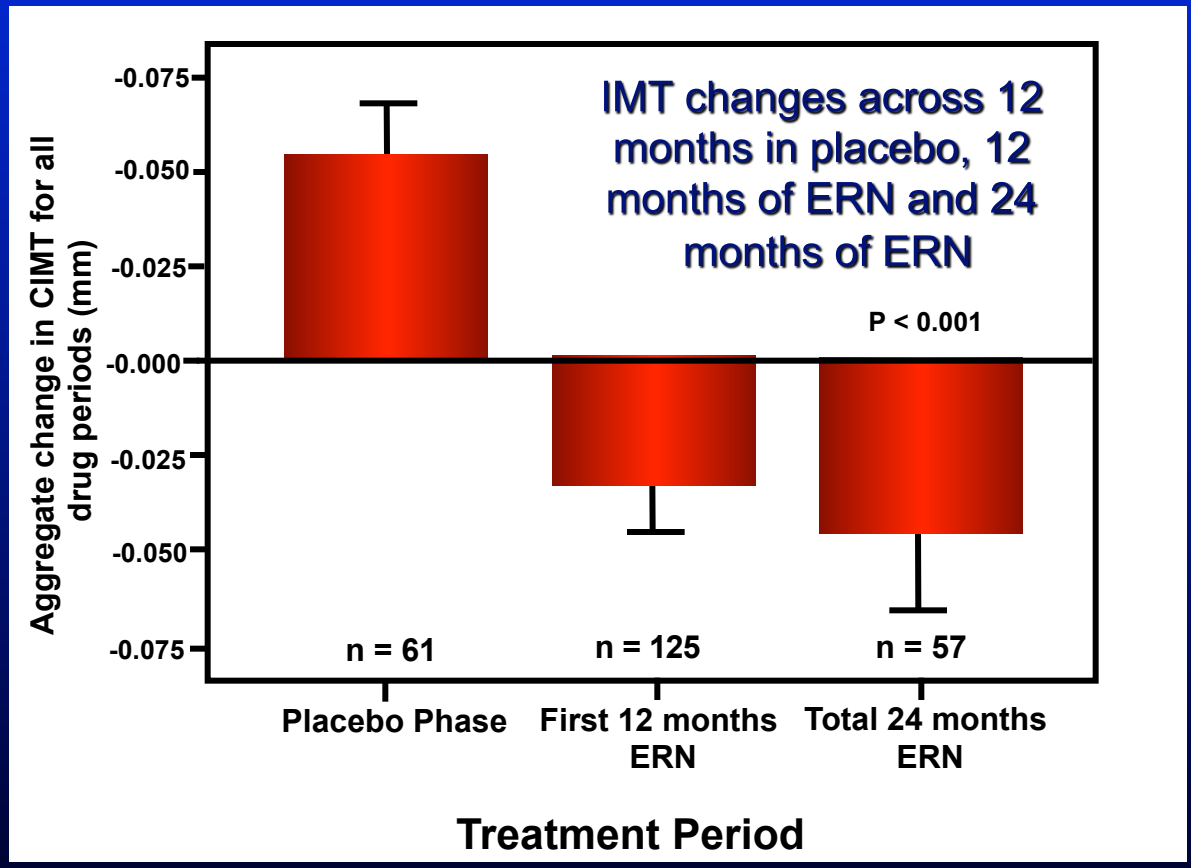
ARterial Biology for the Investigation of The Effects of Reducing Cholesterol (ARBITER) 2



The overall difference in IMT progression between niacin and placebo groups was not significant in diabetics or metabolic syndrome patients

Taylor, AJ. Et al. Circulation 2004;110: December 7

ARterial Biology for the Investigation of The Effects of Reducing Cholesterol (ARBITER) 3



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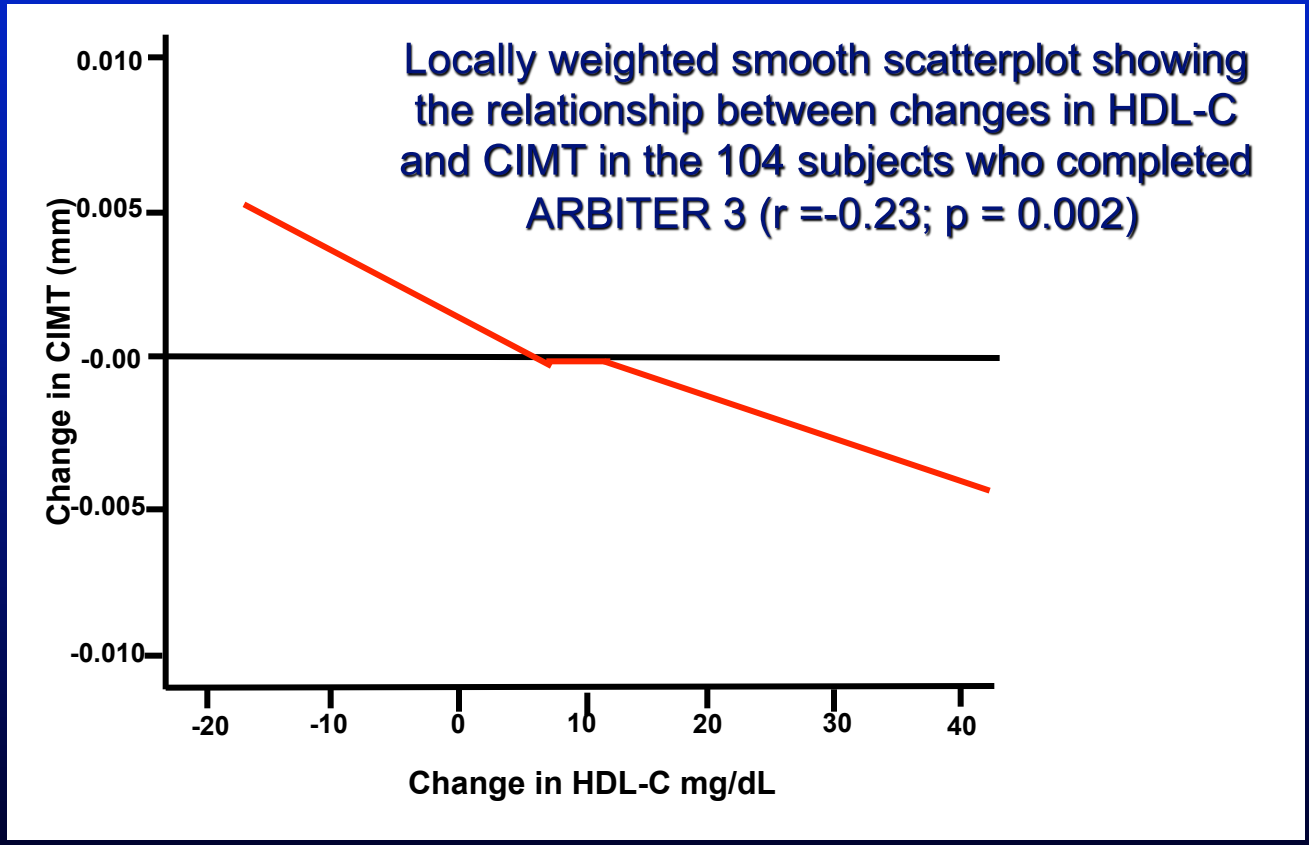


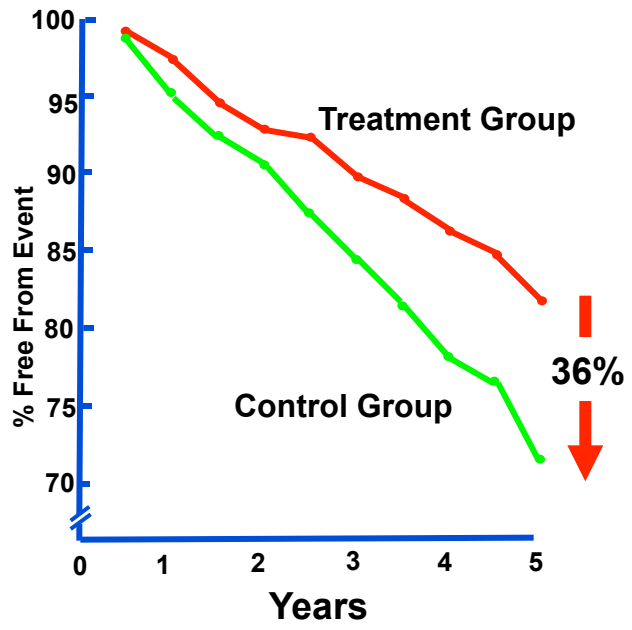
Taylor, AJ. Et al. Current Medical Research and Opinion 2006;22: 2243–2250

Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with Clofibrate and Nicotinic Acid

- Consecutive survivors of an MI below the age of 70 were randomized, four months after the event into a control (n=276) and an open-label treatment group (n=279) for a five year period
  - Clofibrate 1 gram BID & niacin titrated to 1 gm TID
  - Compliance rates: Clofibrate 85% Niacin 59%
  - 6% of treatment arm withdrew from study due to side effects
  - Mean baseline LDL-C = 160 mg/dL and TG = 180 mg/dL

Carlson L & Rosenhammer G Acta Med Scan 1988;223:405-418

Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with Clofibrate and Nicotinic Acid

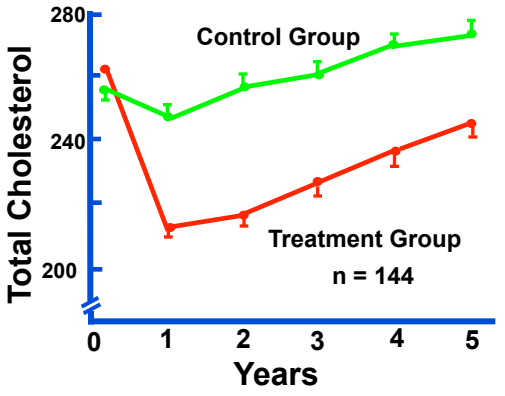


Reduction in total mortality was 26%

Reduction in Ischaemic mortality was 36%

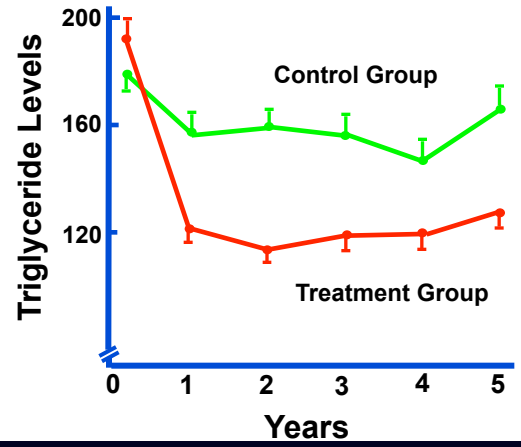
Reduction in major non-fatal IHD events was 33%

Lipid Changes in those completing 5 years of trial



Average reduction was 13% (p<0.001)

Pretreatment level or reduction not related to outcomes



Average reduction was 19% (p<0.001)

Virtually all of the treatment benefit was in those with baseline TG > 120 mg/dL

Carlson L & Rosenhammer G Acta Med Scan 1988;223:405-418

Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with Clofibrate and Nicotinic Acid

- 75% of the survivors of MI had a TG > 120 mg/L
- When treatment with clofibrate and nicotinic acid is started early after an MI, patients with TG > 120 mg/L responded with a reduction of IHD deaths.
- The clinical response was related to the degree of TG lowering
  - **A lowering of TG by > 30% reduced the incidence of IHD death by 60%**
- These values serve as guidelines for the indication to treat survivors of an MI with a TG-lowering agent and also for the degree of desired TG reduction

Carlson L & Rosenhammer G Acta Med Scan 1988;223:405-418

Niacin Effect on Lipids & Lipoproteins

Mechanism of Action

Niacin Discovery

- Vitamin B3 consists of Nicotinic Acid and Nicotinamide
- In 1954 Rudolf Altschul discovered that nicotinic acid, but not nicotinamide lowered cholesterol in rabbits and later showed it inhibited atherosclerosis in cholesterol-fed rabbits
- Both the acid and amide are precursors to the coenzyme Nicotinamide Adenine Dinucleotide (NAD) which is a major electron acceptor in the oxidation of fuel metabolites

Carlson LA. J of Intern Med 2005;258:94-114

Niacin Mechanism of Action

- ↑ Fatty acid catabolism
- ↓ FA synthesis
- ↓ TG synthesis (inhibition of DGAT2)
- ↓ CETP activity and LDL size increase
- ↑ lipidation of HDL via ABCA1 upregulation via PPARγ/LXR
  - ↑ macrophage reverse cholesterol transport and HDL functionality
- Downregulation of hepatic holoparticle receptor
  - Delayed catabolism of apoA-I
- Beneficial modification of some inflammatory markers
- ↓ levels of Lp-PLA2

Niacin Effect on CV Risk Factors

Decrease

- Total cholesterol
- Triglycerides
- VLDL-C
- LDL-C
- Small LDL
- Lp(a)
- ApoB
- TC/HDL-C ratio
- ApoB/A-I ratio
- Fibrinogen
- PAI-I
- MCP-1, VCAM-1

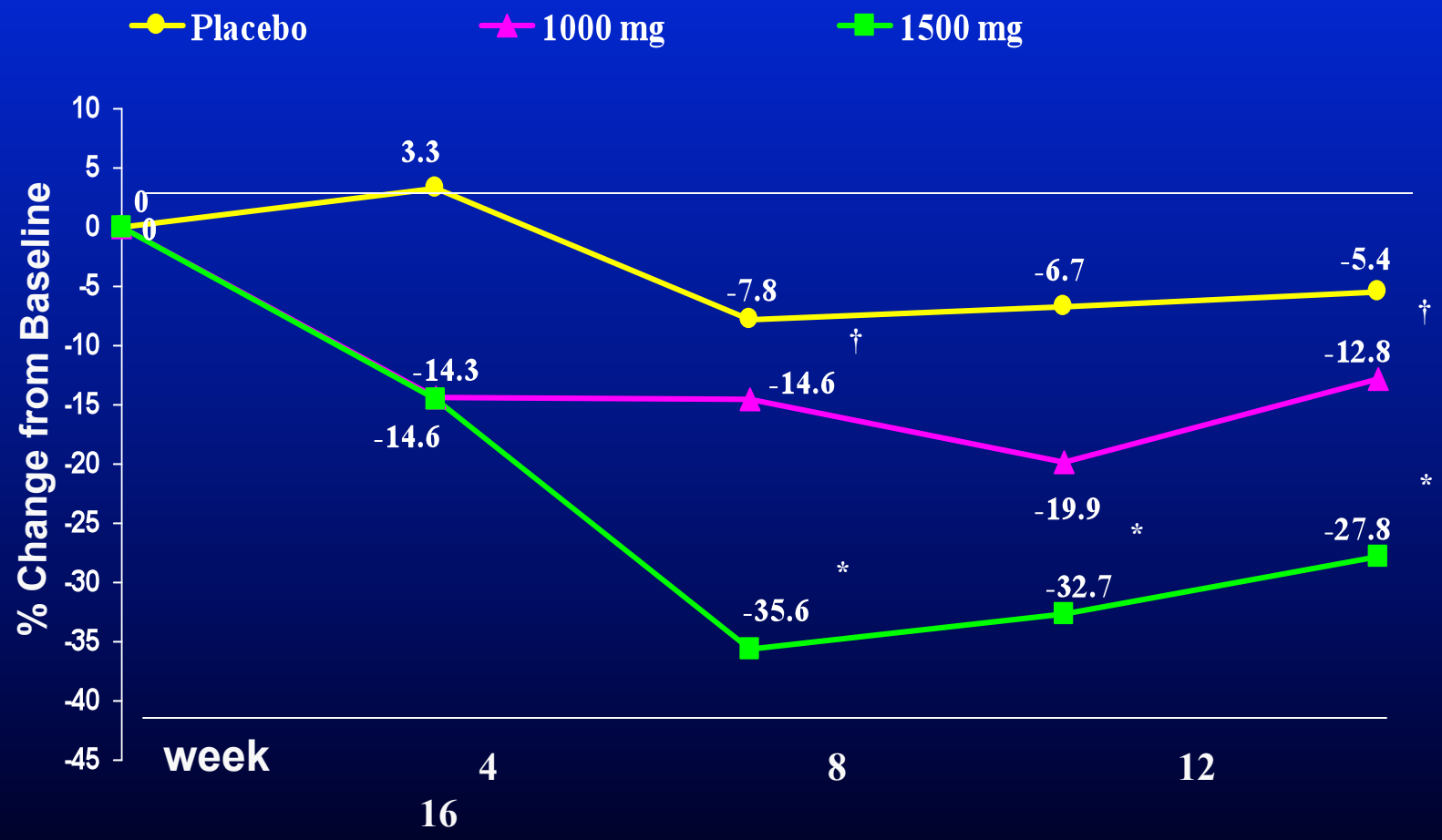
Increase

- HDL-C
- HDL_2-C
- HDL_3-C
- ApoA-I & ApoA-II
- Lp-A-I
- Lp-A-I + Lp-A-II
- Pre-β HDL
- LDL particle size
- PGD_2 and PDJ_2
- Blood glucose
- Uric acid
- Adiponectin

Vaijinath S. Kamanna & Moti L. Kashyap Am J Card 2007;100[suppl]:53M-61N

Assessment of Diabetes Control and EValuation of the Efficacy of Niaspan Trial (ADVENT)

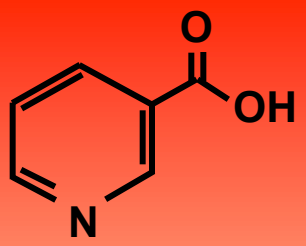
Changes in TG relative to placebo



*P< 0.05 vs. placebo †P<0.05 vs. 1500 mg

Grundy SM, et al. Arch Intern Med. 2002;162:1568-1576.

Niacin: Decreased TG Lipolysis in Adipocytes



Niacin

FFA Liberation

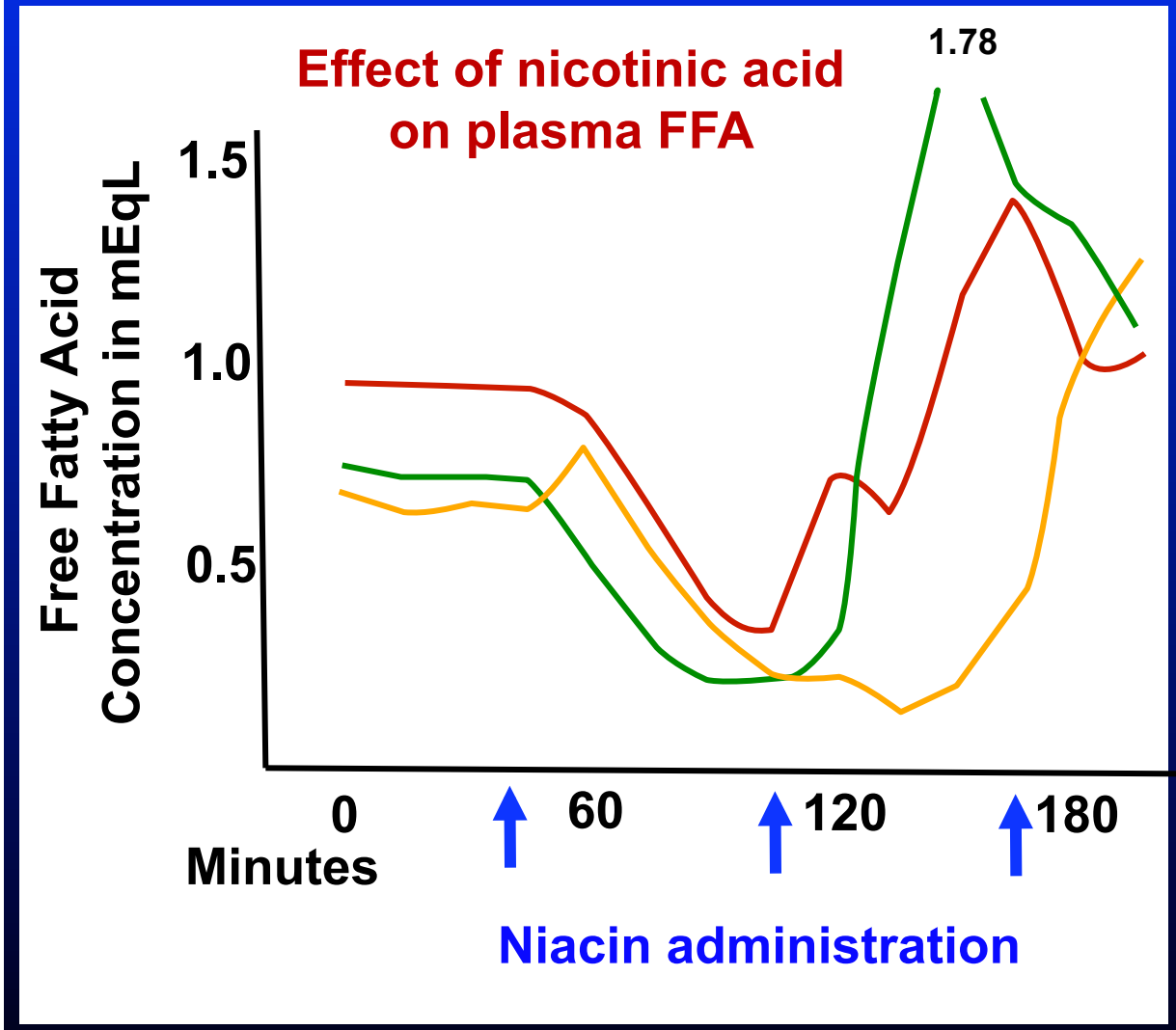
Niacin's action is mediated by activation of a Gi-G-coupled receptor termed the HM7A4 high affinity receptor

Hormone sensitive lipase is inhibited, diminishing release of fatty acids from adipocytes.

Malik SW & Kashyap M. Curr Card Reports 2003:5:470-476

Tunaro et al. Nature Medicine 2003;3:352-355

Niacin Effect on Free Fatty Acids



Concentration of FFA in response to oral administration of 200 mg niacin given at 40 min followed by 100 mg at 1065 min and 165 min.

Within minutes FFA are lowered, followed by a rebound within one1 hour

Carlson LA. J of Intern Med 2005;258:94-114

Niacin Effect on Free Fatty Acids

- Pretreatment with nicotinic acid almost completely inhibits the marked rise in FFA caused by the infusion of noradrenaline without affecting the cardiovascular response
- The length of depression of FFA levels by nicotinic acid is dose dependent, which is one of the reasons immediate release niacin needs to be administered 4 times a day
- The uptake of nicotinic acid in adipocytes is rapid due the presence of a high-affinity receptor highly expressed in adipose tissue

Carlson LA. J of Intern Med 2005;258:94-114

Niacin Effect on Free Fatty Acids

- Whole body metabolism is unchanged after suppression of FFA mobilization by niacin, but oxidative metabolism shifts from fat to carbohydrate
- After niacin administration, cardiac muscle shifts from predominantly using FFA to increased utilization of glucose

Carlson LA. J of Intern Med 2005;258:94-114

Is the Adipocyte Where Niacin Acts?

