

The Role of HDL in Vascular Disease and HDL therapeutics on the horizon

Implications for 2009 ATP LIPID Guidelines

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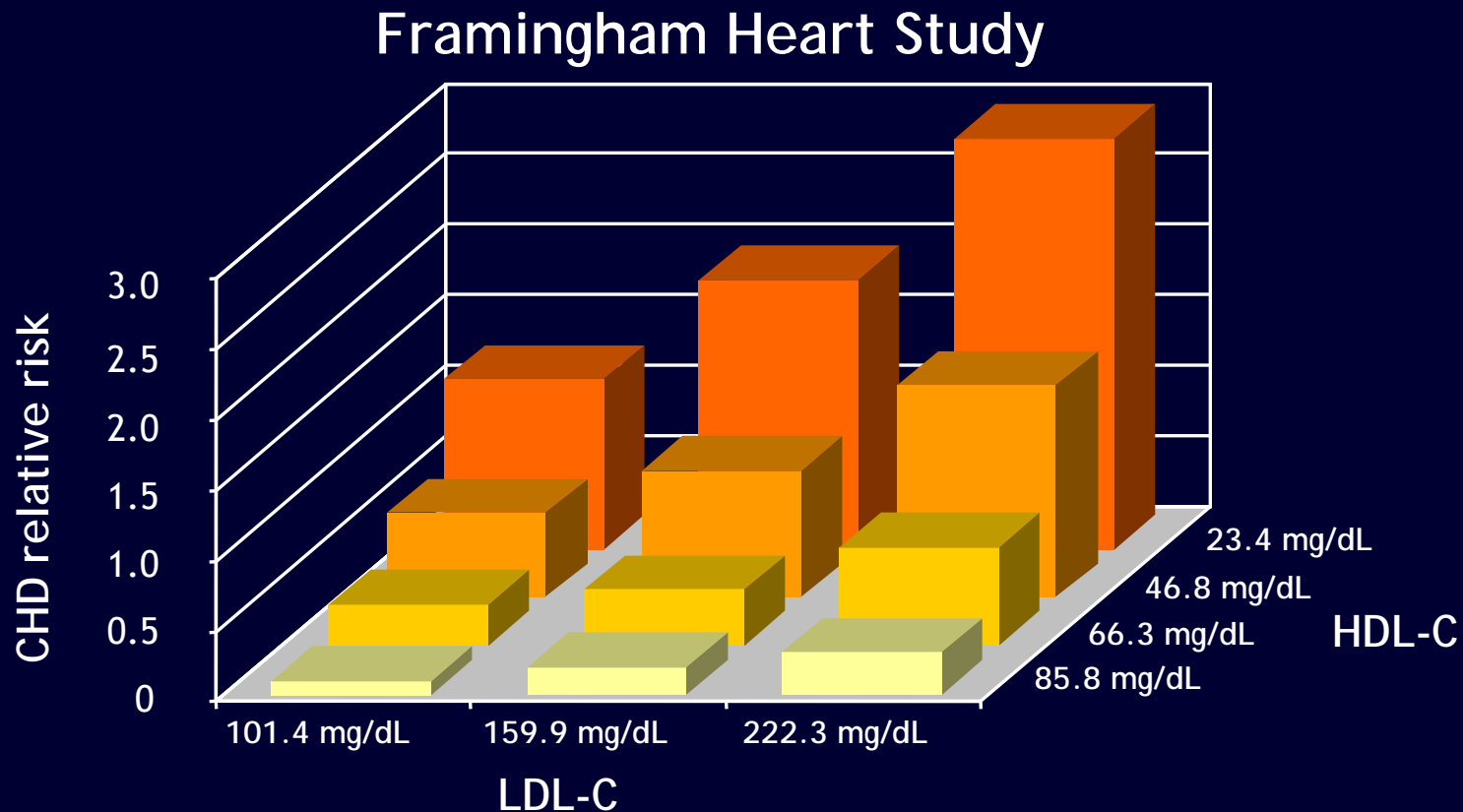
Cases for Discussion

- A 44 man comes to the ed with chest pain and hypotension. He is SOB and his PE shows bp 90/50 pulse 110 rales and an S3. CXR cardiomegaly; ekg acute ant MI. FH +4 for CAD. He is rx with a stent and appropriate meds and improves over 3 days. Labs on admission TC 110 TG 155 LDL 77 HDL 2. Two months later after statins and niacin TC 60, TG 60 LDL 38, HDL 10, Lp(a) 5

Cases for Discussion

- A 53 year old man comes to see you in lipid clinic. 6 months ago he had a small inferior MI . Cath showed mild obstructive diffuse cad and partially occluded r coronary. FH is unknown Pt on no meds prior to mi .PE neg. Labs done on 2-3 occasions prior to mi and treatment show tsh, comprehensive metabolic panel normal. Lipids TC 217, TG 90,LDL 104, HDL 95, Non HDL 122

Suboptimal HDL-C Levels Substantially Increase CHD Risk at All LDL-C Levels

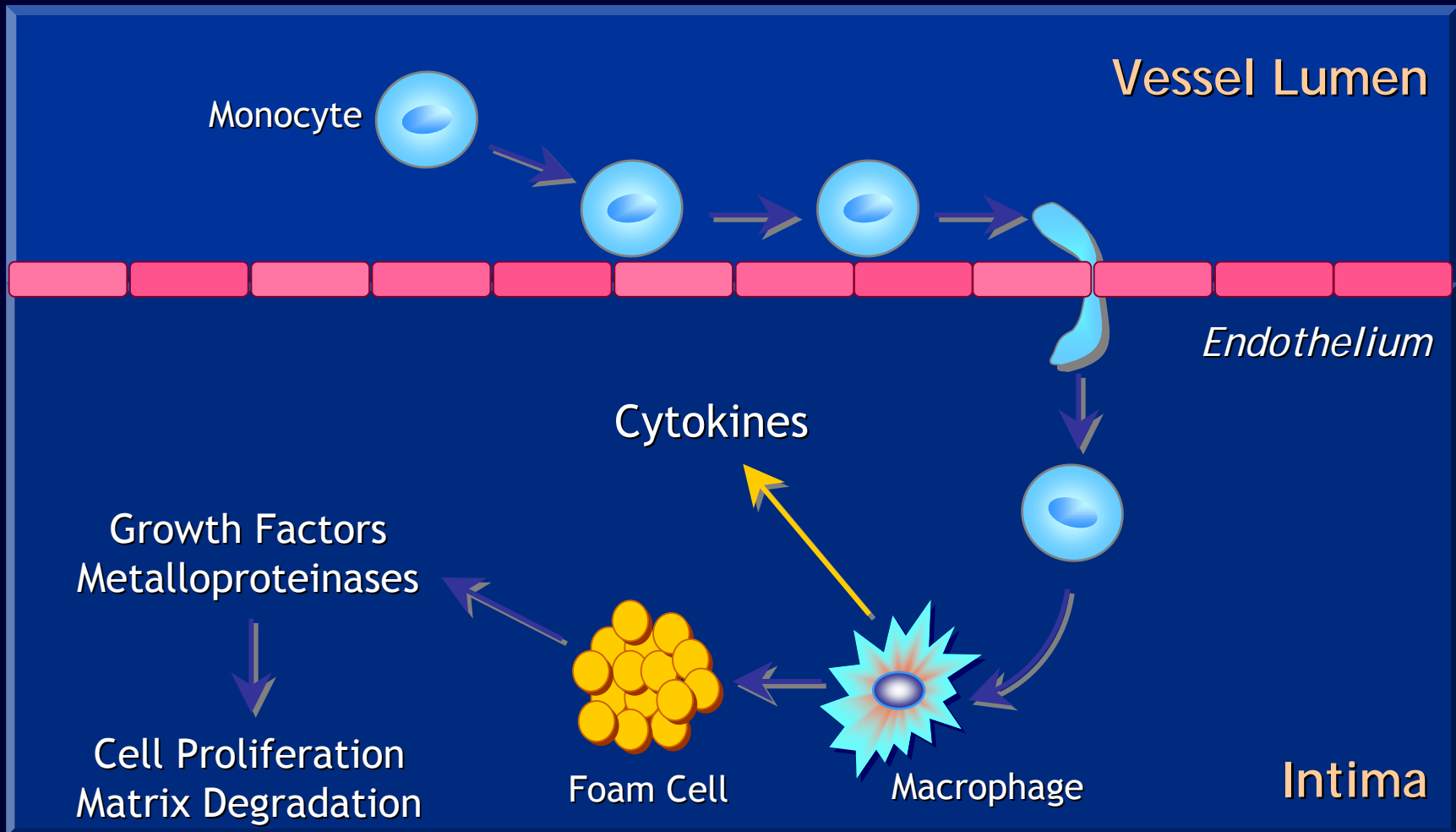


Adapted from Kannel WB. *Am J Cardiol.* 1987;59:80A-90A.