- Niacin's effect on adipocyte lipolysis and fatty acid mobilization is widely recognized, physiologically and clinically this mechanism may only be minor and **may not provide a full explanation of all lipid effects of niacin in humans.**
- In humans, evidence indicates that niacin subacutely causes a profound rebound in lipolysis, such that serum FFA levels are actually increased over 24 hours.
  - This rebound in lipolysis and elevated FFA levels may in part mediate the insulin resistance induced by chronic niacin therapy.
  - Decreased adipocyte lipolysis by niacin would theoretically increase adipose tissue TGs and could result in obesity. Clinically, niacin has not been reported to influence obesity.
- Niacin-induced modulation of TG synthesis occurs during the acute decrease in FFA, but the rebound in FFA would reverse this.
  - Moreover, there is no evidence that the longer term transport (flux rate) of nonesterified fatty acids is decreased after niacin treatment.

Vaijinath S. Kamanna & Moti L. Kashyap Am J Card 2007;100[suppl]:53M-61N

Niacin and Insulin Resistance

Nicotinic acid analogs are drugs that lower plasma Free Fatty Acid (FFA) levels.

Their usefulness is limited, however, because the initial lowering of plasma FFA levels is invariably followed by a sharp FFA rebound that **increases insulin resistance**, at least temporarily.

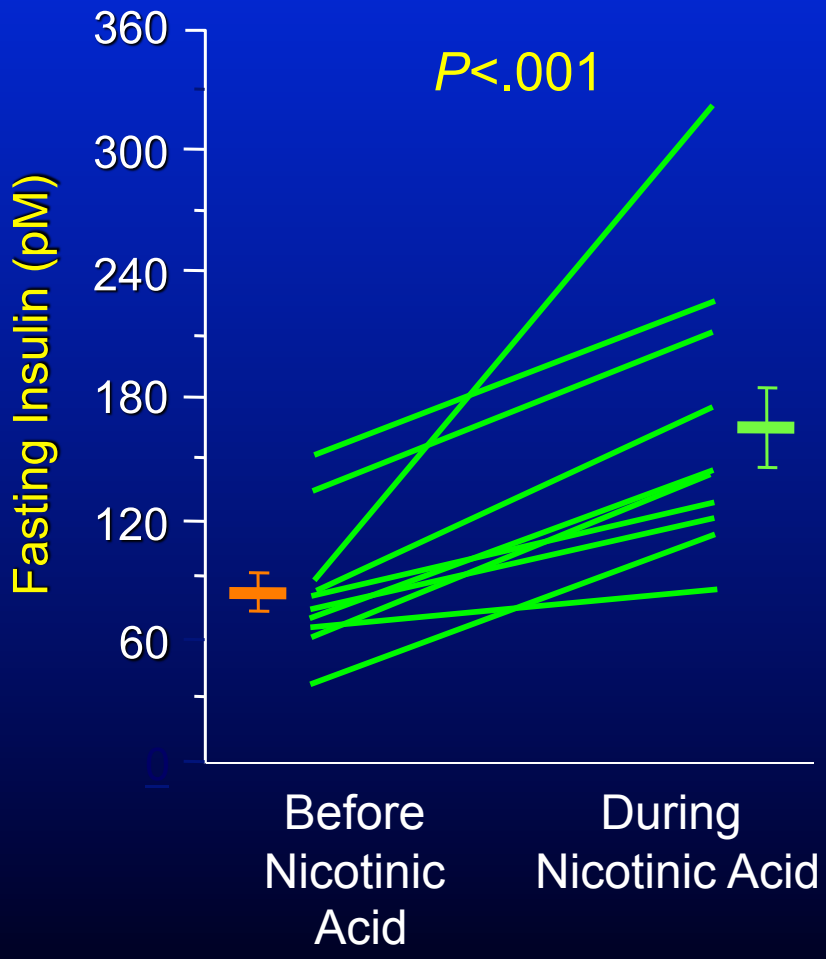
Chen X et al. J Clin Invest 103:365–372, 1999

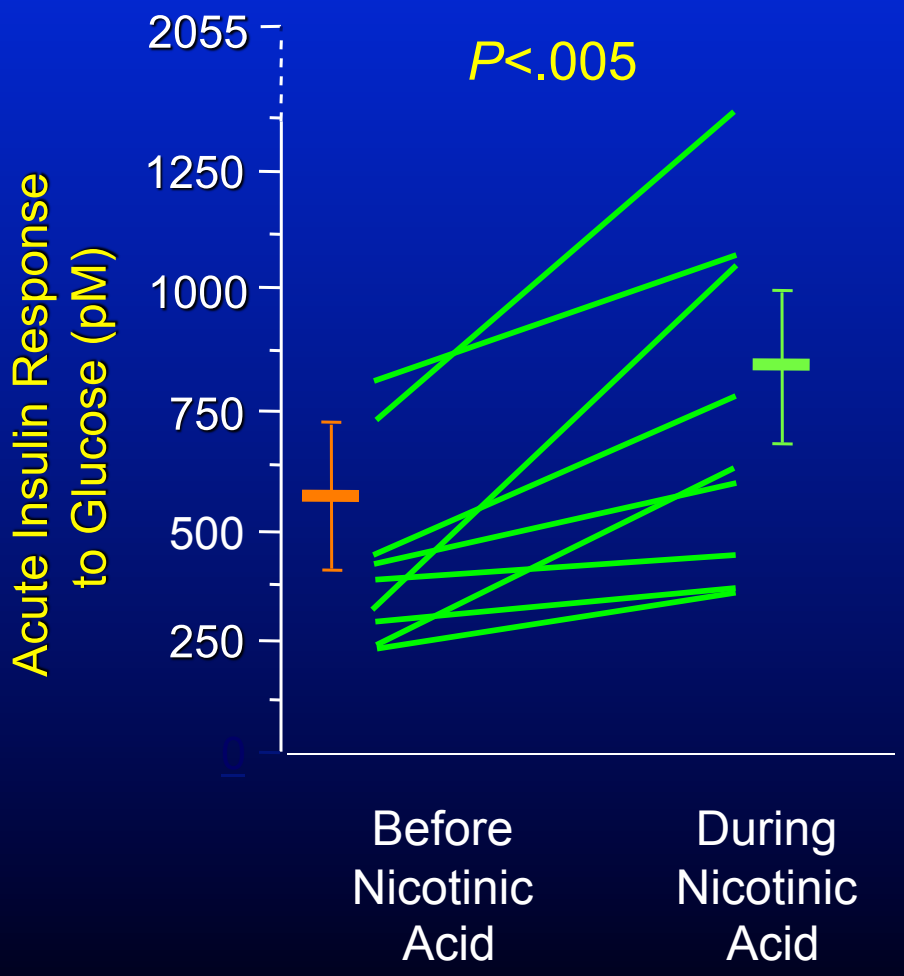
Nicotinic Acid Induced Insulin Resistance

- Insulin resistance is a feature of Type 2 diabetes, aging, hypertension and pregnancy.
  - Hyperglycemia is not a feature of the later 3
- Long term treatment with niacin in pharmacologic doses (2 gm) invariably produces increased insulin with or without hyperglycemia
  - There was a measurable decrease in insulin sensitivity after 2 weeks of treatment
  - The degree of insulin resistance is comparable to that documented in elderly, obese and former gestational diabetics

Kahn S et al. Diabetes 1989 38;562-68

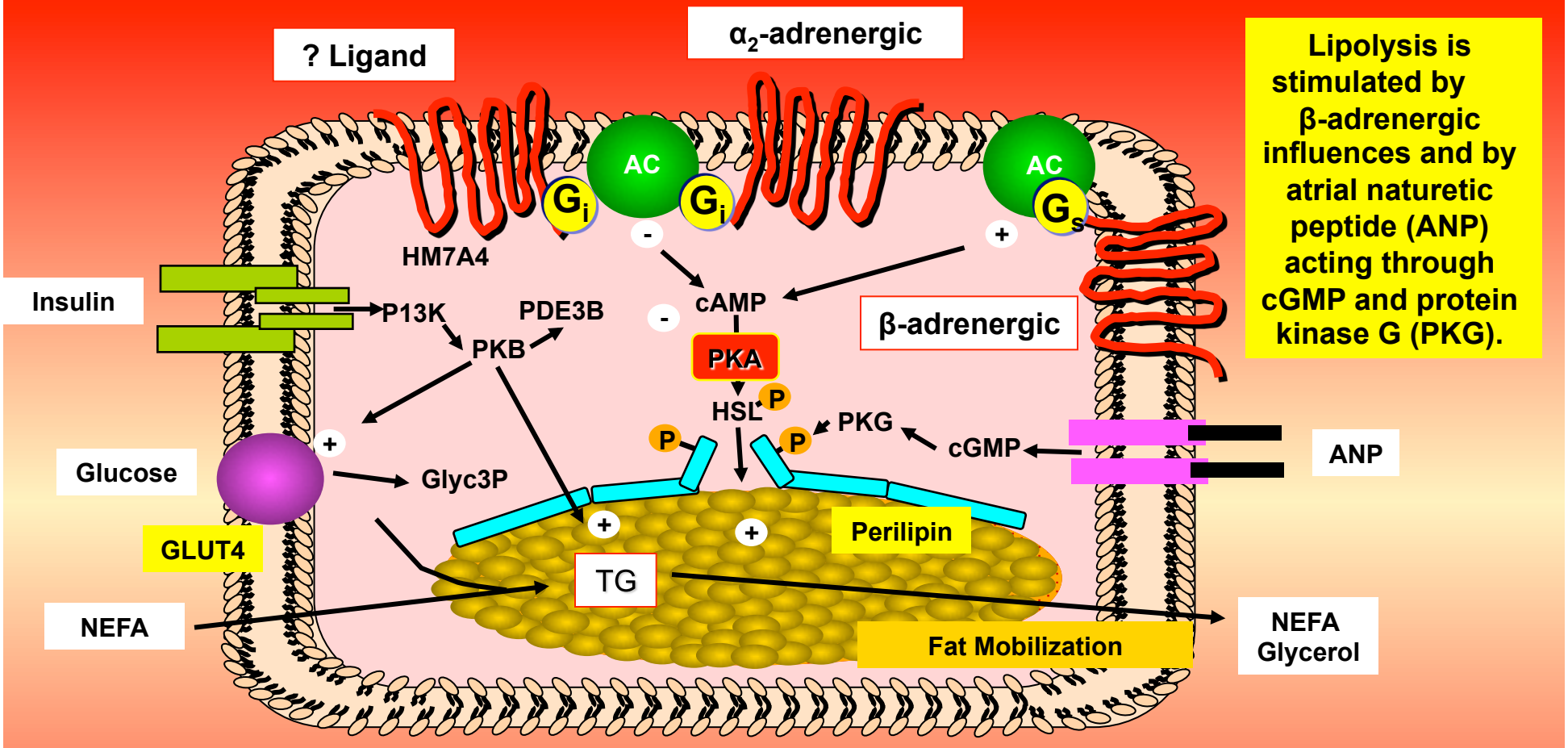
Increased Insulin Secretion Associated With Niacin





Kahn SE, et al. *Diabetes*. 1989;38:562-568.

Regulators of Adipocyte Lipolysis

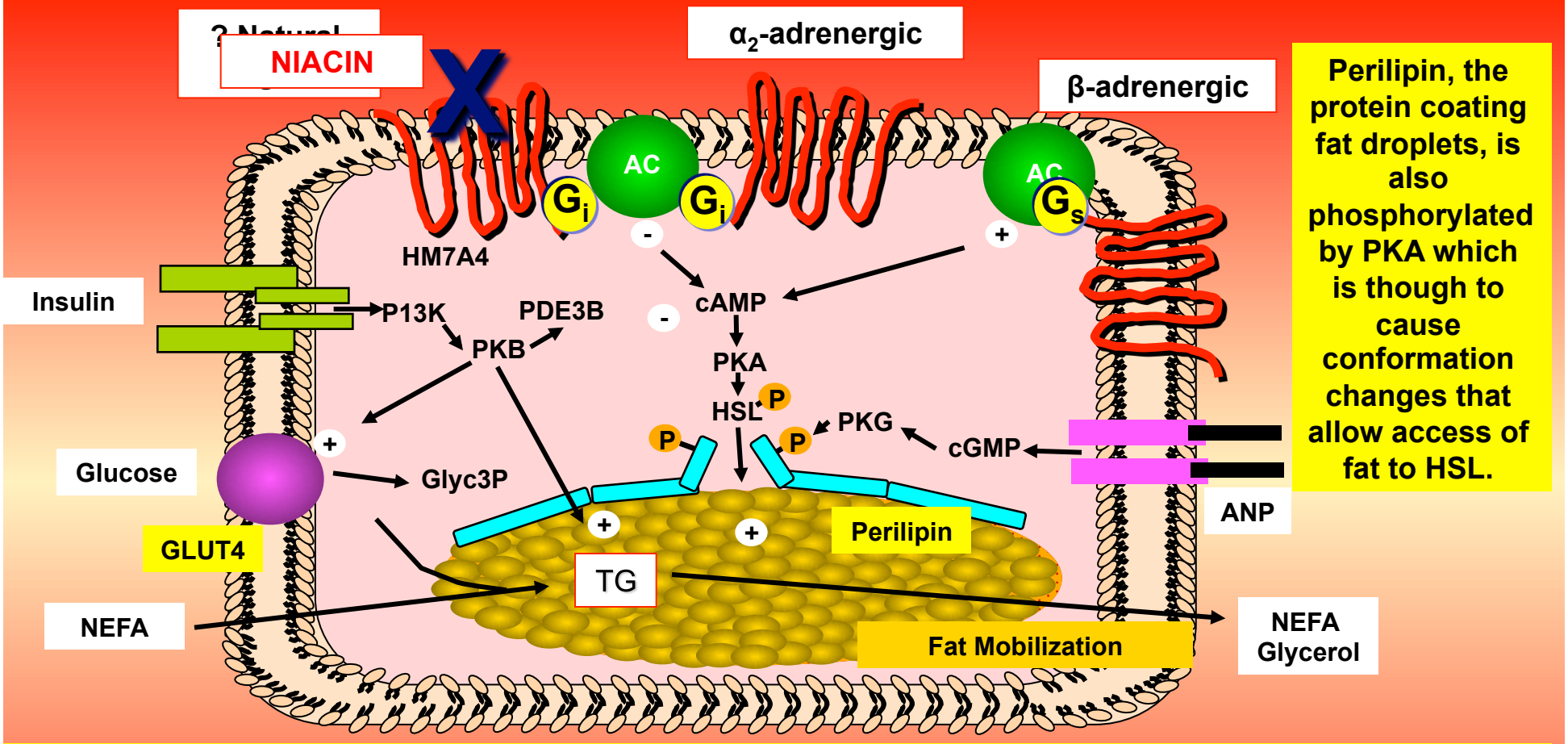


Lipolysis is stimulated by β-adrenergic influences and by atrial naturetic peptide (ANP) acting through cGMP and protein kinase G (PKG).

Lipolysis is catalyzed by hormone-sensitive lipase (HSL), which is activated by phosphorylation by protein kinase A (PKA) when activated by cAMP which in turn is produce by adenyl cyclase (AC), which is regulated by stimulatory or inhibitory G-proteins (Gs, Gi) linked to seven transmenbrane-domain G-protein-coupled receptors.

Karpe F & Frayn KN Lancet 2004;363:1892-1894

Regulators of Adipocyte Lipolysis



Perilipin, the protein coating fat droplets, is also phosphorylated by PKA which is though to cause conformation changes that allow access of fat to HSL.

Antilipolytic influences include α-adrenergic and HM74A (niacin receptor) activation (natural ligand ?). Insulin is the main anti-lipolytic signal in vivo, acting through phosphatidylinositol 3-kinase (P13K) and PKB to phosphorylate and activate phosphodiesterase-3B (PDE3B) which reduces cellular cAMP. Insulin also acts on GLUT4 to increase esterification of FA with glycerol 3-phosphate (Glyc3P) produced from glycolysis,

Karpe F & Frayn KN Lancet 2004;363:1892-1894

Niacin and the Role of GPR109A (HM74A)

Activation of the Gi protein–coupled receptor GPR109A (**HM74A in humans**; PUMA-G in mice) can produce differential responses depending on the location of the receptor. It has been proposed that, when nicotinic acid activates GPR109A on adipocytes, the resultant anti-lipolytic effects contribute to the highly desirable normalization of lipoprotein profiles.

However, when nicotinic acid activates GPR109A on dermal dendritic cells or dermal macrophages, the subsequent mobilization of arachidonic acid and its conversion to vasodilatory prostaglandins (PGD2 and PGE2) results in the characteristic flushing response.

As GPR109A expression extends beyond adipose and immune cells located in the skin (e.g., spleen, lymphoid cells, and lung), it is likely that activation of GPR109A in these cells/tissues may also contribute to the clinical efficacy of nicotinic acid.

The Journal of Clinical Investigation 2005;15:3400-3403

Niacin and HM74A

- HM74A is not expressed in the liver thus negating a physiologic role in hepatic lipoprotein production
- HM74A is not expressed in aortic tissue and does not mediate niacin's anti-oxidative and anti-inflammatory effects in aortic endothelial cells

Thus, Niacin must have other mechanisms of action

Vaijinath S. Kamanna & Moti L. Kashyap Am J Card 2007;100[suppl]:53M-61N

Niacin Effect on Triglycerides

- The data indicate that niacin inhibits TG production at 2 synthetic sites:
  - (a) fatty acid synthesis from acetate, and
  - (b) esterification of fatty acids to form TG
- Because these 2 cellular processes are regulated by various enzyme systems and esterification reactions, niacin may have yet unknown roles in modulating these processes
- Increased hepatocyte apoB degradation by niacin would also decrease the number of VLDL (and their catabolic product, LDL) particles secreted, and explain the lower apoB concentrations observed clinically after niacin treatment.

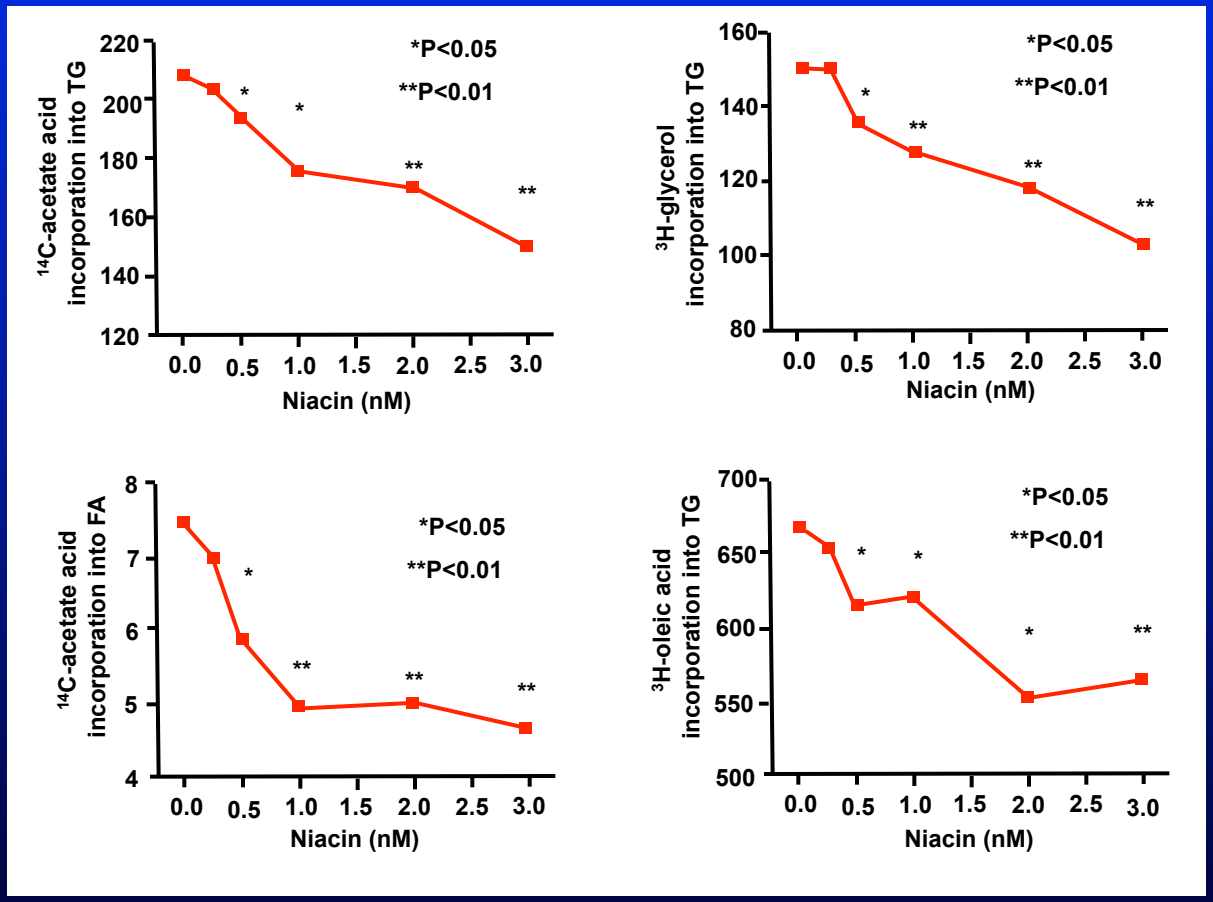
Fu-You Jin, Vaijinath S. Kamanna, Moti L. Kashyap ATVB 1999;19:1051-1059

Niacin Effect on Triglycerides and Apo B

- Niacin, by increasing hepatic post-translational intracellular degradation of apoB, but not altering mRNA expression or uptake, exerts its action to lower the secretion of apoB-containing lipoproteins.
- Furthermore, the selective inhibition of triglyceride synthesis by niacin may limit the lipidation of apoB required for its translocation across the ER membrane and thus facilitate intracellular apoB degradation, suggesting an explanation for reductions in apoB-containing lipoproteins observed clinically after niacin treatment.