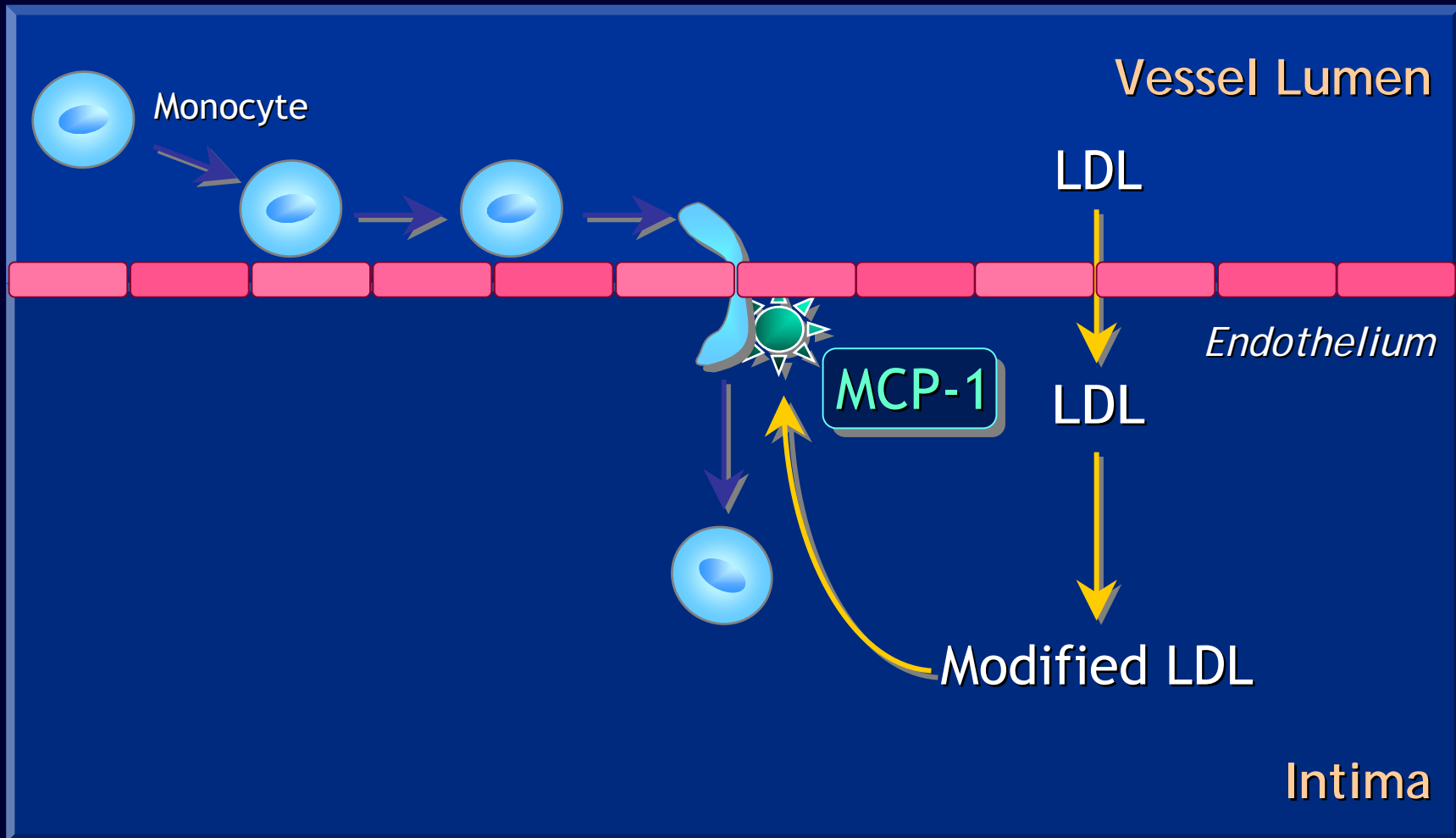
HDL: Multiple Mechanisms of Benefit

- Reverse cholesterol transport (RCT)
- Decrease vessel wall inflammation
 - ↓ expression of cellular adhesion molecules
 - ↓ chemokines (e.g. MCP-1)
 - ↓ oxidized phospholipids
- Protection of LDLs from oxidation
- Improvement in endothelial function
- Limitation of thrombosis

Atherosclerosis Is an Inflammatory Disease

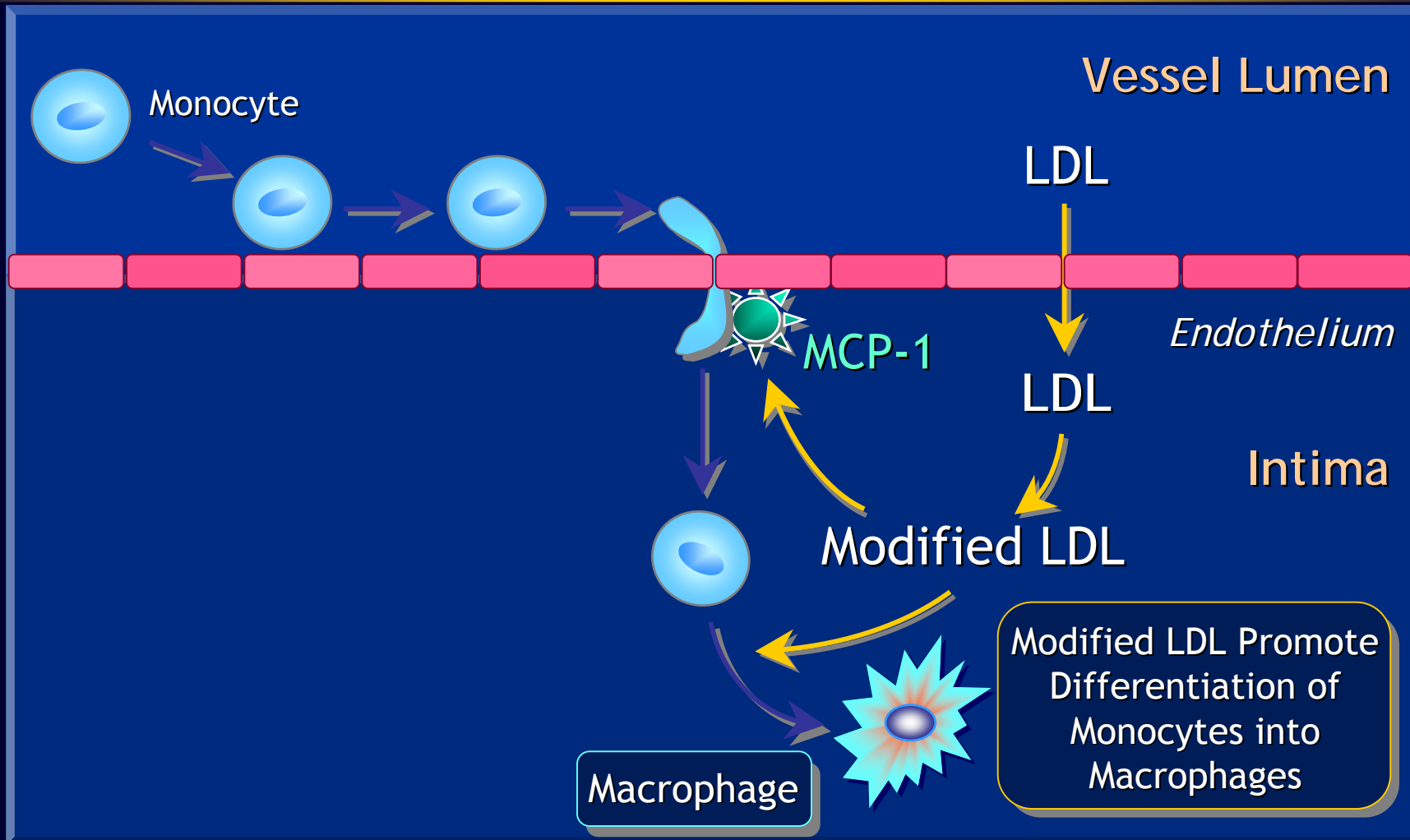


Modified LDL Stimulate Expression of MCP-1 in Endothelial Cells

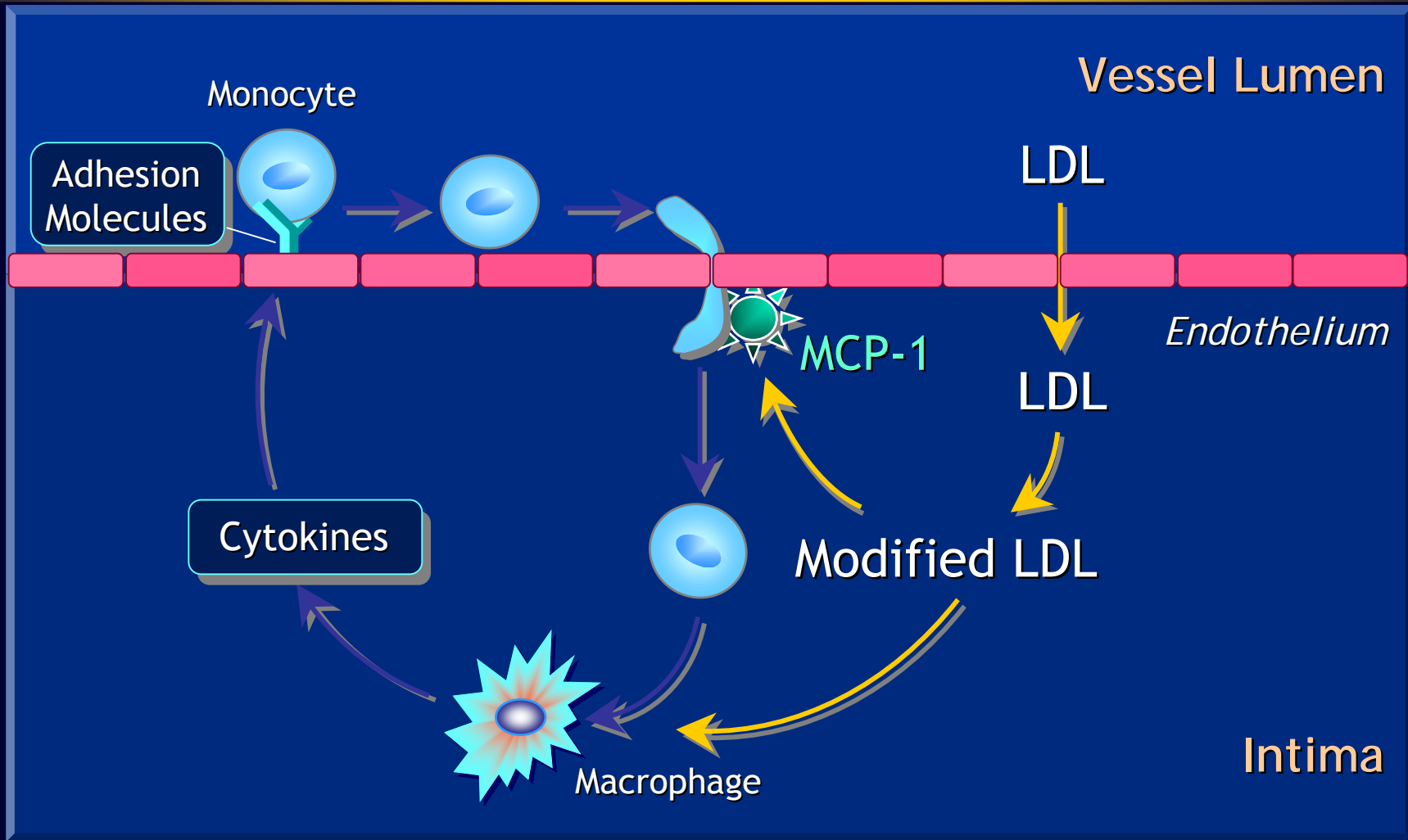