Fu-You Jin, Vaijinath S. Kamanna, Moti L. Kashyap ATVB 1999;19:1051-1059

Niacin Effect on Fatty Acids, Glycerol & TG

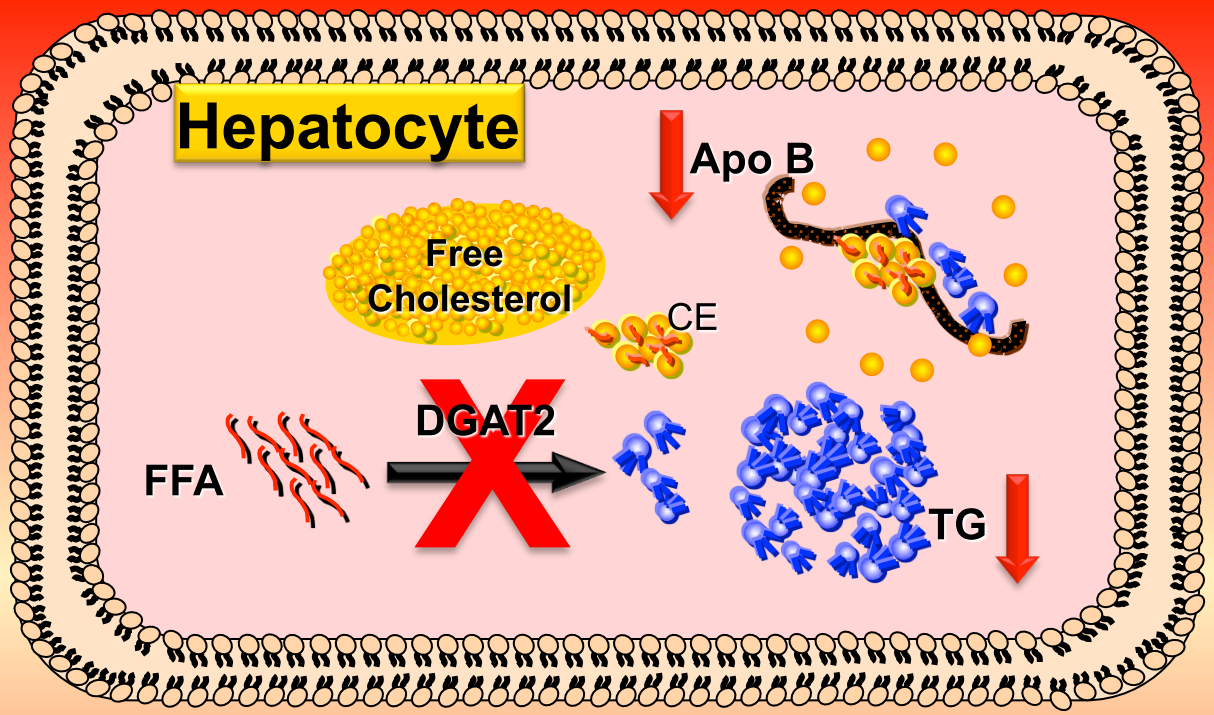


Niacin inhibits TG by preventing Fatty acid (FA) synthesis from acetate and esterification of FA to glycerol

Data are mean ± SE of 3 separate experiments done in triplicate.

Fu-You Jin, Vaijinath S. Kamanna, Moti L. Kashyap ATVB 1999;19:1051-1059

Niacin: Hepatic Mechanism of Action

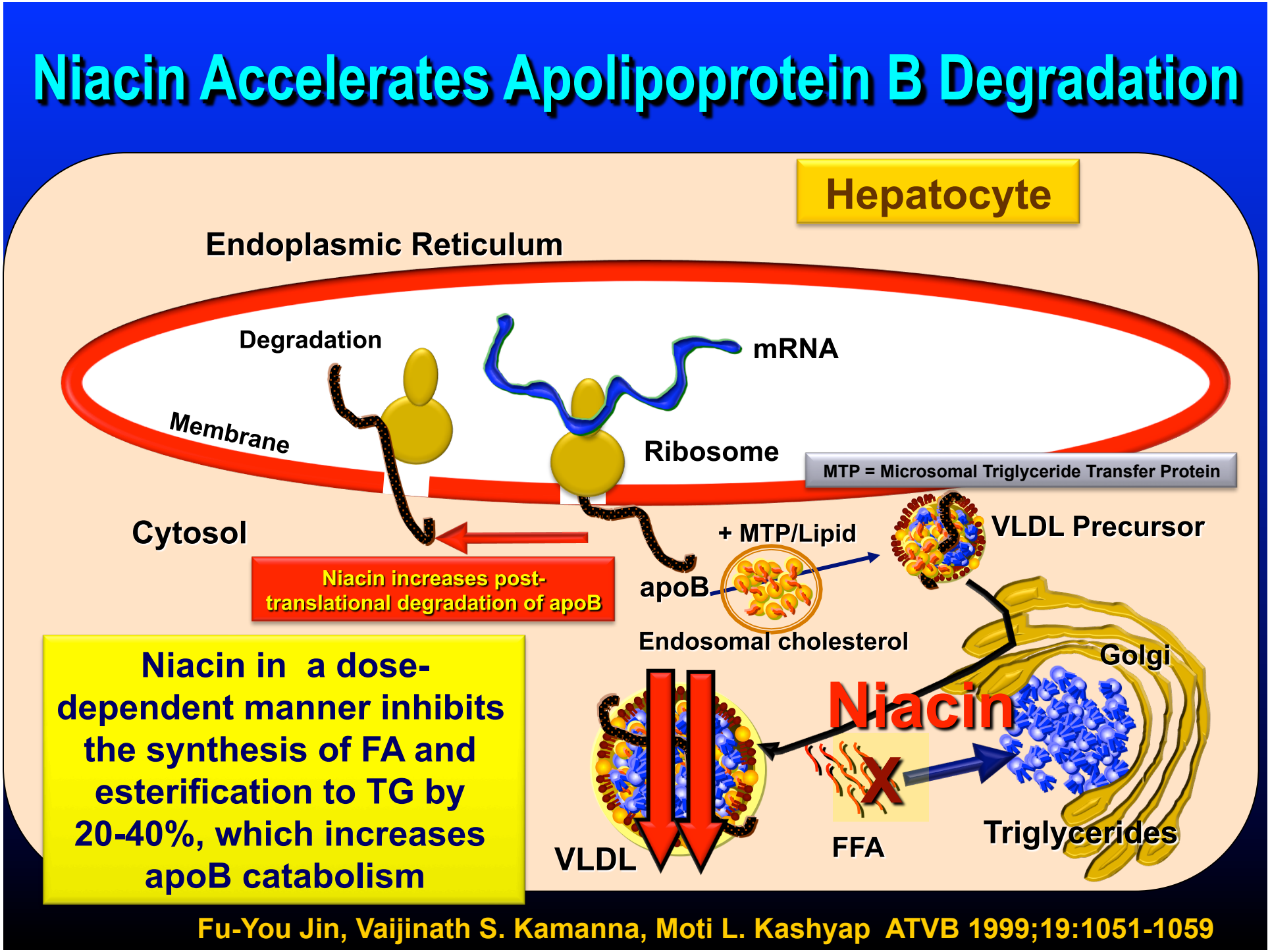


- Niacin non-competitively and directly inhibits DGAT2 reducing TG synthesis
- Post-translational degradation of Apo B

Diacylglycerol 2 acyltransferase (DGAT2) plays a role in the hepatic assembly of de novo synthesized fatty acid into VLDL particles

Malik SW & Kashyap M. Curr Card Reports 2003:5:470-476

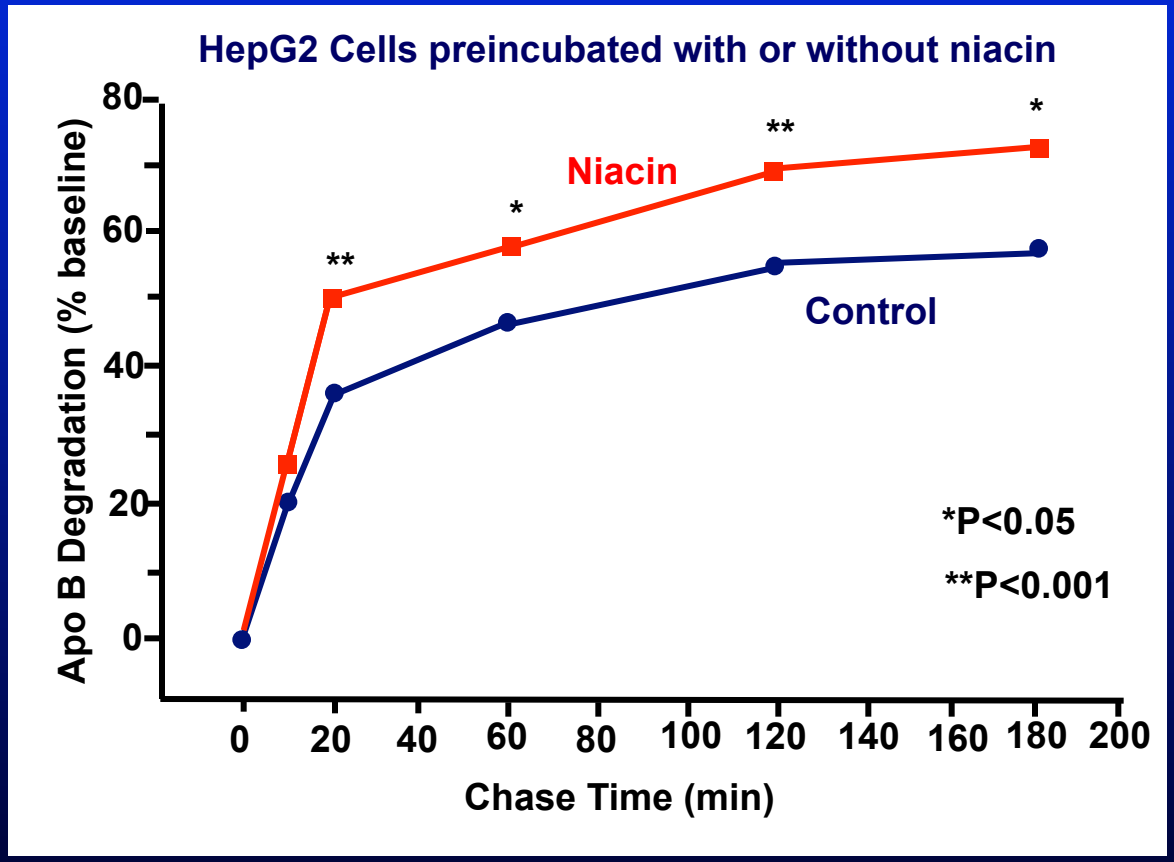
Niacin Accelerates Apolipoprotein B Degradation



Niacin in a dose-dependent manner inhibits the synthesis of FA and esterification to TG by 20-40%, which increases apoB catabolism

Fu-You Jin, Vaijinath S. Kamanna, Moti L. Kashyap ATVB 1999;19:1051-1059

Niacin Effect on Apo B Degradation



Niacin increases hepatic post-translational intracellular degradation of apoB

Data are mean ± SE of 3 separate experiments done in triplicate.

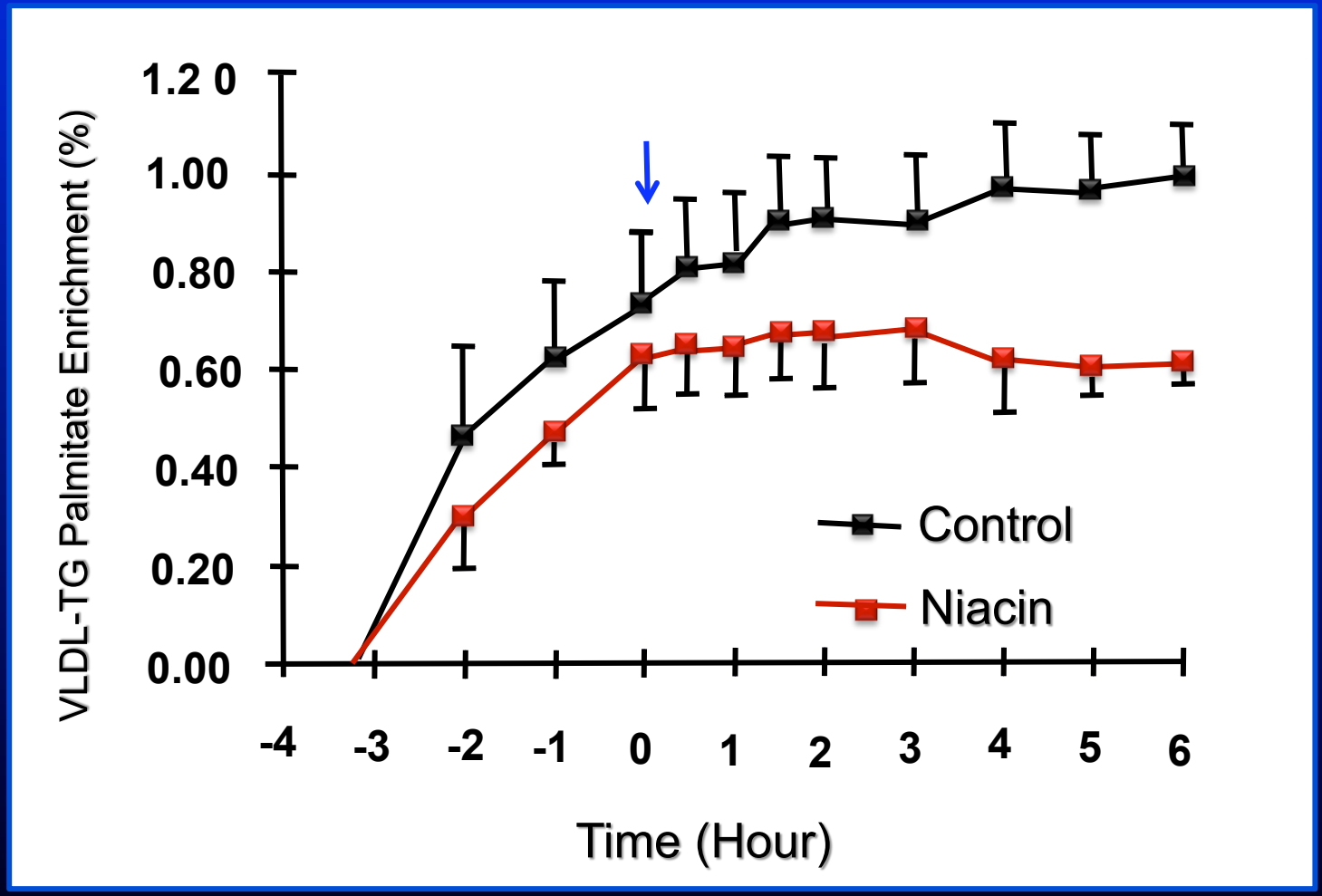
Fu-You Jin, Vaijinath S. Kamanna, Moti L. Kashyap ATVB 1999;19:1051-1059

Niacin Effect on Triglycerides and Apo B

- Plasma turnover kinetic studies following injection of ^{3}H-glycerol indicates that niacin decreased the synthetic rate of VLDL-TGs by 21%
  - This suggests niacin's target is TG synthesis in the liver

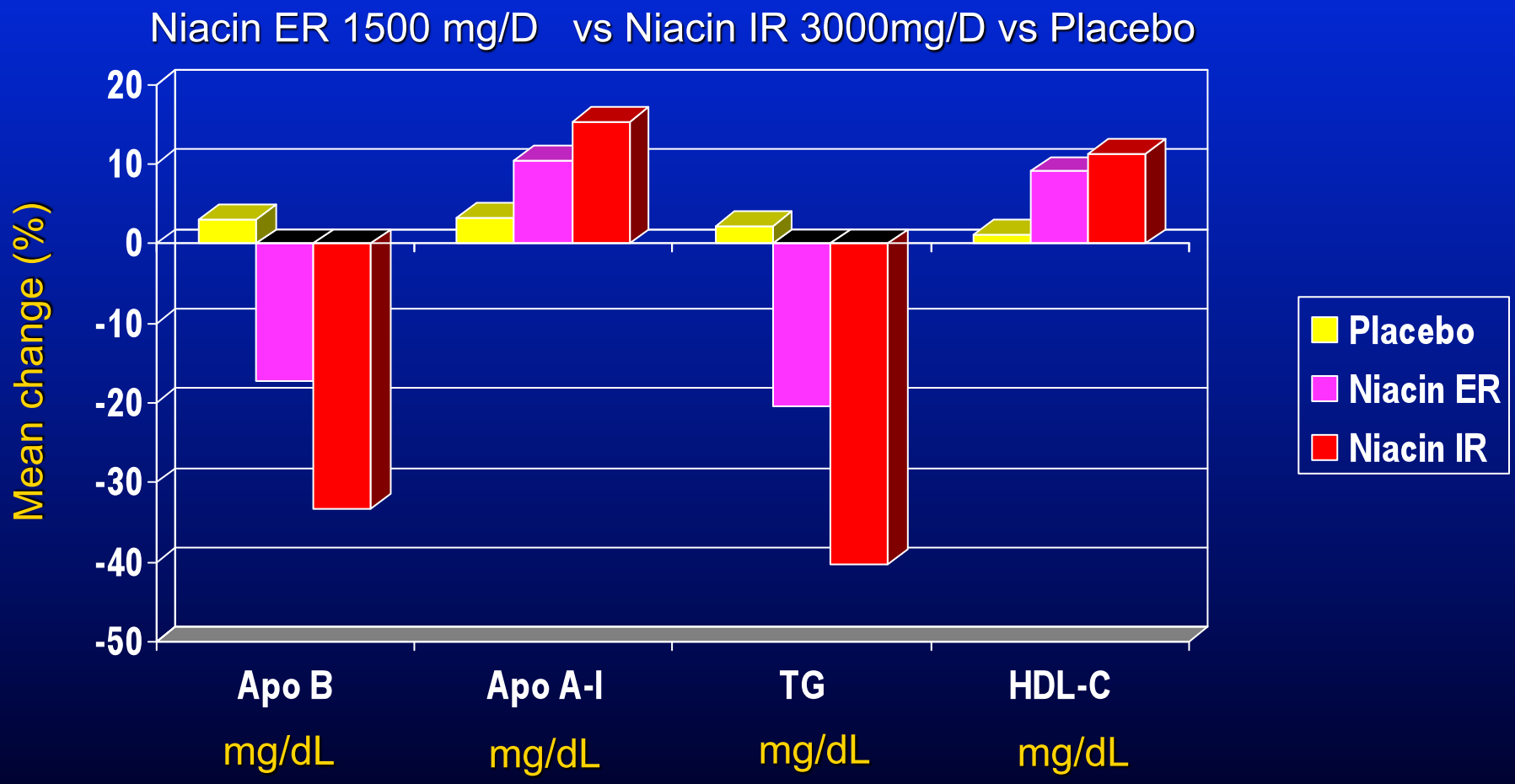
Vaijinath S. Kamanna & Moti L. Kashyap Am J Card 2007;100[suppl]:53M-61N

Niacin Effect on VLDL-Triglyceride



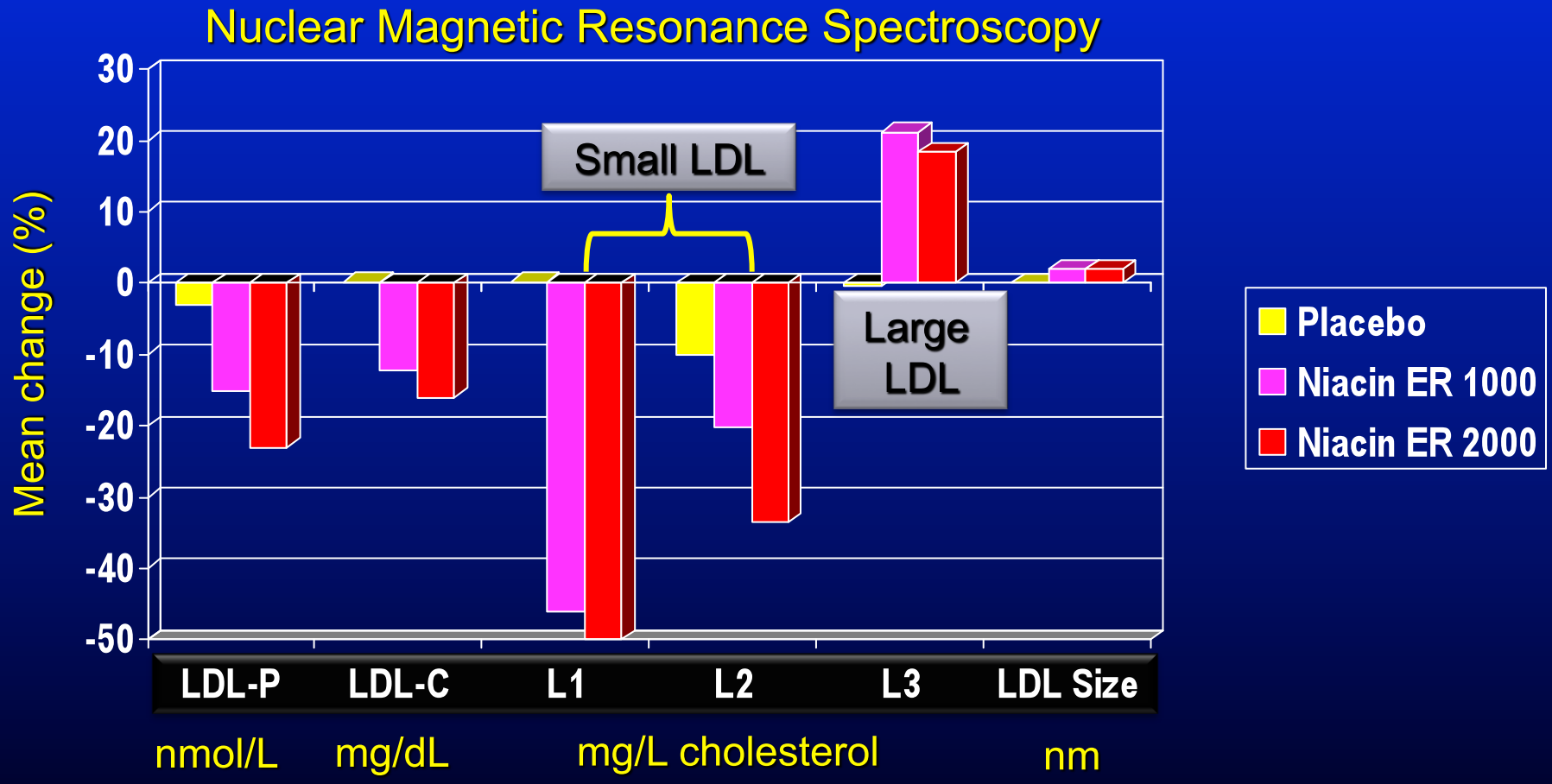
Wang W et al. Am J Physiol Endocrinol Metab. 2001;43:E540–E547,

Niacin on Lipids and Apolipoproteins



Superko HR et al. Am J Cardiol 2004;94:588–594

Niacin and LDL- P, LDL-C and LDL Size Parameters



Morgan J et al. Am J Cardiol 2003;91:1432–1436

Extended Release Niacin: LDL-P & HDL-P

- The primary end point was to study the effect of ERN on LDL particle numbers in patients with stable CAD and well-controlled LDL levels.
- Men and women with CAD (defined by the presence of ischemia or infarction on single-photon emission computed tomographic nuclear myocardial perfusion imaging or >50% stenosis of an epicardial coronary artery by angiography) and statin controlled LDL cholesterol levels (<100 mg/dL) were enrolled.
- Patients were maintained on their stable medications throughout the study.

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Extended Release Niacin: LDL-P & HDL-P

- Initially, subjects took one study tablet (500 mg of ERN or placebo) at night for 2 weeks. After 2 weeks, subjects were instructed to increase to two study tablets nightly (1000 mg of ERN or placebo) for the duration of the study period.