MCP-1=monocyte chemotactic protein 1.
Navab M et al. *J Clin Invest* 1991;88:2039-2046.

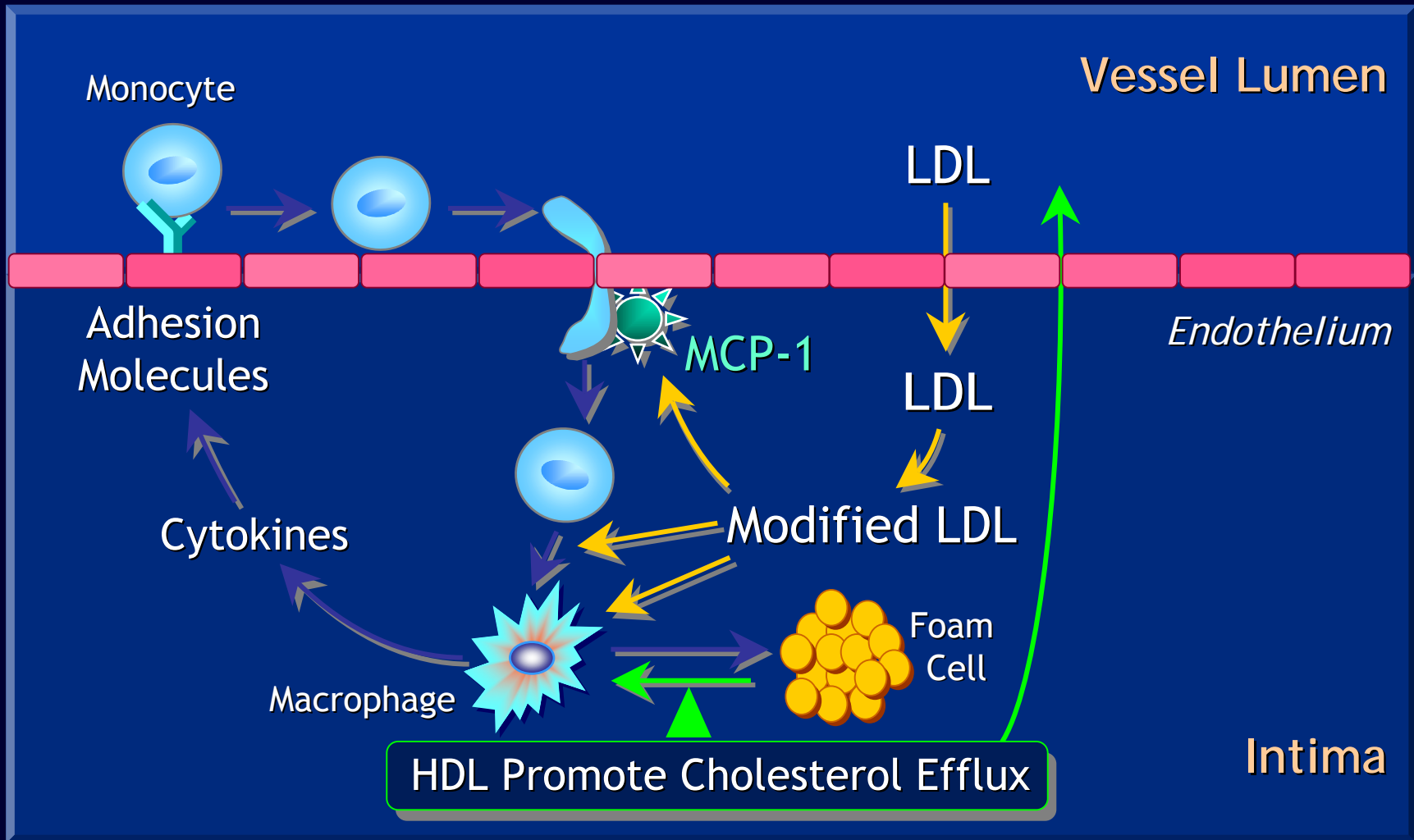
Differentiation of Monocytes Into Macrophages