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Extended Release Niacin: LDL-P & HDL-P

Table 1 Baseline study population characteristics

Characteristic	Placebo (n = 27)	ERN (n = 27)
Age, y	57 ± 7	60 ± 10
Gender (men/women)	25/2	25/2
Diabetes mellitus	6 (22%)	5 (19%)
Tobacco use (current)	1 (4%)	2 (7%)
ACE inhibitor therapy*	12 (44%)	20 (75%)
Nitrate therapy*	2 (7%)	10 (36%)
Angiotensin-receptor blocker therapy	5 (19%)	2 (7%)
Aspirin	27 (100%)	27(100%)
Statin	27 (100%)	(100%)
Total cholesterol, mg/dL	144 ± 24	136 ± 20
HDL cholesterol, mg/dL	41 ± 6	39 ± 7
LDL cholesterol, mg/dL	82 ± 19	76 ± 20
Triglycerides, mg/dL	143 ± 71	133 ± 59

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Extended Release Niacin: LDL-P & HDL-P

Table 2 Change in lipid parameters from baseline to follow-up

Lipid parameter	Placebo (n = 27)	ERN (n = 27)
Total cholesterol, mg/dL (%)	3.1 ± 23.2 (2.1)	−5.1 ± 12.3 (3.1)*
LDL, mg/dL (%)	0.1 ± 20.9 (1.0)	−3.6 ± 12.3 (0.86)
HDL, mg/dL (%)	0.2 ± 6.2 (1.1)	2.7 ± 4.3 (7.5)*
Triglycerides, mg/dL (%)	10.2 ± 62.3 (15)	−27.5 ± 40.7 (15)*

ERN, extended-release niacin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Data are presented as mean change from baseline ± standard deviation (percentage).

*$P < .05$ indicates significant change from baseline.

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Extended Release Niacin: LDL-P & HDL-P

Table 3 Change in particle number from baseline to follow-up

Variable	Placebo (n = 27)		ERN (n = 27)	
	Baseline	Follow-up	Baseline	Follow-+Up
Total LDL particle number, nmol/L	1126.4	1155.8	1032.7	942.0*,†
Large LDL, nmol/L	177.3	156.3	171.7	195.6
Medium LDL, nmol/L	187.3	197.3	169.4	141.9*,†
Small LDL, nmol/L	930.6	980.9	845.8	727.9*,†
Total HDL particle number, μmol/L	31.0	31.3	29.3	29.2
Large HDL, μmol/L	4.1	4.0	4.3	5.5*,†
Medium HDL, μmol/L	3.6	3.7	3.8	3.9
Small HDL, μmol/L	23.3	23.6	21.2	29.8*,†

ERN, extended-release niacin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Data are expressed as mean number of particles for LDL (nanomoles per liter) and HDL (micromoles per liter).
*$P < .05$ indicates significant change from baseline on therapy.
†$P < .05$ indicates significant difference between placebo- and ERN-treated groups at follow-up.

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Extended Release Niacin: LDL-P & HDL-P

- ERN significantly decreased the mean number of small HDL particles and increased the mean number of large HDL particles (P = .027, P < 0.001 respectively).
- There were no significant changes in HDL particle numbers for any subclass in the placebo-treated patients.
- At 3 months, the mean numbers of large HDL (P < 0.001) particles were significantly higher and small HDL particles (P = .027) were significantly lower in the ERN-treated patients compared to the placebo-treated patients.
- The mean percent increase in HDL particle numbers from baseline to follow-up tended to be greater in the ERN-treated patients compared to placebo treated patients for large (P = .078) and small HDL (P = .075), although these changes were not statistically significant

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

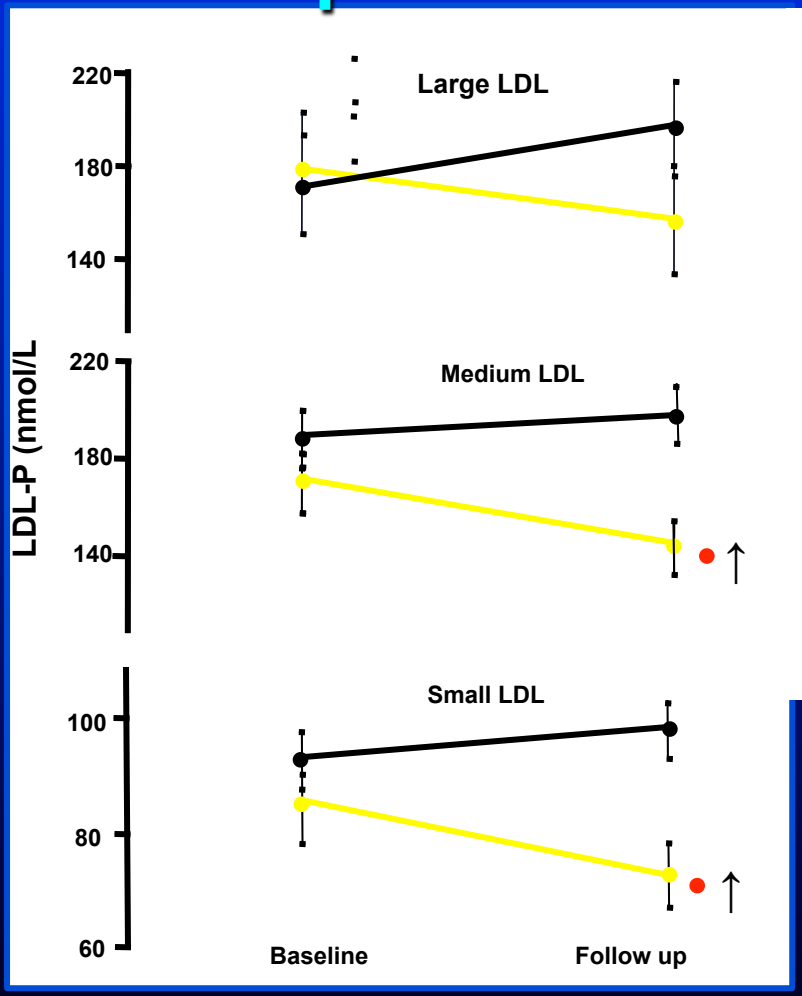
Extended Release Niacin: LDL-P & HDL-P

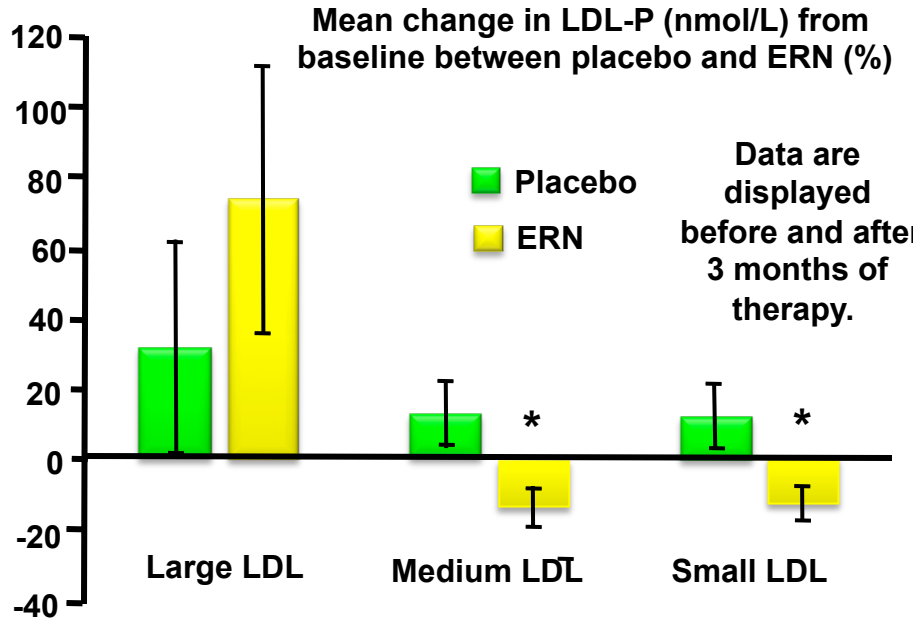
The average total number of HDL particles at baseline was similar for patients receiving ERN or placebo and **there were no significant changes from baseline to follow-up in either treatment group**.

Also, the average number of total HDL particles at follow-up was similar between ERN- and placebo-treated patients.

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Extended-release niacin reduces LDL particle number without changing total LDL-C in patients with stable CAD on statin



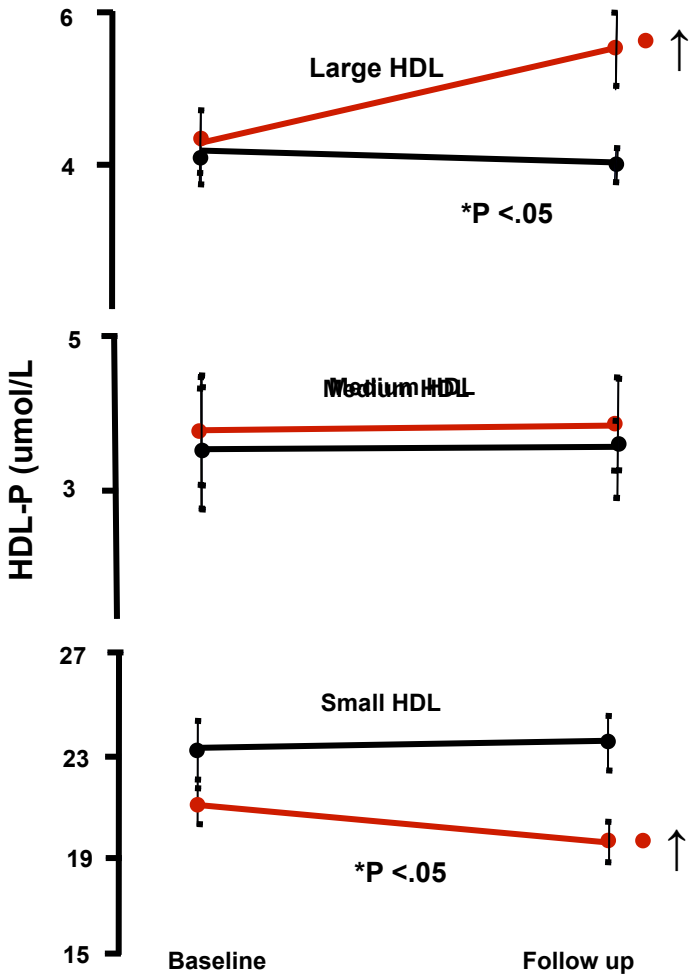


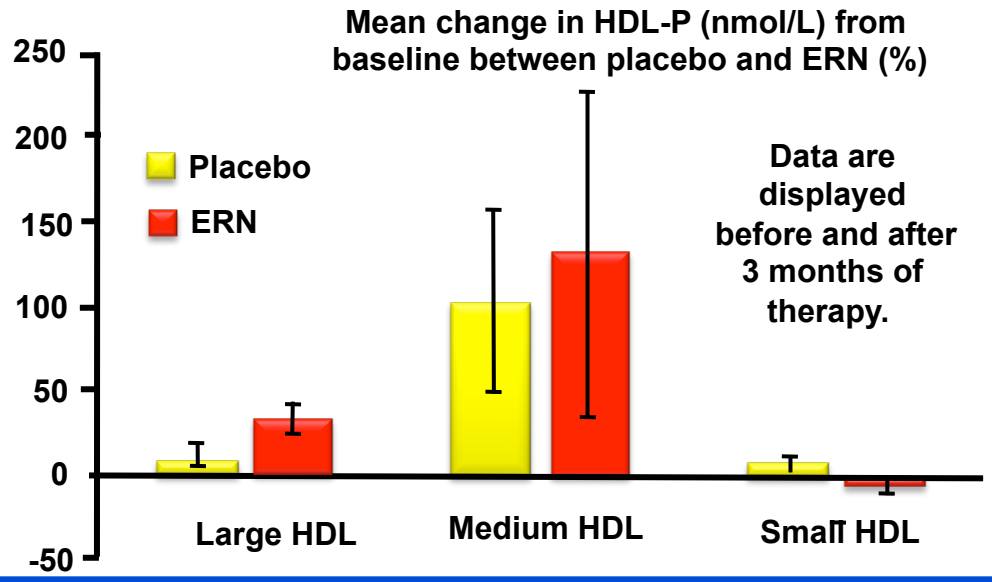
Fifty-four patients with stable coronary artery disease (CAD) and well statin controlled LDL levels were randomly assigned to 3 months of ERN (1 g/day) or placebo in addition to their baseline medications. Lipoprotein particle number was analyzed by proton nuclear magnetic resonance spectroscopy at baseline and after 3 months.

ERN-induced alterations in lipoprotein particle numbers may contribute to its anti-atherosclerotic effects, and these effects may not be evident from the standard lipid profile.

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Extended-release niacin increases HDL particle number in patients with stable CAD on statin



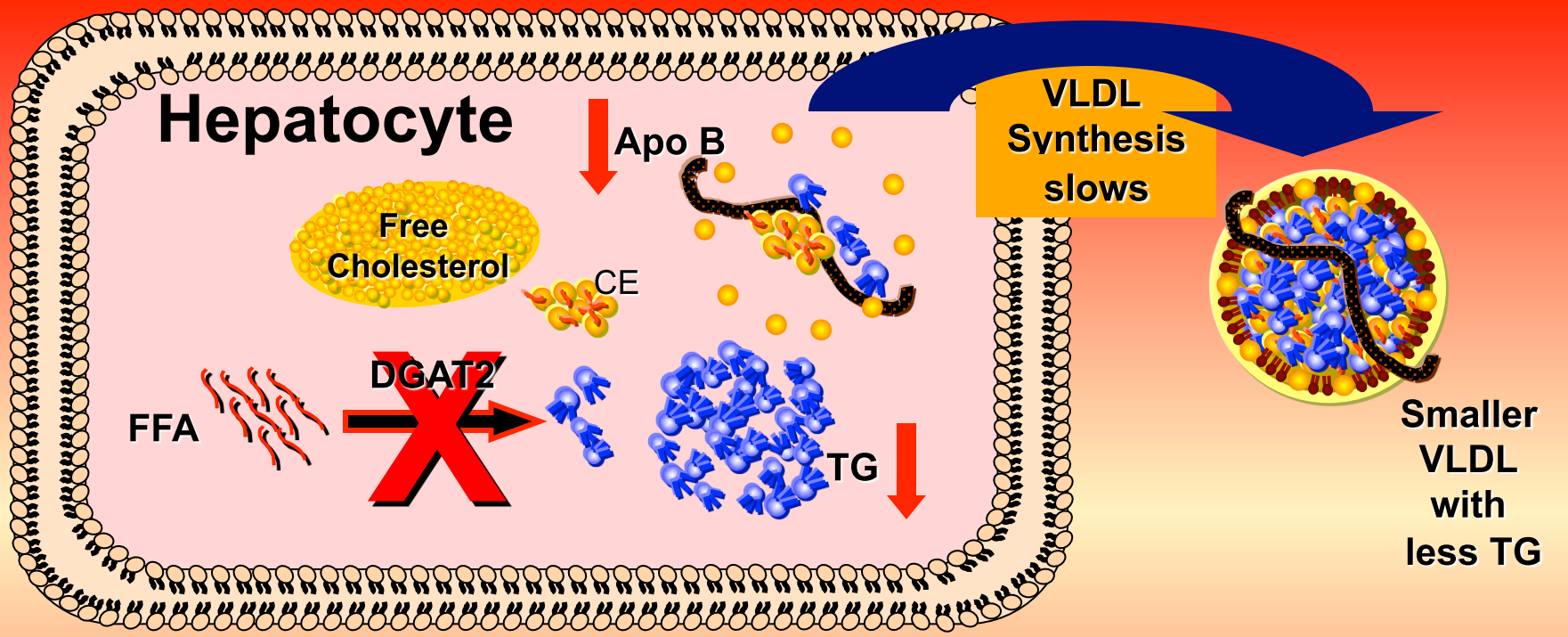


Fifty-four patients with stable coronary artery disease (CAD) and well-controlled LDL levels were randomly assigned to 3 months of ERN (1 g/day) or placebo in addition to their baseline medications. Lipoprotein particle number was analyzed by proton nuclear magnetic resonance spectroscopy at baseline and after 3 months.

ERN raised HDL cholesterol levels by 2.7%, significantly increased the number of large HDL particles (P < .001), and decreased the number of small HDL particles (P = .027) compared to placebo. There were no significant changes in lipid values or particle numbers in the placebo-treated patients.

Jafri H et al. Journal of Clinical Lipidology (2009) 3, 45–50

Niacin: Hepatic Mechanism of Action



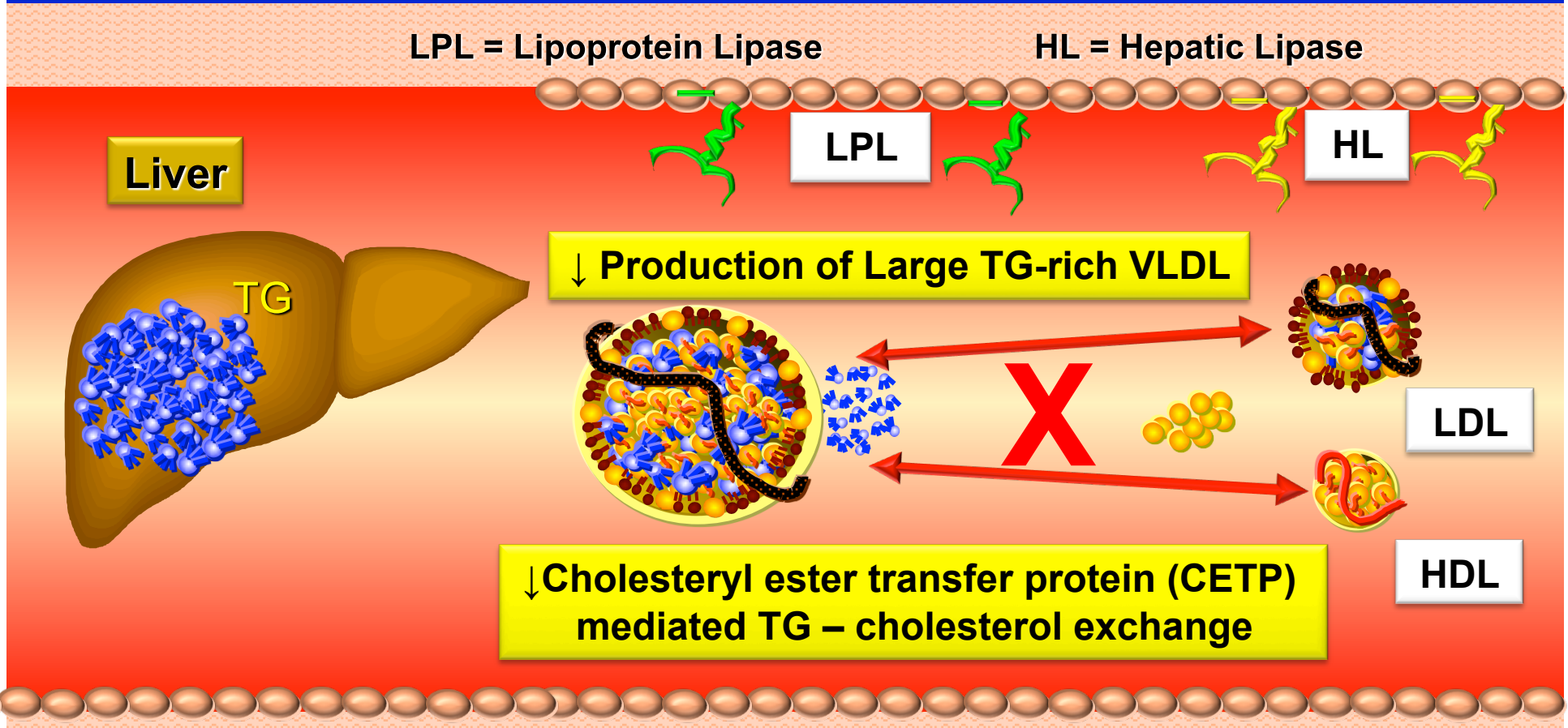
VLDL and ultimately LDL production decreases and the TG poor VLDLs are less atherogenic and do not form remnants & small LDL into VLDL particles

- Niacin non-competitively and directly inhibits DGAT2 reducing TG synthesis
- Post-translational degradation of Apo B

[redacted]

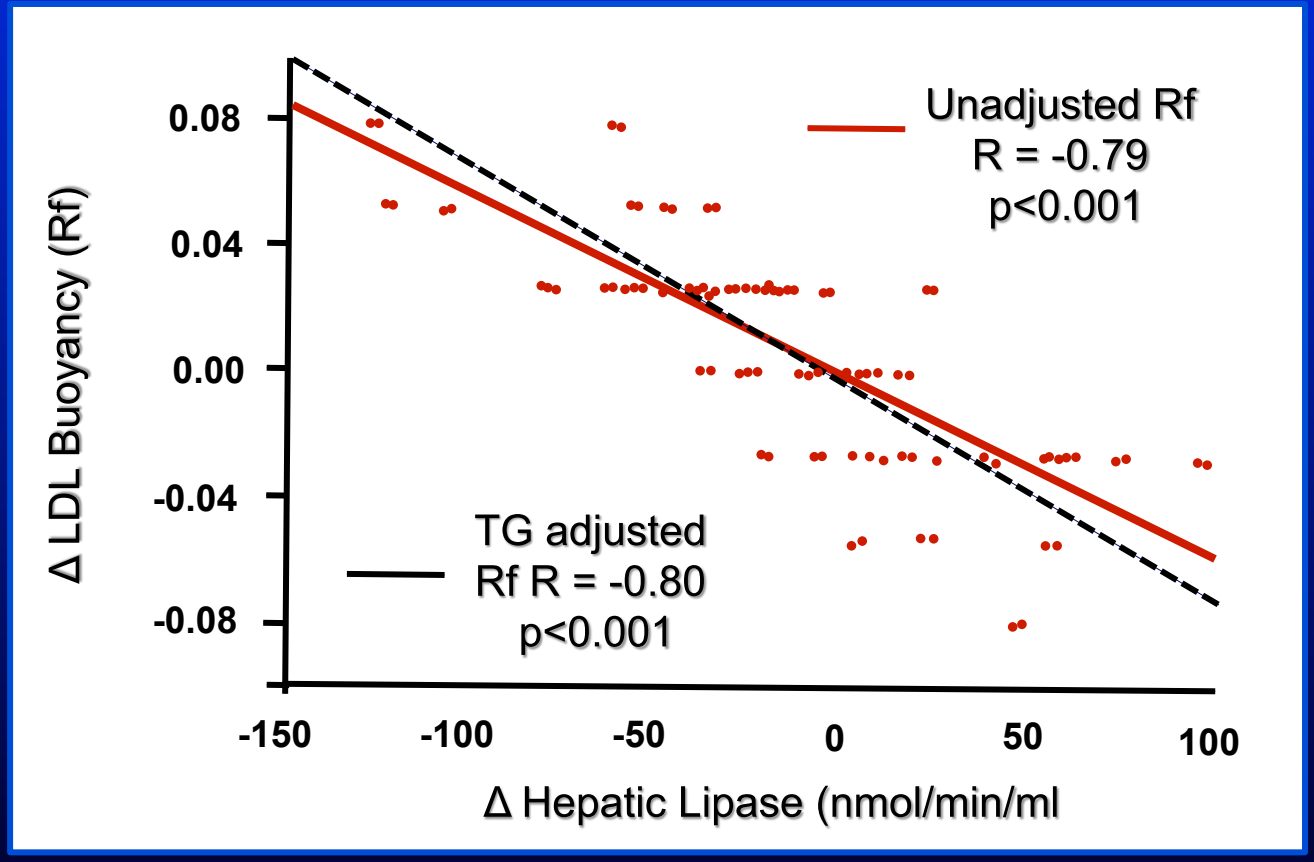
Malik SW & Kashyap M. Curr Card Reports 2003:5:470-476

Decreased CETP Mediated CE/TG Exchange Creates Larger LDL & HDL



LDLs and HDLs retain their CE and shift to a larger size: LDL-C & HDL-C may increase: LDLs become more amenable to LDLr endocytosis

Familial Atherosclerosis Treatment Study (FATS)



Linear regression analysis of changes in HL activity and changes in LDL buoyancy (symbols and solid regression line).