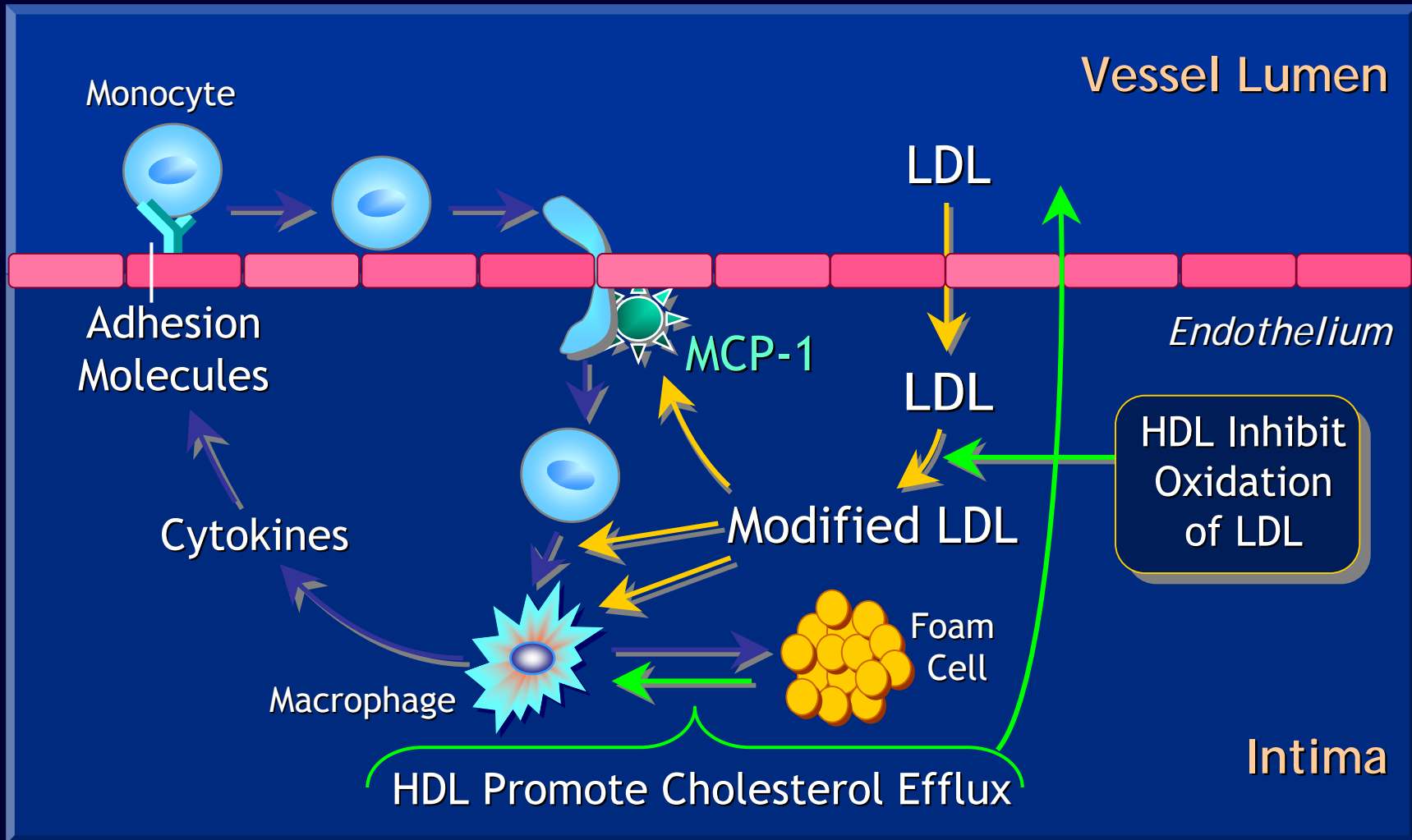
Modified LDL Induces Macrophages to Release Cytokines That Stimulate Adhesion Molecule Expression in Endothelial Cells