Dashed line represents regression line of linear regression analysis with TG-adjusted changes in LDL buoyancy.

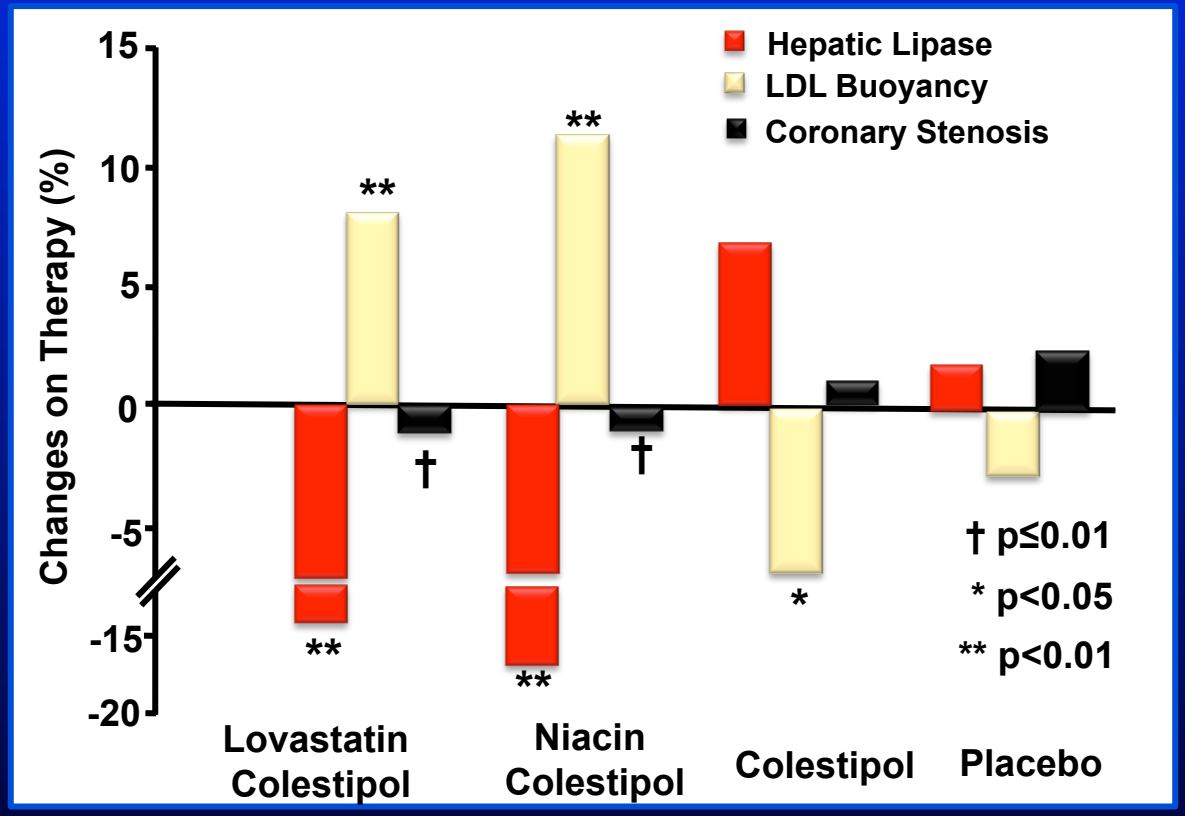
Niacin – Colestipol

Colestipol - Lovastatin

These studies support the hypothesis that therapy-associated changes in HL alter LDL density, which favorably influences CAD progression.

Zambon A et al. Circulation. 1999;99:1959-1964

Familial Atherosclerosis Treatment Study (FATS)

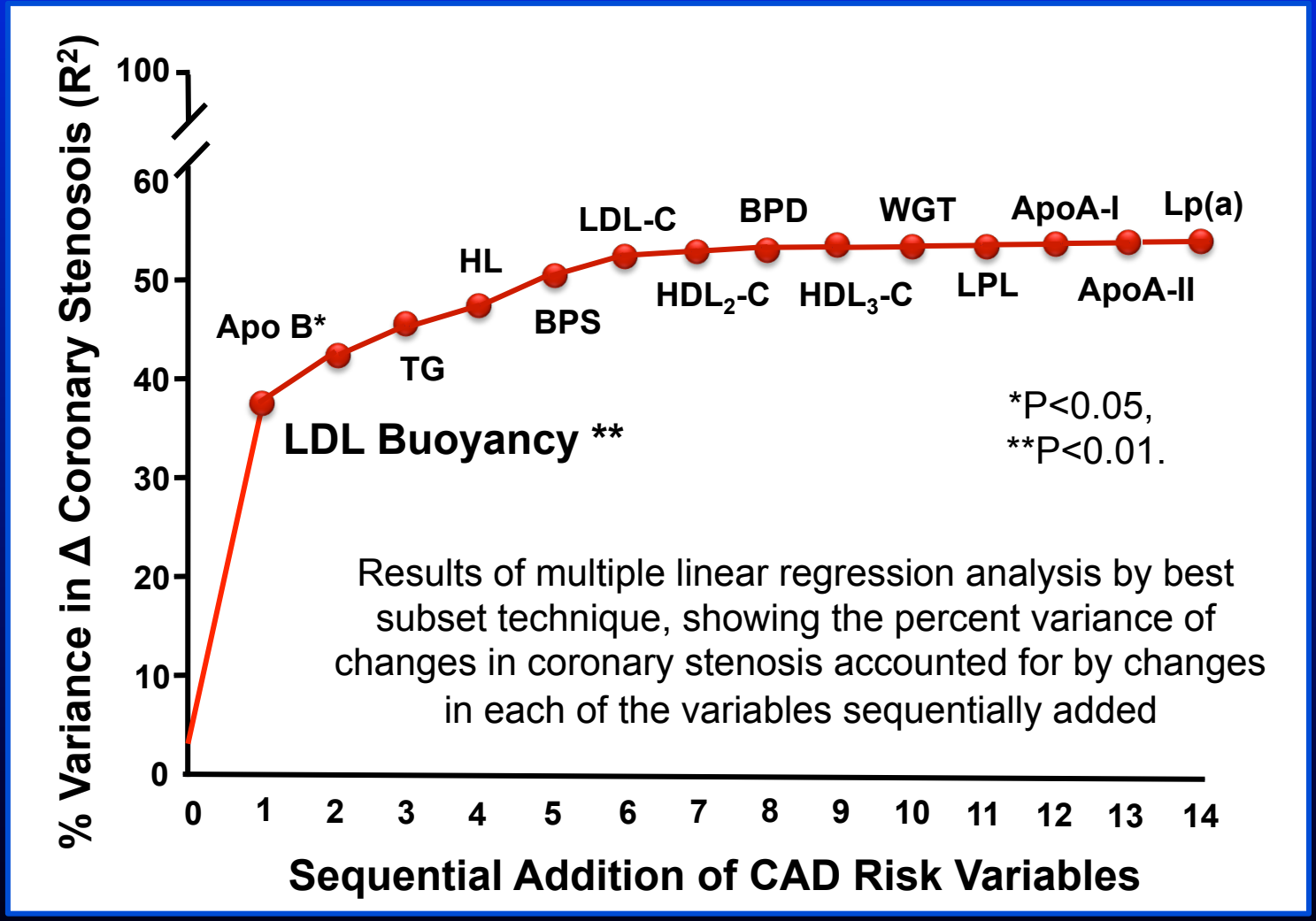


Coronary stenosis was significantly decreased in subjects taking lovastatin – colestipol (P<,0.01) or niacin-colestipol (P=0.01) compared with subjects receiving conventional treatment (whole group: placebo plus colestipol)

HL activity falls significantly in response to intensive lipid-lowering therapy with statin or niacin.

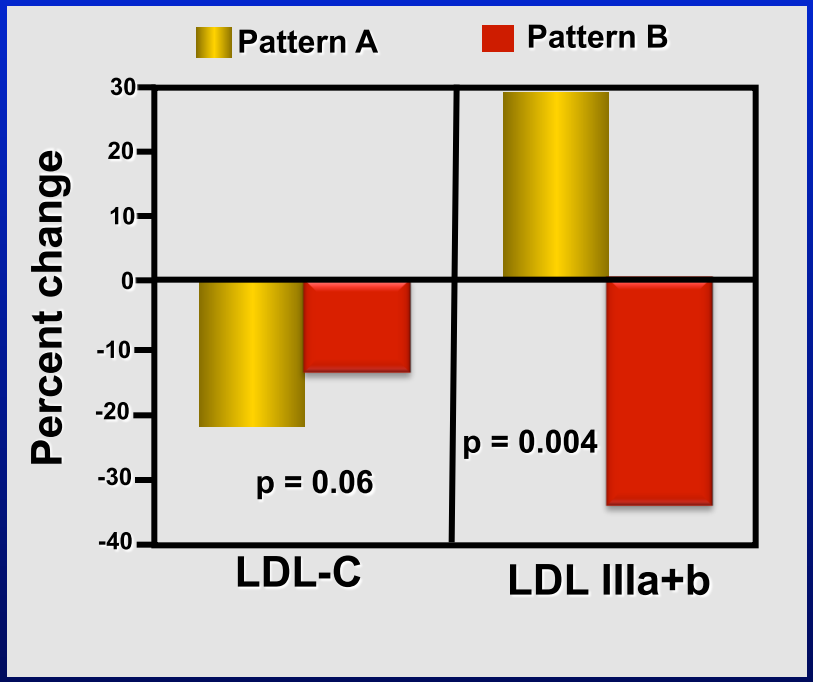
Zambon A et al. Circulation. 1999;99:1959-1964

Familial Atherosclerosis Treatment Study (FATS)



Zambon A et al. Circulation. 1999;99:1959-1964

Niacin and LDL Particles



Percent change in LDL-C versus change in small LDL regions IIIa and IIIb after 1500 mg of Niacin ER in subjects with Pattern A or B

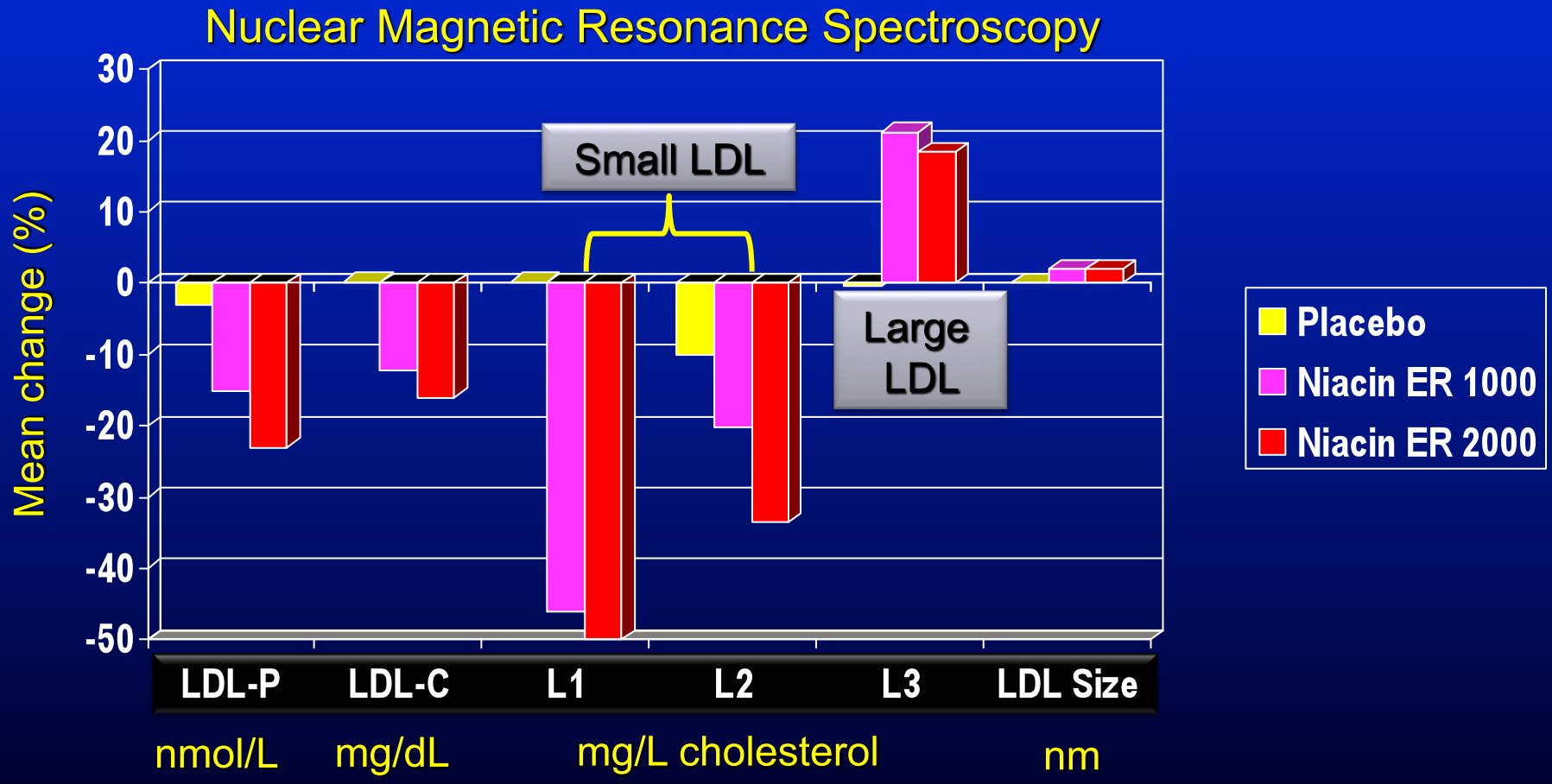
There is a significantly different response with regard to decreased LDL cholesterol in subjects with LDL pattern A versus those with B.

Thus, niacin decreased small LDL significantly more in patients with an abundance of small LDL particles (LDL pattern B) but decreased LDL cholesterol more in patients with predominantly large LDL particles (LDL pattern A).

This differential effect can best be appreciated by a 14% decrease in LDL cholesterol and a 34% decrease in small LDL IIIa/IIIb in patients with LDL pattern B treated with 1,500 mg/day of extended-release niacin compared with a 22% decrease in LDL cholesterol but a 29% increase in small LDL IIIa/IIIb in patients with LDL pattern A

Superko HR et al. Am J Cardiol 2004;94:588–594)

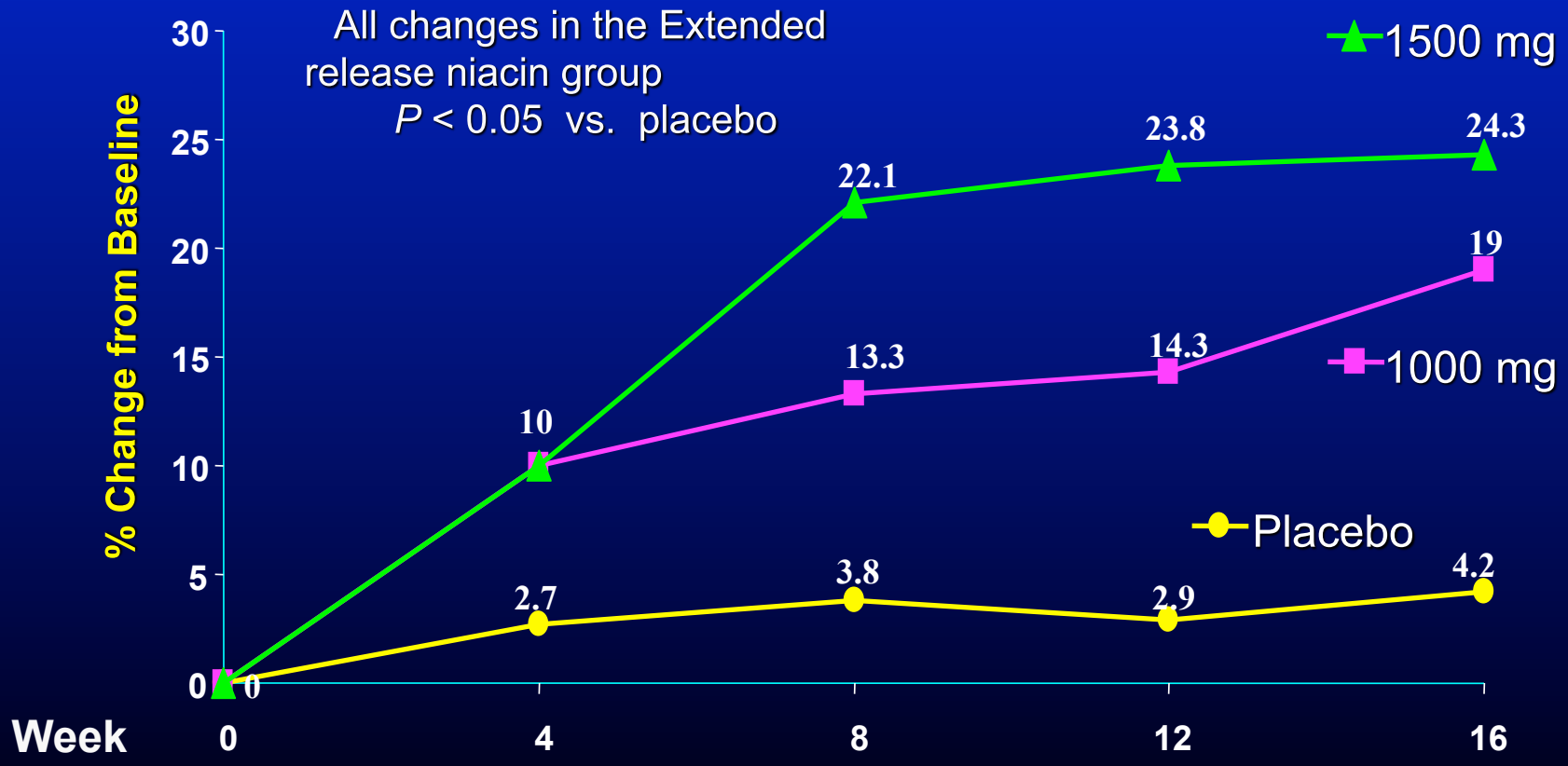
Niacin and LDL- P, LDL-C and LDL Size Parameters



Morgan J et al. Am J Cardiol 2003;91:1432–1436)

Assessment of Diabetes Control and EValuation of the Efficacy of Niaspan Trial (ADVENT)

Changes in HDL-C relative to placebo



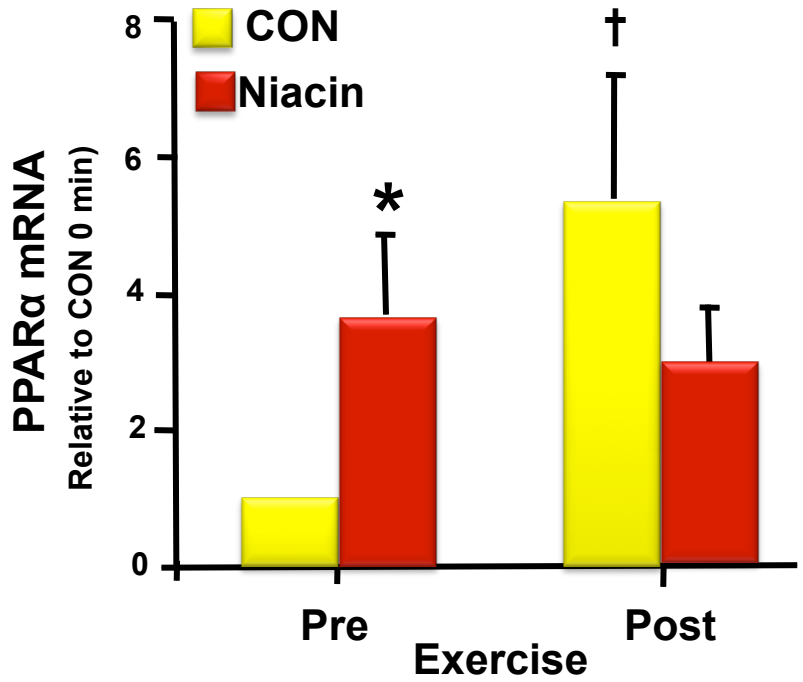
Grundy SM, et al. Arch Intern Med. 2002;162:1568-1576.

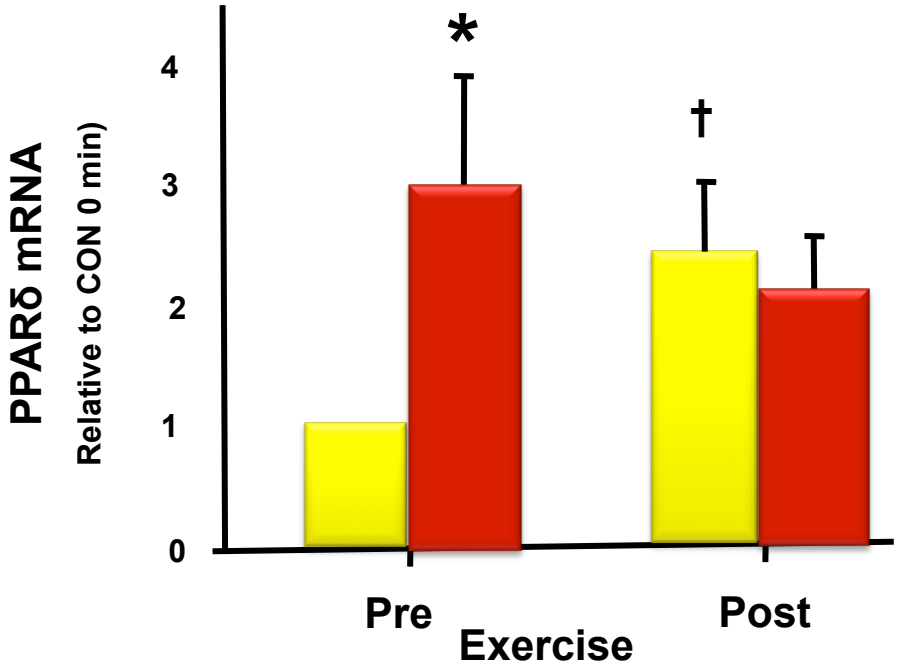
Niacin Effect on PPARs

- These very exciting data point out that possibly nicotinic acid may act as a ‘fraudulent fatty acid’.
- Fraudulent fatty acids are fatty acid-like molecules not metabolized by mitochondria but activating the peroxisomal system, thus leading to metabolic consequences similar to those exerted by nicotinic acid.
- In particular, among fraudulent fatty acids, nicotinic acid (or most likely nicotinoyl CoA, the major metabolite) is the only one activating all three peroxisomal isotypes as well as ABCA1.

Sirtori CR, Galli C, Franceschini G. Eur J Clin Invest 1993;23:686–689.

Niacin and Peroxisome Proliferator Activated Receptors Alpha & Delta



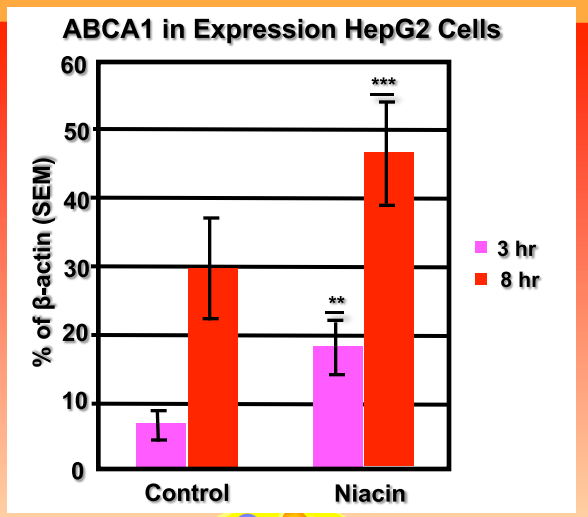


Volunteers were administered nicotinic acid with the objective of reducing lipolysis during the ensuing exercise. The administration of nicotinic acid, surprisingly, led to a marked increase of PPARa and PPARδ mRNA levels in muscle. This rise was similar to that noted after exercise and was accompanied by an increased expression of the PPAR co-activator 1-a (PGC1a) mRNA. The authors concluded that 'nicotinic acid ingestion decreased FFA availability but it promoted induction of PPARa/d and PGC1a gene expression to a similar degree as prolonged exercise

Watt MJ et al. J Mol Endocrinol 2004;33:533–544.

Niacin and Hepatic HDL Lipidation

Hepatocyte with excess cholesterol



RXR

PPARγ

Free or unesterified cholesterol (FC)

Niacin's major metabolite is PGD2 and its metabolite is 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2), a potent endogenous PPARγ activator

CE

Pre-beta$_2$ or
coidal or

Hepatic Sinusoid

The FC is esterified by the enzyme LCAT to cholesteryl ester (CE) creating larger alpha HDL particles

Lipid–free apoA-I or prebeta$_1$ HDL

ATP Binding Ca
Transporter A1 (A

Rubic T et al. Biochemical Pharmacology 67 (2004) 411–419

Reverse Cholesterol Transport Pathways

In mitigating against atherosclerosis, it is critical that HDL or lipid-poor apoA-I be present to promote regression of foam cells.

The existence of pathways for macrophage cholesterol transport implies that effective intervention against atherosclerosis may require LDL-C lowering with statins in combination with specific agonists to increase the function of ABCA1 and ABCG1 as well as SR-B1

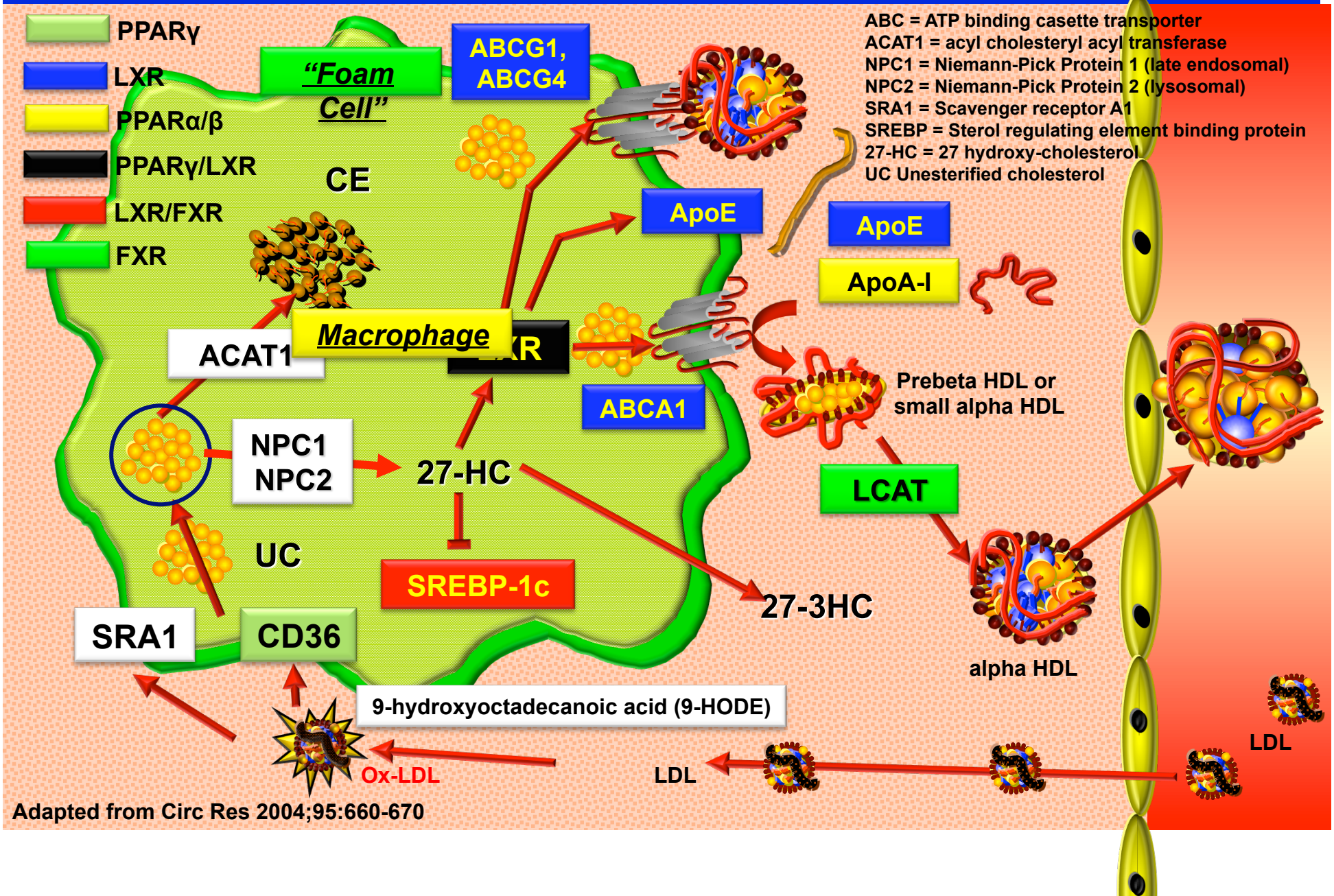
Wang, MD et al. J Lipid Res. 2007;48:6 J Lipid Res. 2007;48:643-655

Niacin Effect on Macrophages

- Niacin has also been shown to interfere with the cyclic AMP (cAMP)/ protein kinase A (PKA) pathway and massively stimulate prostaglandin D2 (PGD2) formation.
- The major metabolite of PGD2, 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2), has been identified as the most potent endogenous PPARγ activator.
- Niacin stimulated the translocation of PPARγ and the transcription of PPARγ, CD36 and ABCA1 in monocytoid cells, whereas the LDL-receptor (LDL-R) was unchanged.
  - Thereby niacin enhanced HDL-mediated cholesterol efflux from the cells resulting in a reduced cellular cholesterol content.
- These new actions of niacin on several key effectors of reverse cholesterol transport out of the vessel wall provide a rational to expect regression of atherosclerosis and test the combination of niacin with statins for an over additive clinical benefit.

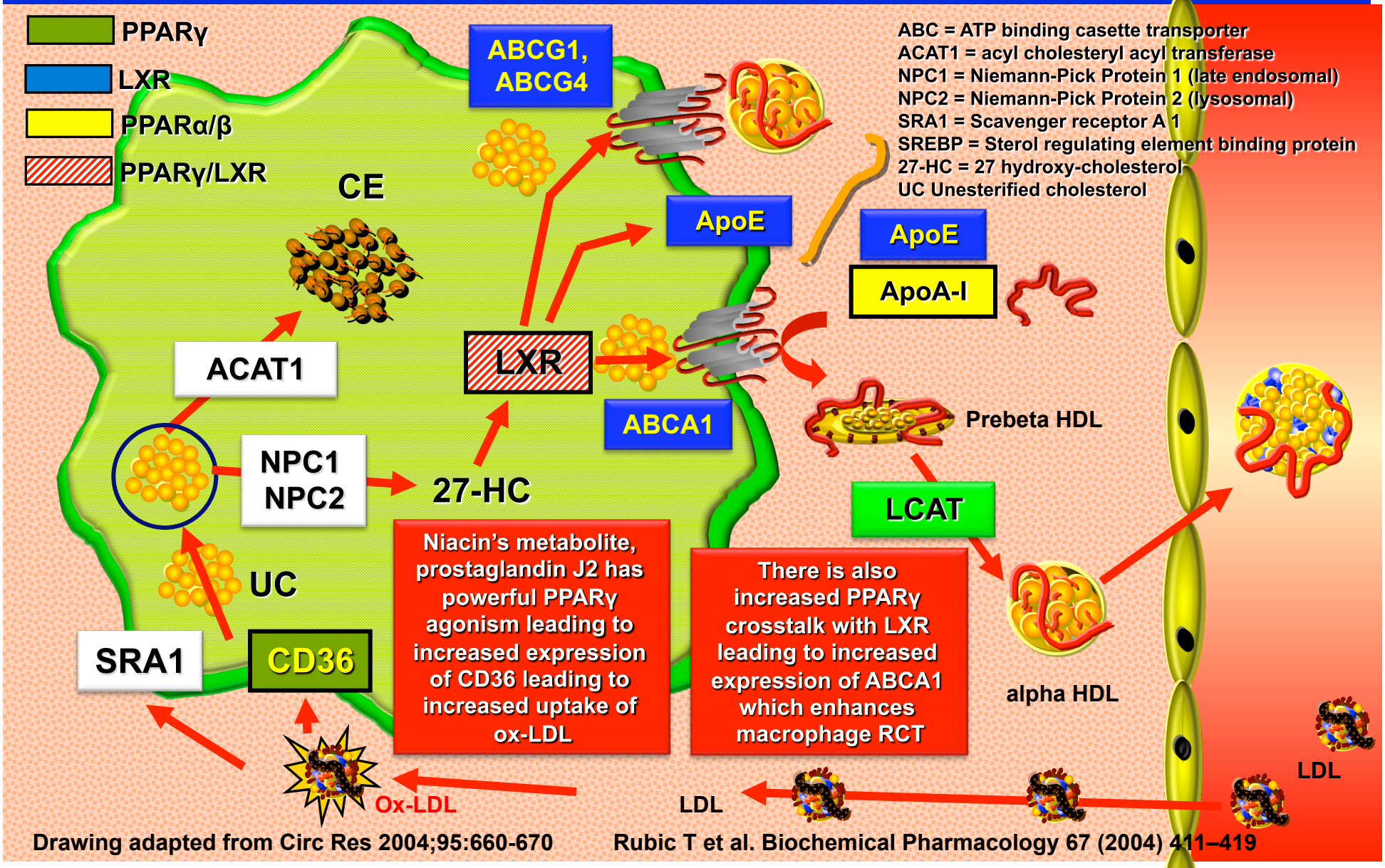
Rubic T et al. Biochemical Pharmacology 67 (2004) 411–419

Macrophage Uptake & Processing of Lipoproteins



Adapted from Circ Res 2004;95:660-670

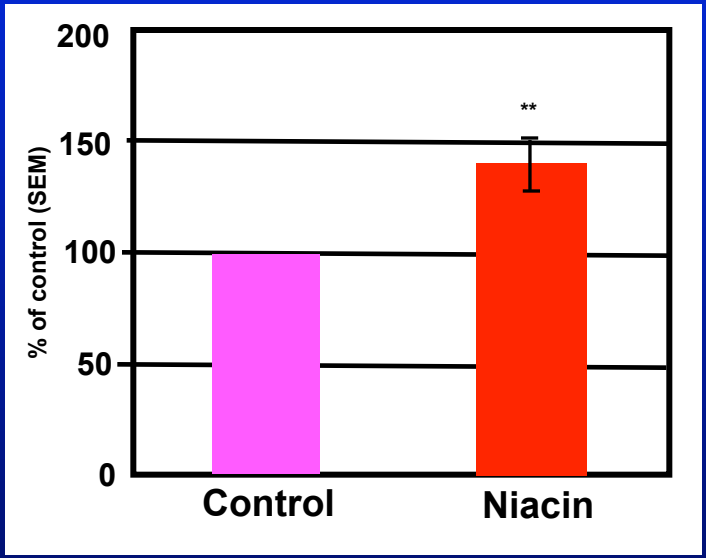
Niacin's Effect on Macrophage Uptake & Processing of Lipoproteins



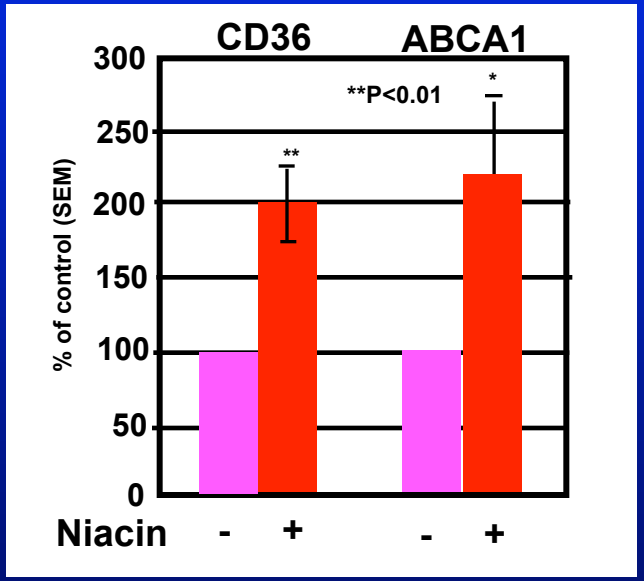
Drawing adapted from Circ Res 2004;95:660-670

Rubic T et al. Biochemical Pharmacology 67 (2004) 411–419

Niacin Effect on Macrophages



Mean fluorescence in MM6r cells stained for PPARγ after incubation under control conditions or presence of niacin



Effects of niacin on CD 36 and ABCA1 transcription (levels of mRNA) in hu8man monocytes

Rubic T et al. Biochemical Pharmacology 67 (2004) 411–419

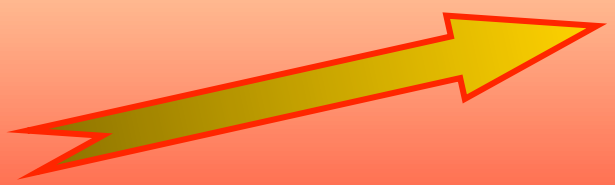
Niacin Inhibits Hepatic Lipase and Decreases HDL Particle Lipolysis

Reduced HDL lipolysis (removal of core TG, surface phospholipids and apoproteins)

Niacin is associated with larger mature α-HDL species

Niacin Inhibits Hepatic Lipase

Large HDL (HDL_2 or H4, H5)

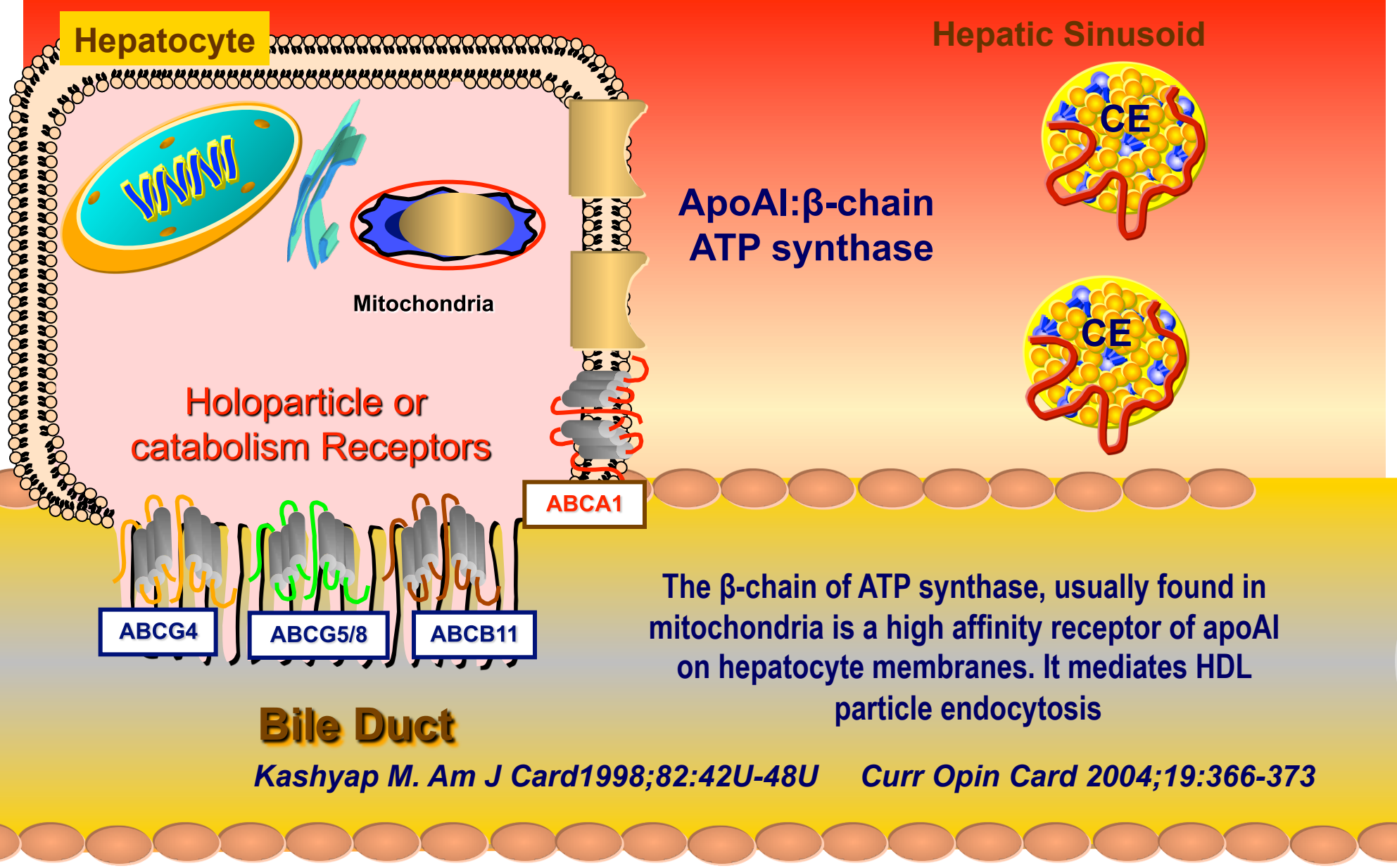


Large HDL Particles not excreted by Kidneys

HDL-C ↑

Rashid S. et al. Circulation 2003;107:3066-3072

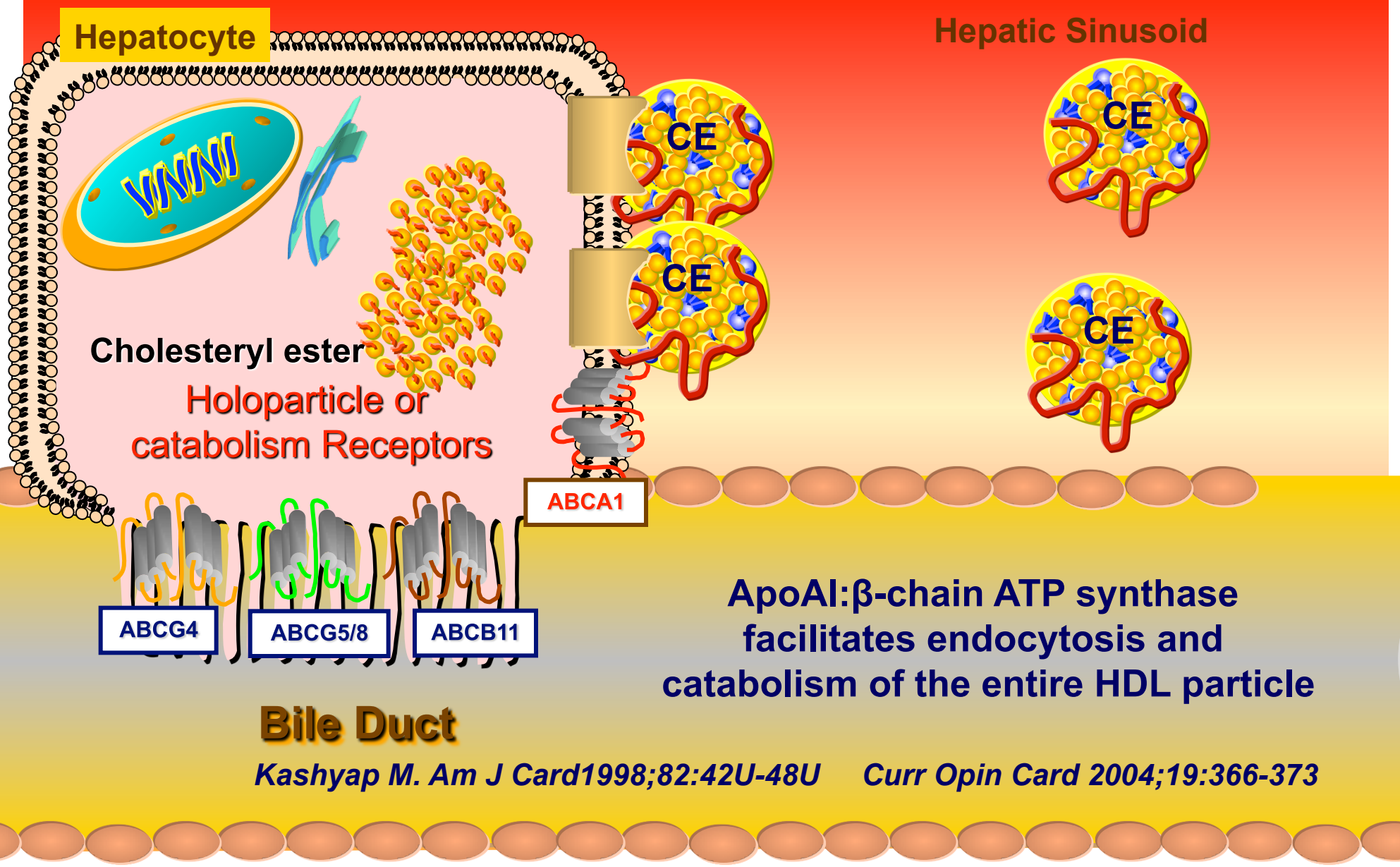
Hepatocyte: Direct RCT



The β-chain of ATP synthase, usually found in mitochondria is a high affinity receptor of apoAI on hepatocyte membranes. It mediates HDL particle endocytosis