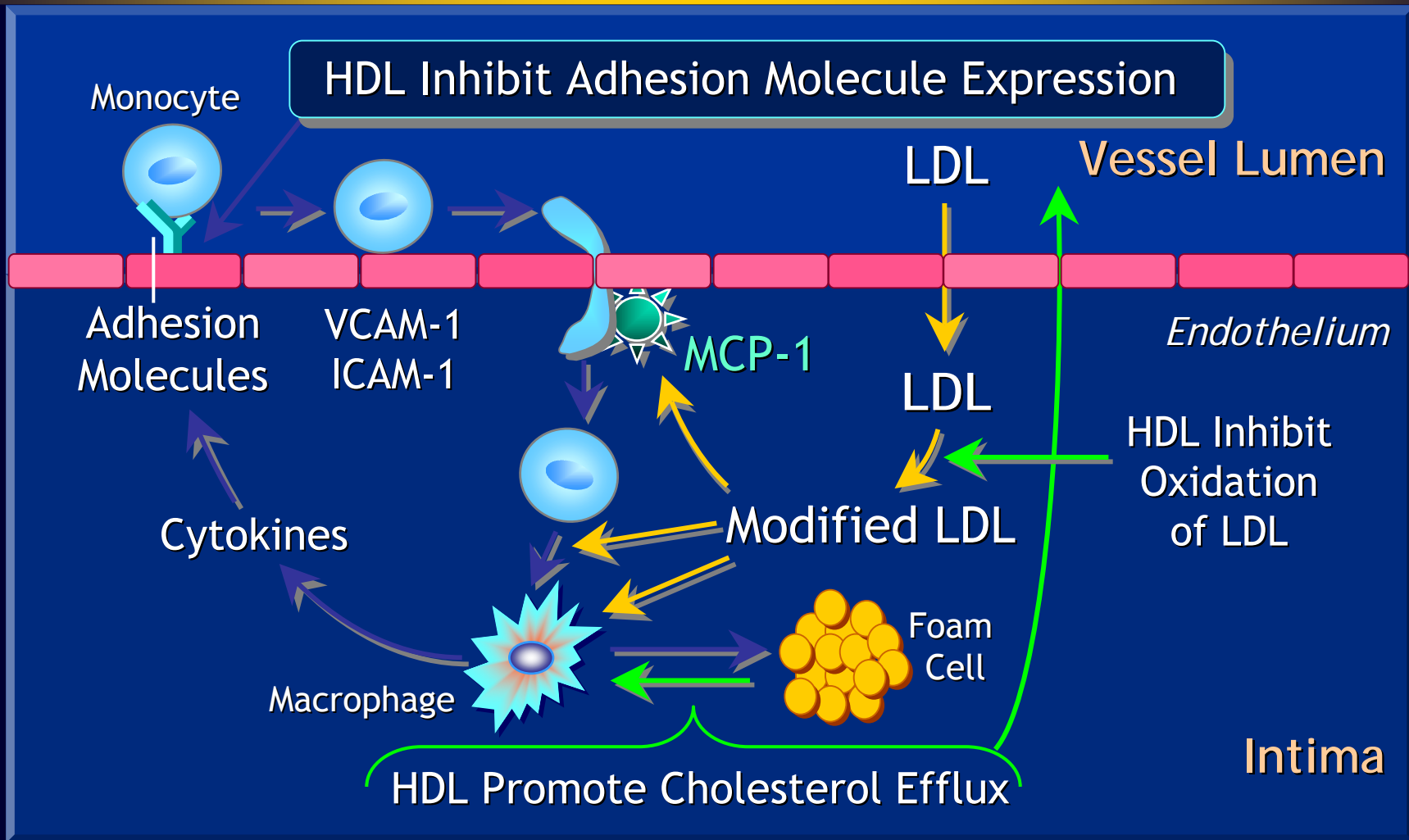
HDL Prevent Formation of Foam Cells



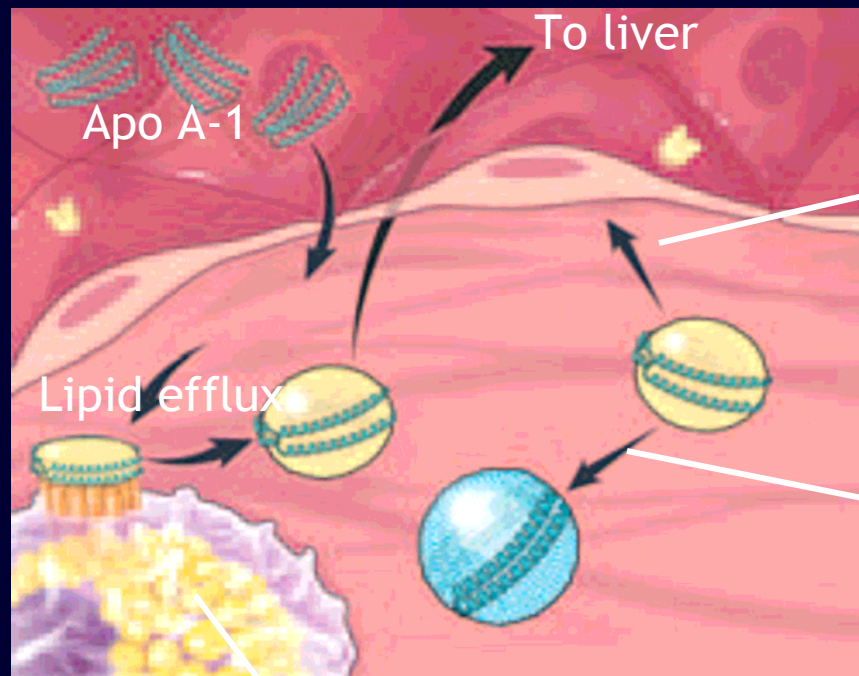
HDL Inhibit the Oxidative Modification of LDL