Kashyap M. Am J Card1998;82:42U-48U *Curr Opin Card 2004;19:366-373*

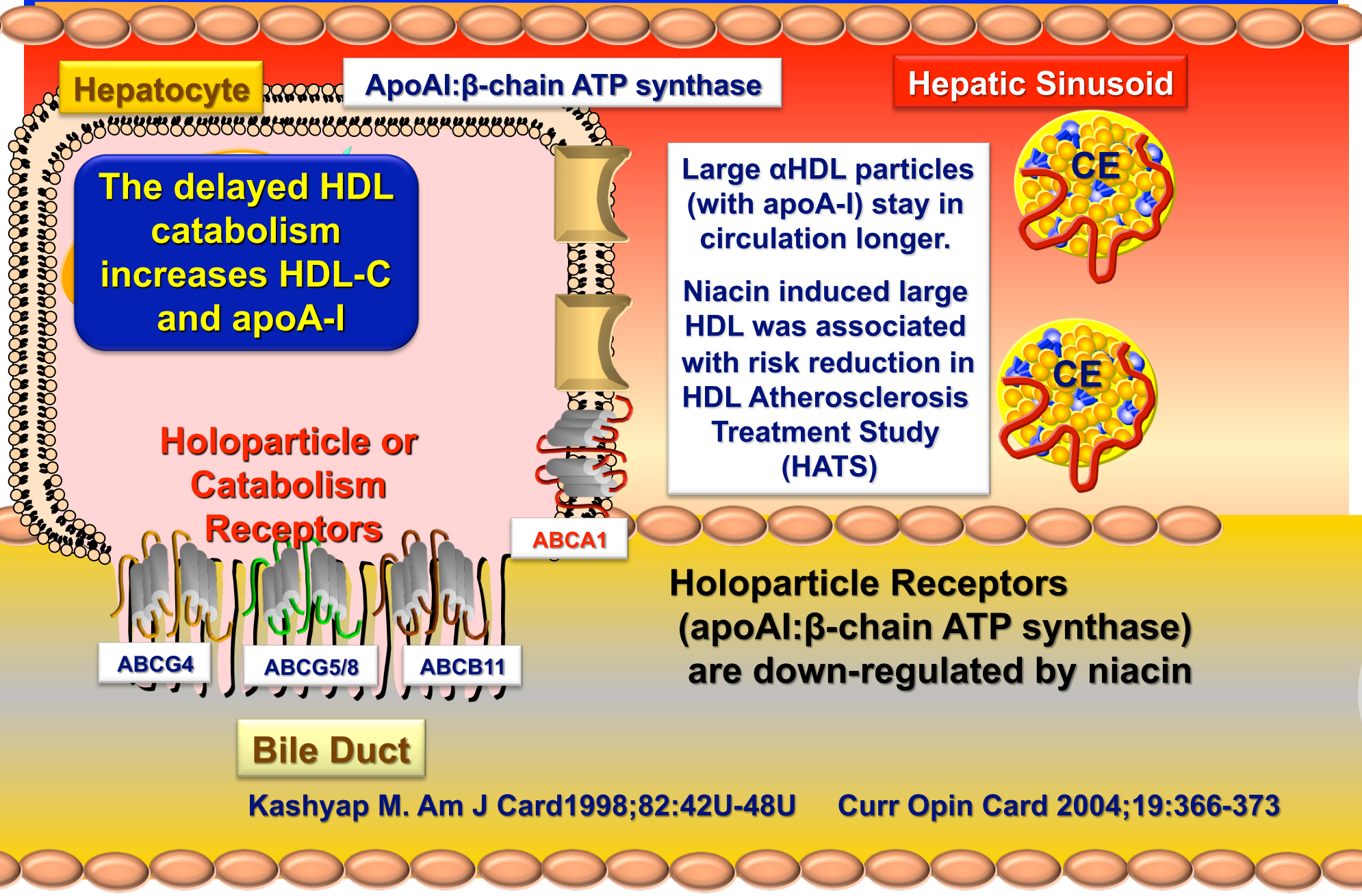
Hepatocyte: Direct RCT



ApoAI:β-chain ATP synthase facilitates endocytosis and catabolism of the entire HDL particle

Kashyap M. Am J Card1998;82:42U-48U *Curr Opin Card 2004;19:366-373*

Niacin and Direct RCT



Kashyap M. Am J Card1998;82:42U-48U Curr Opin Card 2004;19:366-373

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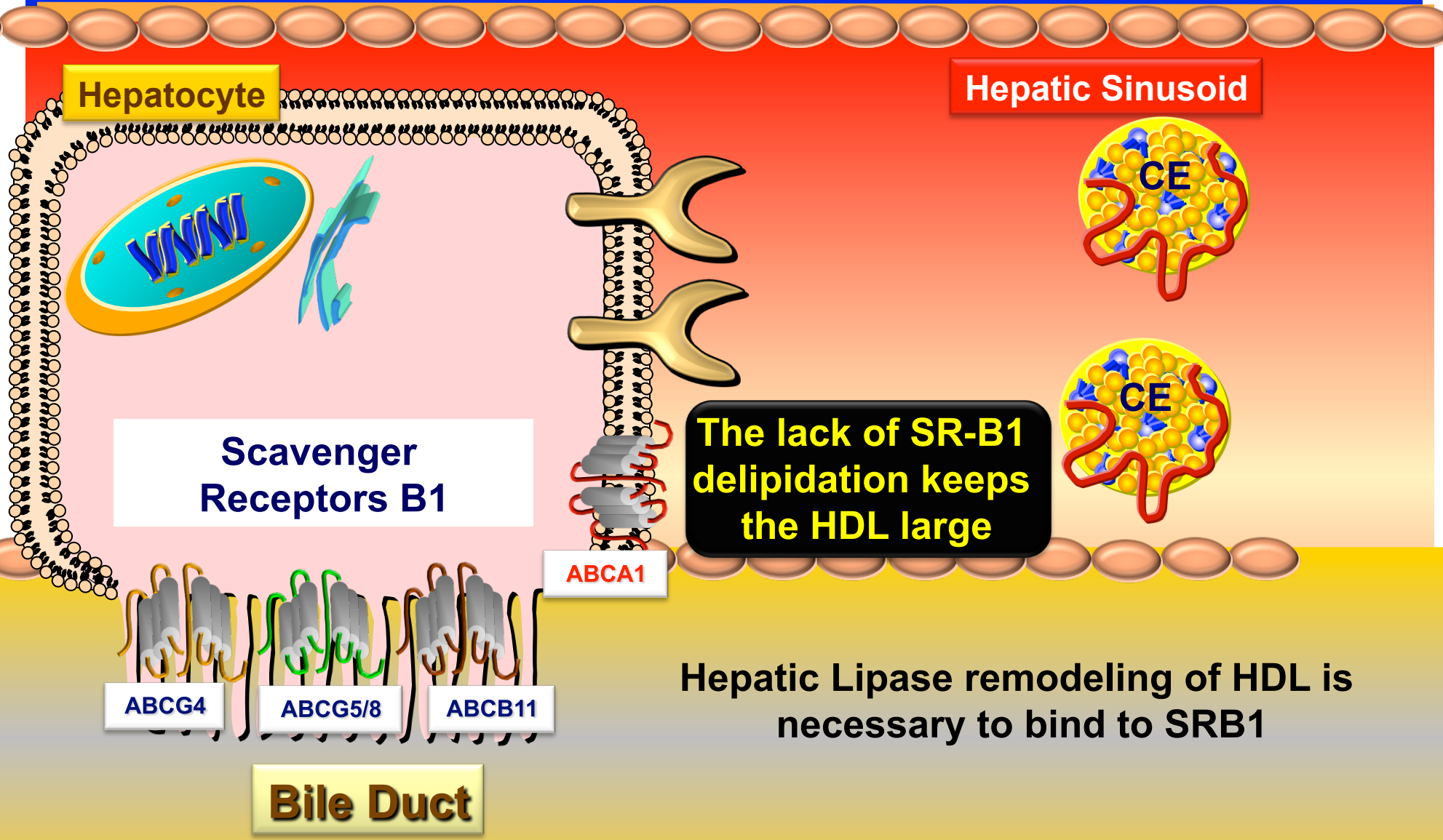
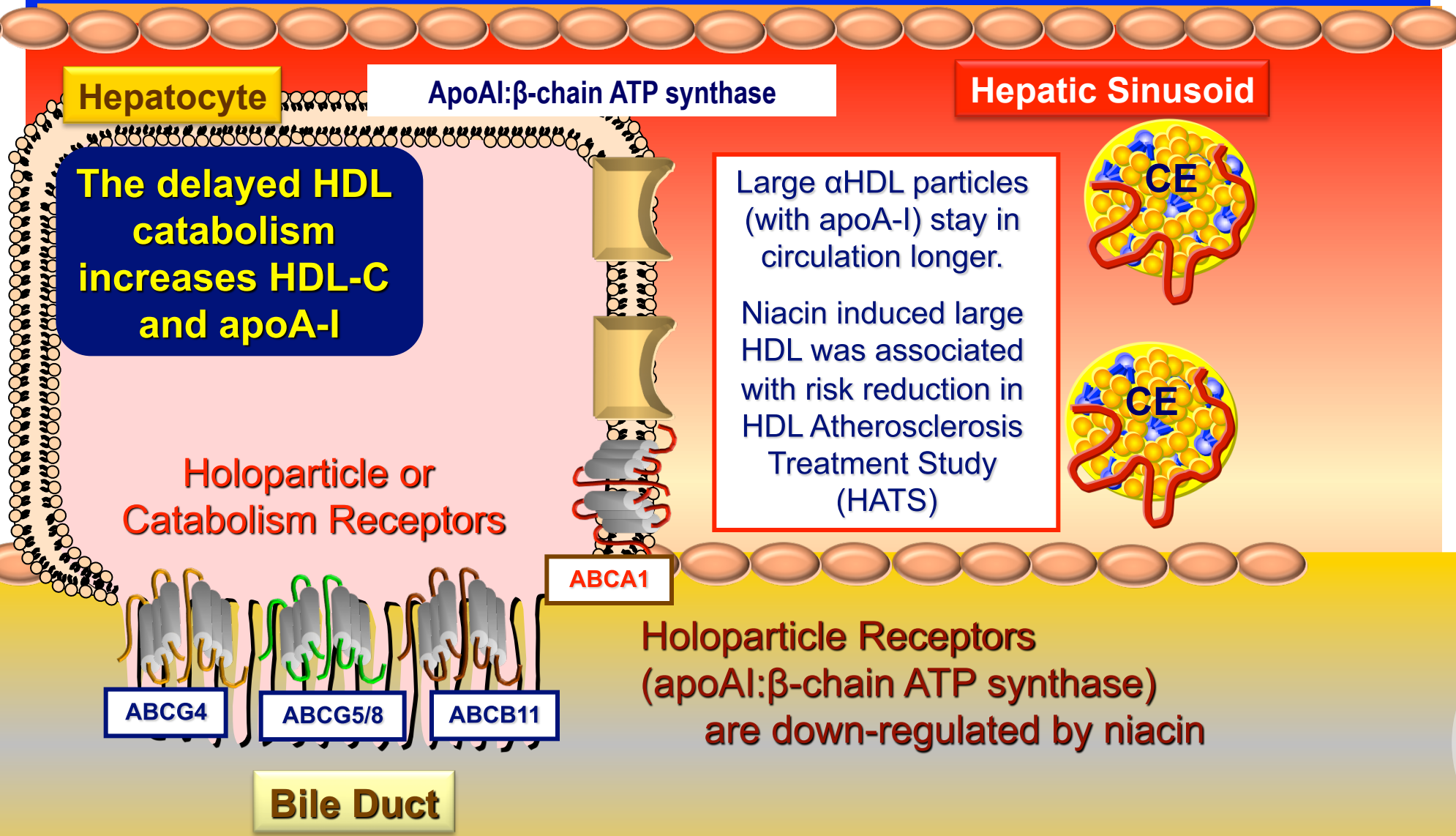


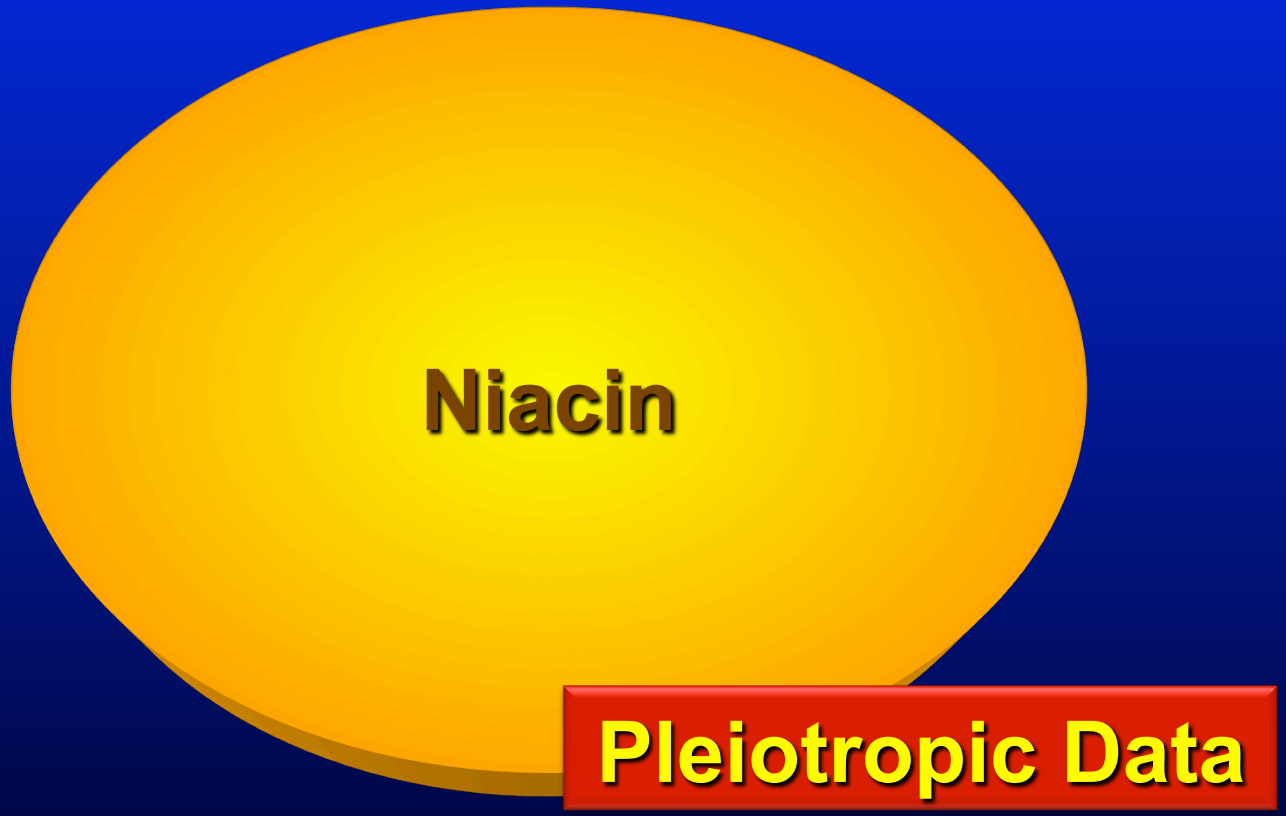
Hepatic Lipase remodeling of HDL is necessary to bind to SRB1

Collet et al. J Lipid Res 1999;40:1185-93

Niacin and Direct RCT



Kashyap M. Am J Card1998;82:42U-48U *Curr Opin Card 2004;19:366-373*


Niacin
Pleiotropic Data

Non Lipid Mechanisms of Niacin

- Nicotinic acid is a precursor to the coenzyme Nicotinamide Adenine Dinucleotide (NAD) which is a major electron acceptor in the oxidation of fuel metabolites
  - Thus niacin increases cellular concentrations of NAD^+
- Niacin upregulates the expression of glucose-6-phosphate dehrdrogenase, the rate limiting enzyme in the pentose phosphate pathway and principal source of cellular reduced NADPH
  - Increased NADPH decrease cellular ROS through regulating ROS-generating oxidases or maintaining antioxidant enzymes, catalase and glutathione reductase in active forms

Vaijinath S. Kamanna & Moti L. Kashyap Am J Card 2007;100[suppl]:53M-61N

Non Lipid Mechanisms of Niacin

- Significantly increases NADPH levels
- Inhibits angiotensin II-induced ROS production
- Inhibits LDL oxidation
- Inhibits tumor necrosis factor-α induced redox-sensitive VCAM-1 and monocyte chemotactic protein-1 mRNA expression
- Inhibits TNF-α and oxidized LDL induced monocyte adhesion to endothelial cells

Vaijinath S. Kamanna & Moti L. Kashyap Am J Card 2007;100[suppl]:53M-61N

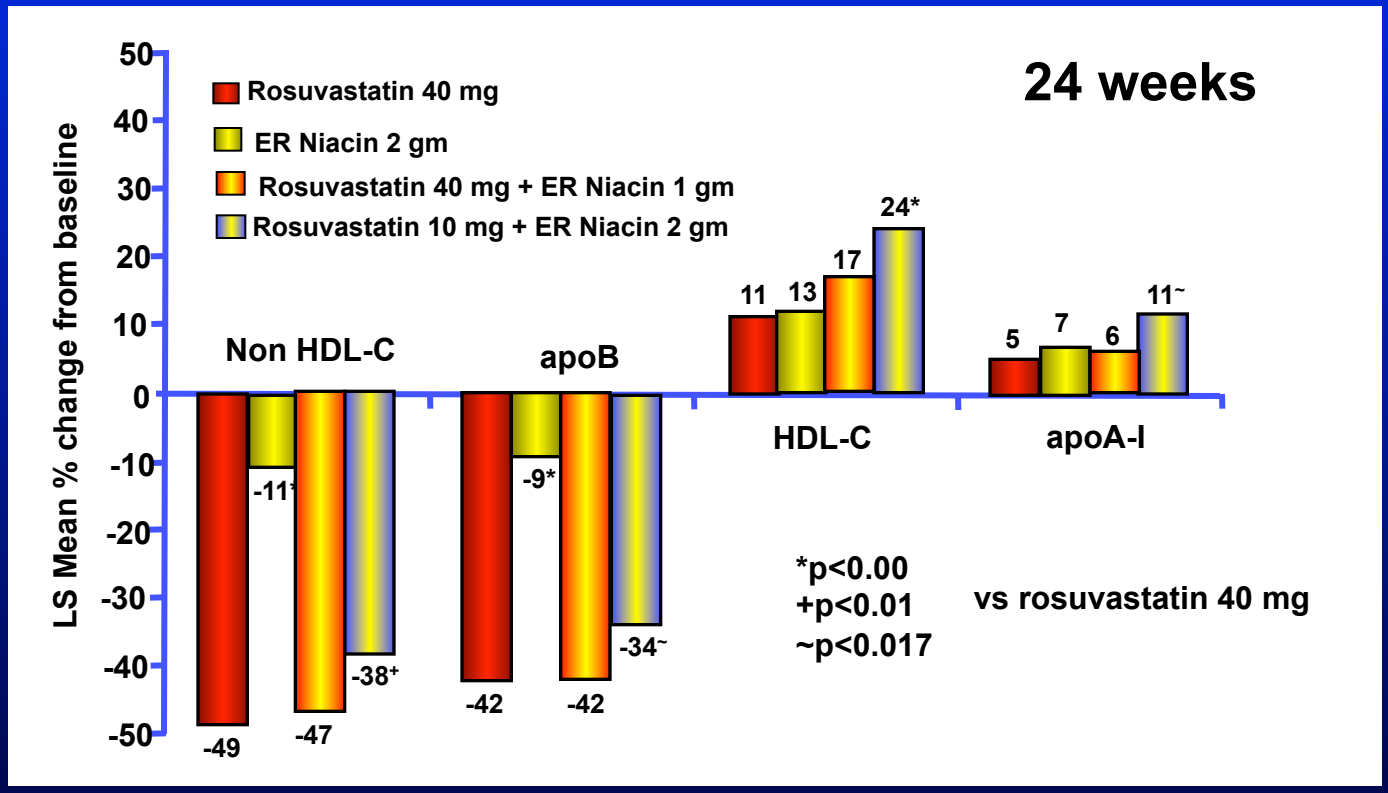
Assessment of Diabetes Control and EValuation of the Efficacy of Niaspan Trial (ADVENT) Effect of Niacin on hs-C-Reactive Protein

The median changes from baseline for hs-CRP suggested a dose related, **although non-significant**, trend of -2% (placebo), -11% (1000 mg) and -20% (1500 mg) for the respective groups.

Grundy SM, et al. *Arch Intern Med*. 2002;162:1568-1576.


Niacin
Surrogate Data

Effects of Rosuvastatin and Extended-release Niacin in Patients with Combined Hyperlipidemia with Low HDL-C

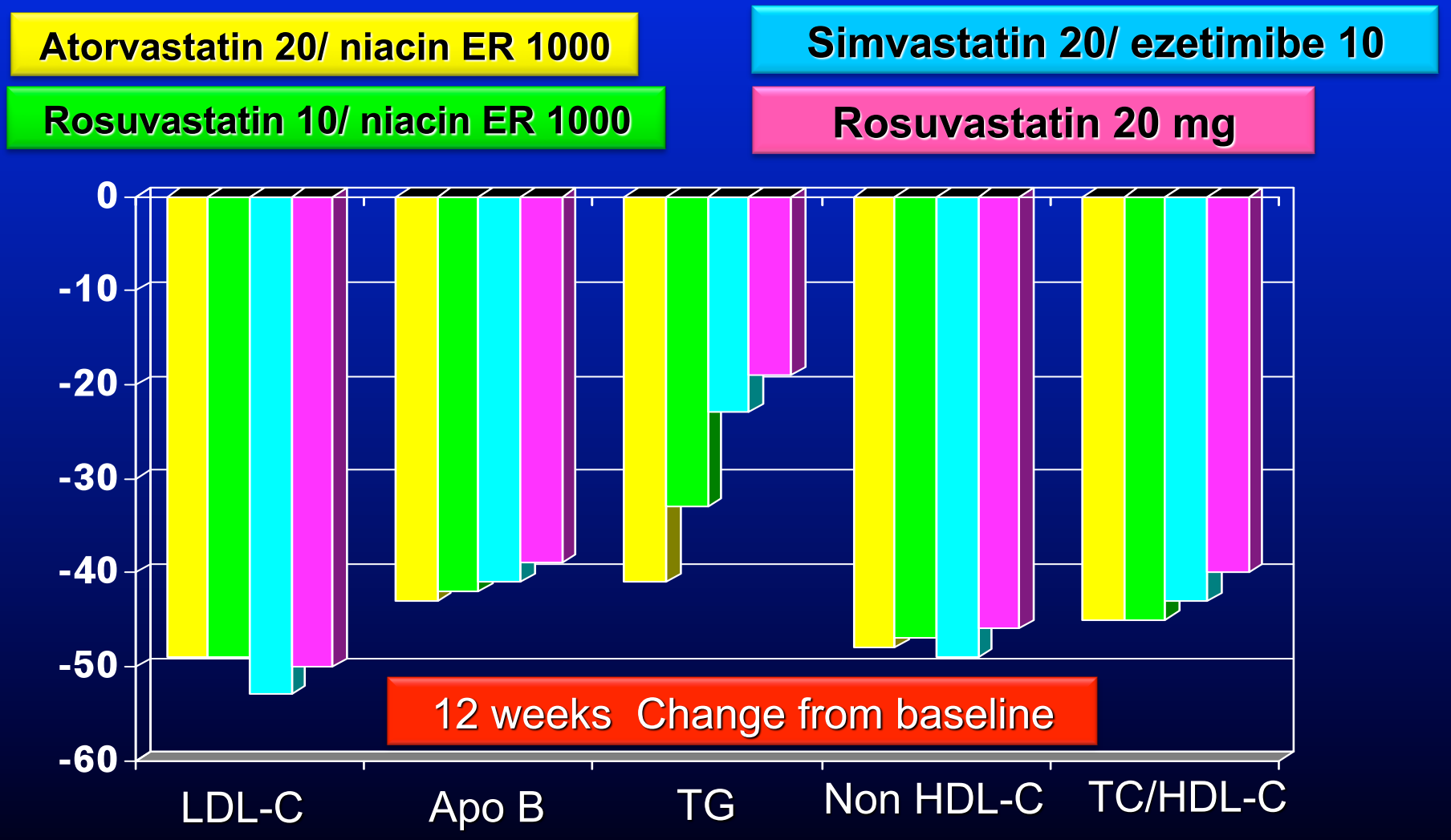


Monotherapy was equal on HDL-C and apoA-I

Rosuvastatin was better tolerated than either ER niacin or combination therapy

Capuzzi DM et al. Amer J Card 2003;91:1304-1310

COMParative Effects on Lipid Levels of Niaspan and a Statin vs other Lipid-Modifying Therapies (COMPELL)



McKenney JM et al. Atherosclerosis 2007;19:432-437

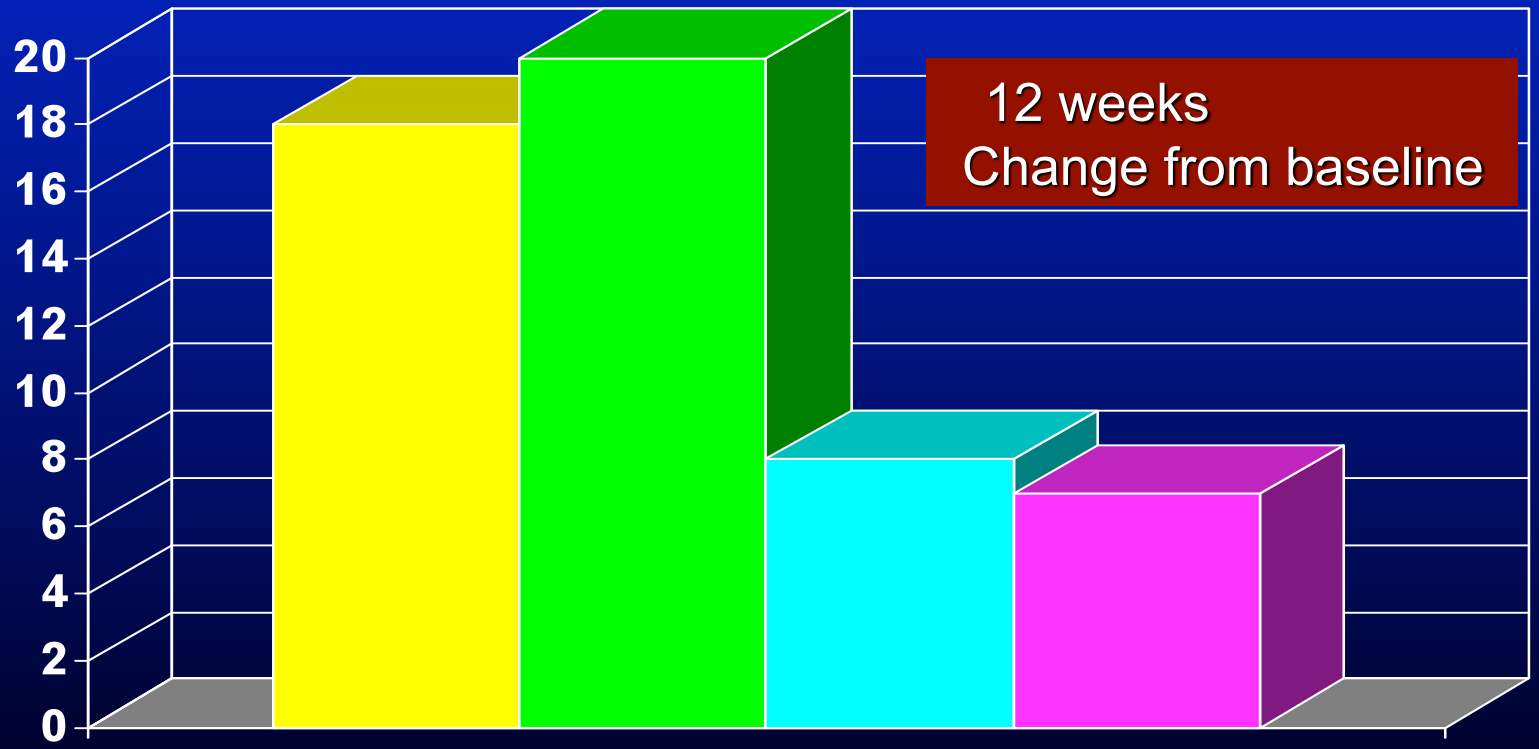
COMParative Effects on Lipid Levels of Niaspan and a Statin vs other Lipid-Modifying Therapies (COMPELL)

Atorvastatin 20/ niacin ER 1000

Rosuvastatin 10/ niacin ER 1000

Simvastatin 20/ ezetimibe 10

Rosuvastatin 20 mg



HDL-C

McKenney JM et al. Atherosclerosis 2007;19:432-437

Ezetimibe – Niacin Study

- Retrospective review of medical records of 53 patients in 2 lipid clinics most of whom (81%) had ASHD, who received ezetimibe as add-on therapy to stable doses of niacin and other lipid medications. Mean percentage changes of lipoprotein cholesterol and triglyceride levels were determined.
- The niacin formulation was extended-release in 31 patients (58%), immediate-release in 17 (32%), and slow-release in 5 (9%). Most patients (75%) were also taking a statin.
- Add-on ezetimibe therapy yielded mean reductions of 18% for total cholesterol (P<0.001), 25% for low-density lipoprotein (LDL) cholesterol (P<0.001), and 17% for triglycerides (P<0.001). High-density lipoprotein (HDL) cholesterol did not change significantly (+2%).
- Only 7 patients (13%) met Adult Treatment Panel III (ATP III) LDL cholesterol goals before the addition of ezetimibe, but 24 (45%; P<0.001 compared with baseline) attained these goals after addition of ezetimibe to the therapeutic regimen.
- Ezetimibe effectiveness did not correlate with the baseline dose of niacin or the dose/efficacy of the statin used. The addition of ezetimibe to niacin-based therapy for dyslipidemia was well tolerated.

Jelesof NE et al. Endocrine Practice 2006;12:159-164

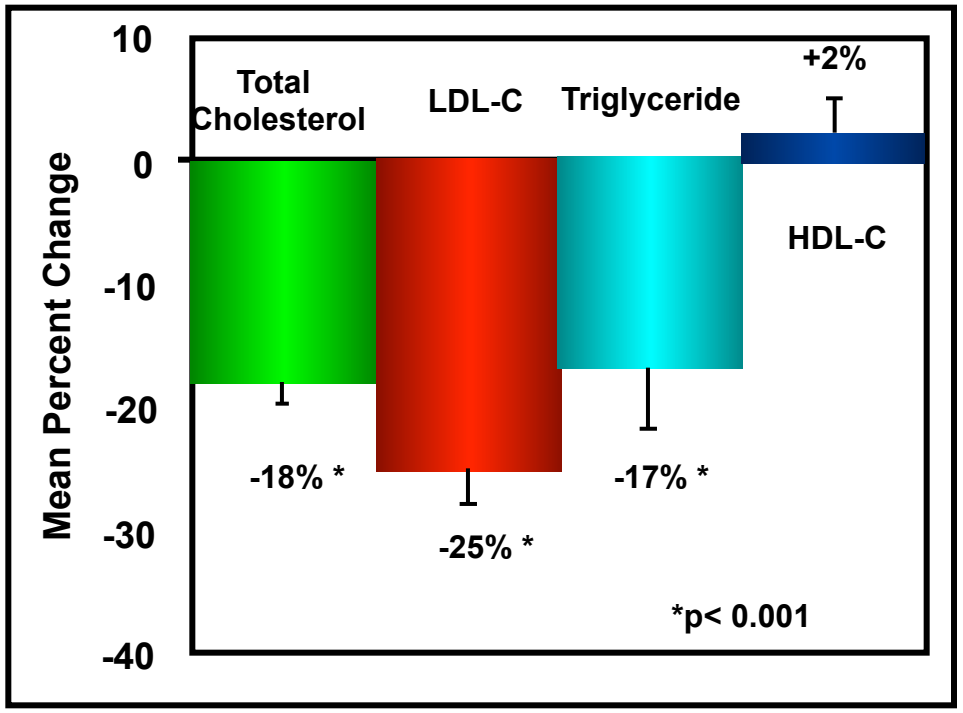
Ezetimibe – Niacin Study

The addition of ezetimibe to niacin-based regimens lowered the LDL cholesterol level by 25% and did not change the level of HDL cholesterol.

This combination can be useful in multidrug regimens for high-risk patients with dyslipidemia who are not achieving ATP III treatment goals.

Jelesof NE, Ballantyne C et al. Endocrine Practice 2006;12:159-164

Ezetimibe – Niacin Study



Mean percentage change from baseline for lipoprotein variables in 53 patients after the addition of 10 mg of Ezetimibe daily to stable dose medication regimens incorporating niacin.

Jelesof NE, Ballantyne C et al. Endocrine Practice 2006;12:159-164

Ezetimibe – Niacin Study

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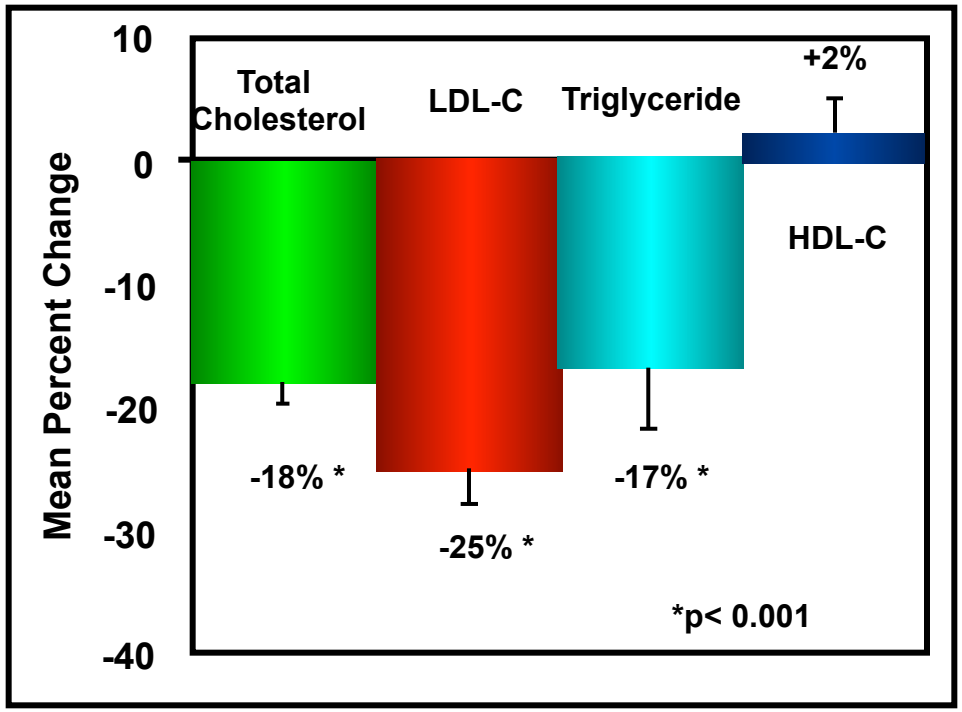

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Jelesof NE, Ballantyne C et al. Endocrine Practice 2006;12:159-164

Raising HDL-C with Fibrates and Niacin Meta-analysis of all Trials

- Data from 53 trials (16,802 subjects) using fibrates and 30 trials (4,749 subjects) using niacin were included.
- Random-effects model showed for fibrates and niacin, respectively.
  - 11% versus 10% reduction in total cholesterol
  - 36% versus 20% reduction in triglycerides
  - 8% versus 14% reduction in LDL-C
  - 10% versus 16% increase in HDL-C

Rakesh S. Birjmohun et al. J Am Coll Cardiol 2005;45:185–97

Raising HDL-C with Fibrates and Niacin Meta-analysis of all Trials

Apart from flushes in the niacin group, both fibrates and niacin were shown to be well-tolerated and safe.

Fibrates reduced the risk for major coronary events by 25% (95% confidence interval 10% to 38%), whereas current available data for niacin indicate a 27% reduction.

Rakesh S. Birjmohun et al. J Am Coll Cardiol 2005;45:185–97

Raising HDL-C with Fibrates and Niacin Meta-analysis of all Trials

Conclusions

- Fibrates reduce major coronary events and increase HDL-C levels without significant toxicity.
- Niacin has a more potent effect on HDL-C levels, whereas data on cardiovascular event rate reduction are limited.
- Future studies need to evaluate whether additional HDL increase by fibrates or particularly newer niacin formulations on top of statin therapy translates into further event reduction in high-risk subjects, without significant toxicity.

Rakesh S. Birjmohun et al. J Am Coll Cardiol 2005;45:185–97

Raising HDL-C with Fibrates and Niacin Meta-analysis of all Trials

Conclusions

In summary, both fibrates and niacin provide a safe and effective way of increasing HDL-C, the latter being the most potent one.

Whereas for both, particularly for fibrates, intervention data have emerged to show beneficial effects on CV outcome; their ability to enhance CV event reduction when added to statin monotherapy has been shown in small trials with niacin and may be shown with larger ongoing trials with fenofibrate.

Rakesh S. Birjmohun et al. J Am Coll Cardiol 2005;45:185–97


Niacin
Side Effects

Niacin, Skin and Flushing

- Current evidence indicates that the niacin flush is mediated by the arachidonic acid metabolite prostaglandin D2.
- Recently, it was also shown that skin Langerhans cells are the primary cell types responsible for the niacin-induced prostaglandin D2 release and flushing response
- Thus, HM74A indirectly mediates niacin-induced flushing through production of prostaglandin D2 and prostaglandin E2 by immune cells such as Langerhans cells and macrophages.

Vaijinath S. Kamanna & Moti L. Kashyap Am J Card 2007;100[suppl]:53M-61N

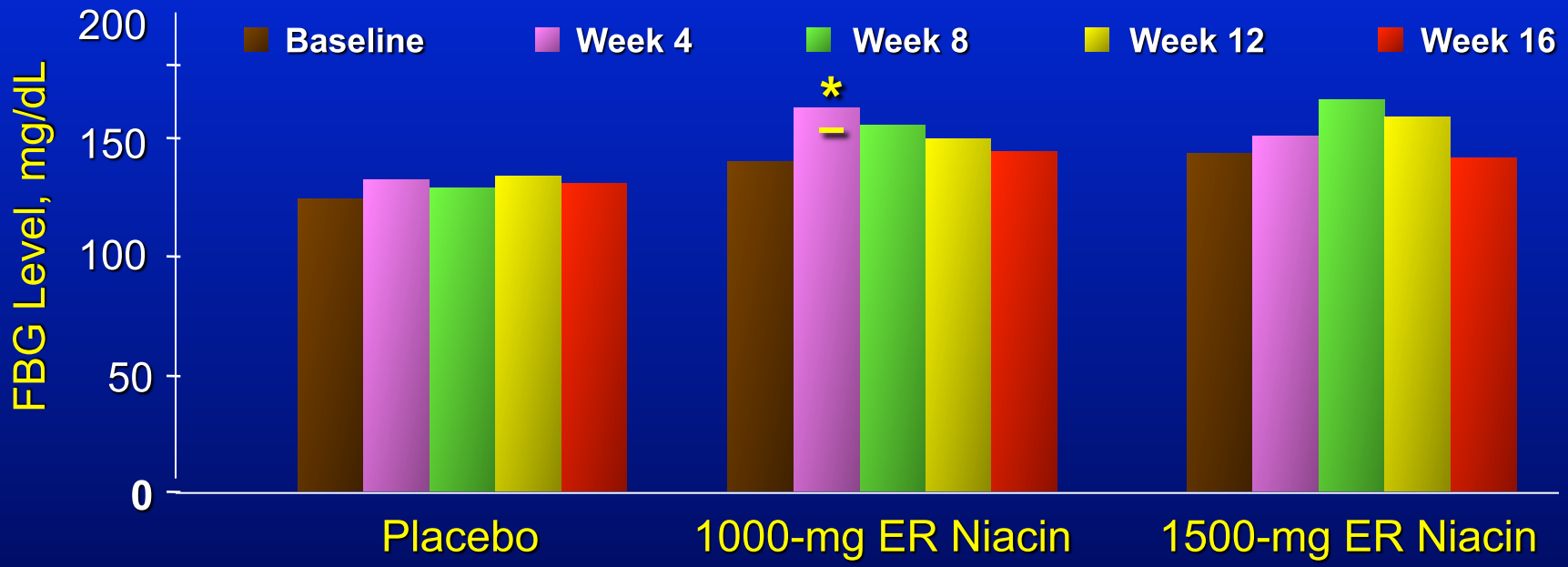
Arterial Disease Multiple Intervention Trial (ADMIT)

The ADMIT Study demonstrates that lipid modifying doses of niacin can be safely used in patients with stable, controlled Type 2 diabetes.

Niacin can be considered as an alternative to statins or fibrates in patients with diabetes in whom these agents are not tolerated or in whom they fail to sufficiently correct the hypertriglyceridemia or low HDL-C.

JAMA 2000;284:1263-1270

Assessment of Diabetes Control and EValuation of the Efficacy of Niaspan Trial (ADVENT)
Effect of Niacin on Fasting Blood Glucose Levels

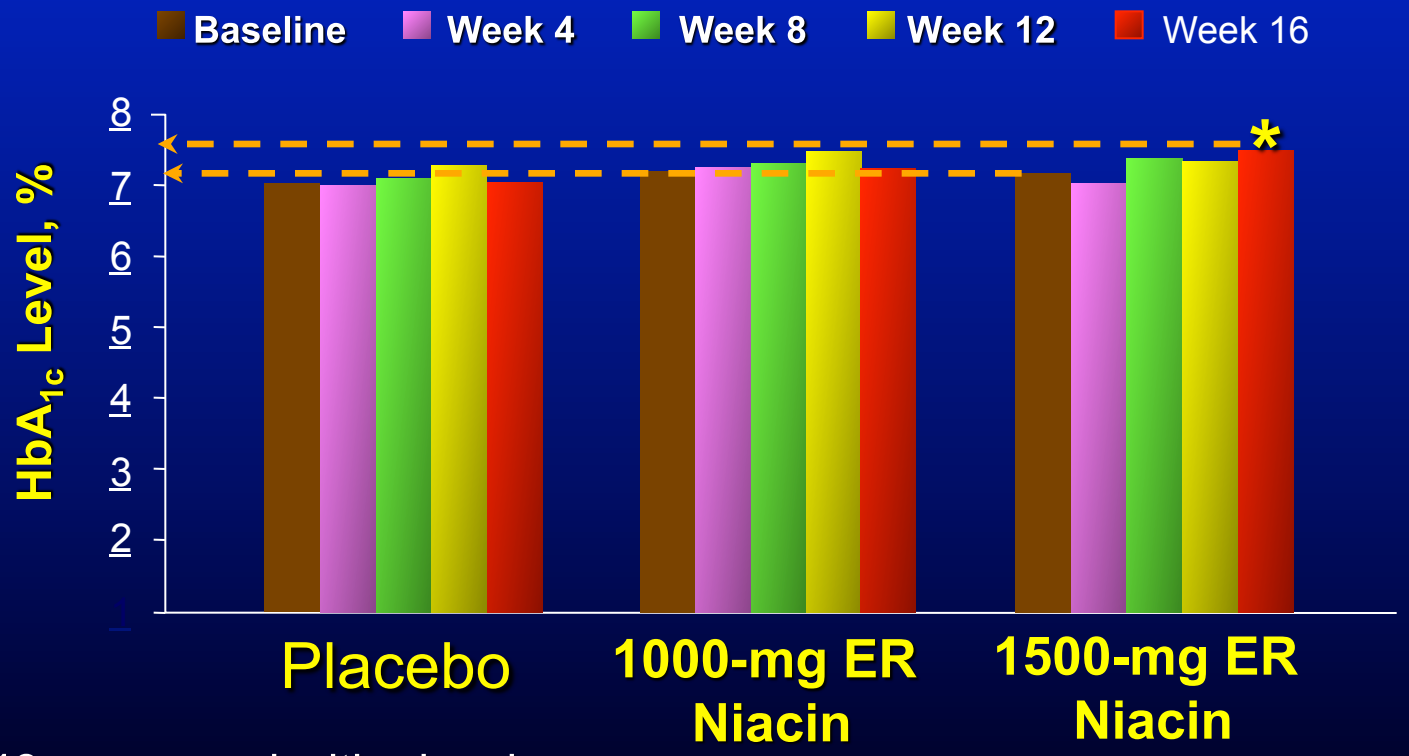


"In both niacin groups, we found an initial rise in FBG levels between weeks 4 and 8; this value returned to the baseline level by week 16... These findings suggest that adjustments in concomitant antidiabetic therapies were being made to control FBG levels in some patients. "

* *P*=.05, compared with baseline

Grundy SM, et al. *Arch Intern Med*. 2002;162:1568-1576.

Assessment of Diabetes Control and EValuation of the Efficacy of Niaspan Trial (ADVENT) Effect of Niacin on Hemoglobin A_1C Level



* *P*=.048, compared with placebo

Grundy SM, et al. *Arch Intern Med*. 2002;162:1568-1576.

Assessment of Diabetes Control and EValuation of the Efficacy of Niaspan Trial (ADVENT) Summary: Glycemic Control

Niaspan 1.0 gm increased HDL-C 20% without affecting HgbA1c in 88%. **Aggravating it in 12%**

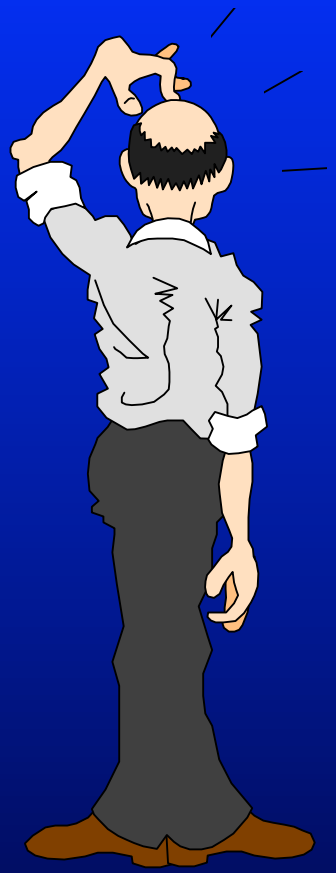
Niaspan 1.5 gm increased HDL-C 24%, decreased TG 29% and in majority had no effect on glycemic control (71%). **Aggravating it in 29%**

Adverse changes in glycemic control were easily managed with **additional glycemic medication**.

Niaspan can be used with statins or TG lowering drugs without increase in LFTs or muscle weakness.

Grundy SM, et al. Arch Intern Med. 2002;162:1568-1576.
Grundy S, et al. JACC 37(2), p 249A Feb 2001

Happy Lipiding



Tdayspring@aol.com

Lipidaholics Anonymous Newsletter

National Lipid Association

www.lipid.org

Questions, Thoughts ?