HDL Inhibit Adhesion Molecule Expression



Under Normal Circumstances, HDL is Anti-Inflammatory

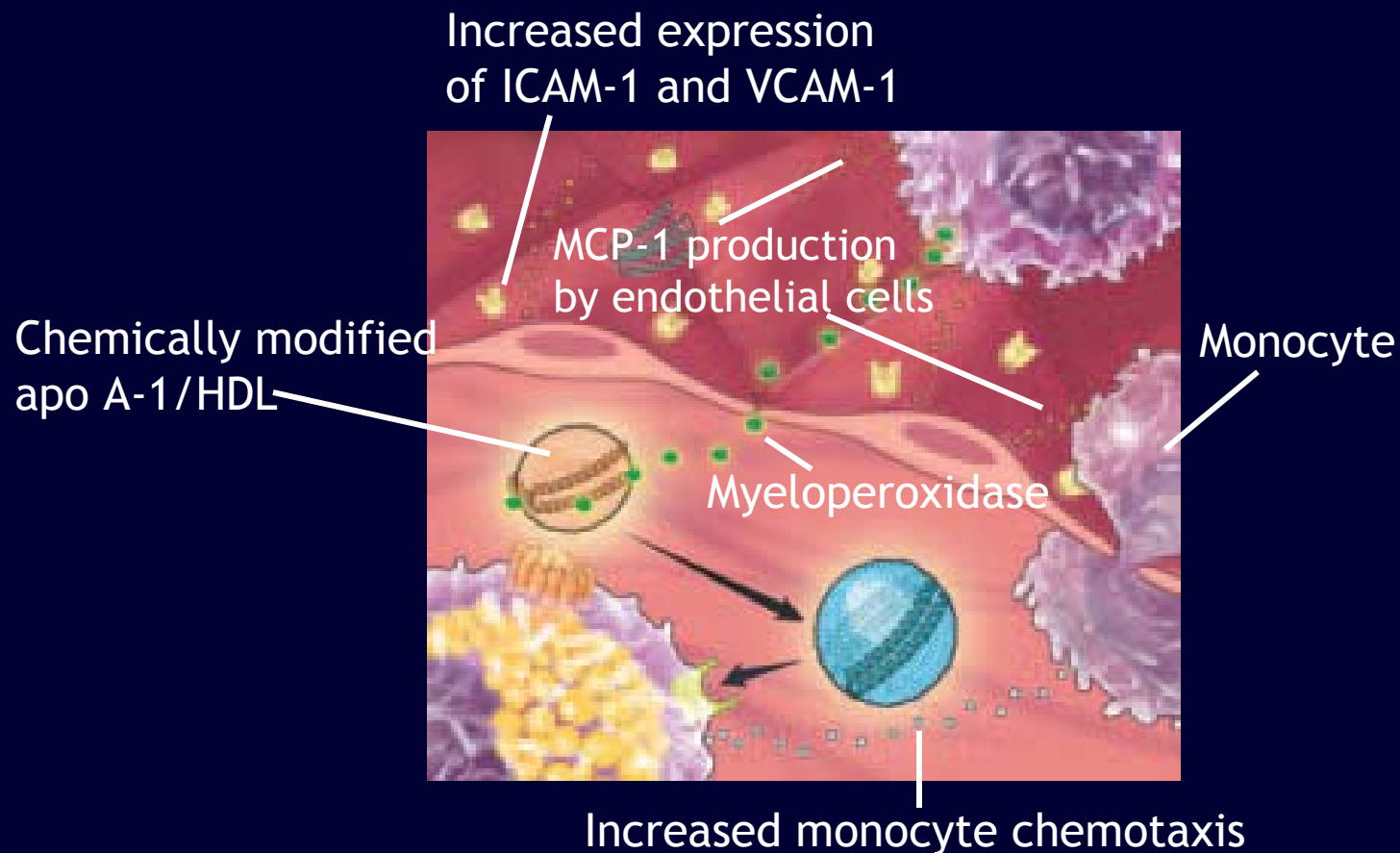


Inhibition of
MCP-1 expression
by endothelial cells

Inhibition of
LDL oxidation

Lipid-laden macrophage

In Systemic Inflammation, HDL Can Become Pro-Inflammatory



Systemic Inflammation/Oxidative Stress

- 1) Infection
- 2) Coronary disease
- 3) Diabetes mellitus
- 4) Metabolic syndrome
- 5) Smoking
- 6) Rheumatologic conditions
- 7) Chronic kidney disease
- 8) Surgery
- 9) Obstructive sleep apnea
- 10) Saturated fat diet

Chronic acute-phase response

Proinflammatory HDL

+

+

-

LDL oxidation

Vascular inflammation

Reverse cholesterol transport

-

-

+

Anti-inflammatory HDL

Proven Therapies

Statins
Apolipoprotein mimetic peptides
Polyunsaturated fat diet
Exercise/Diet

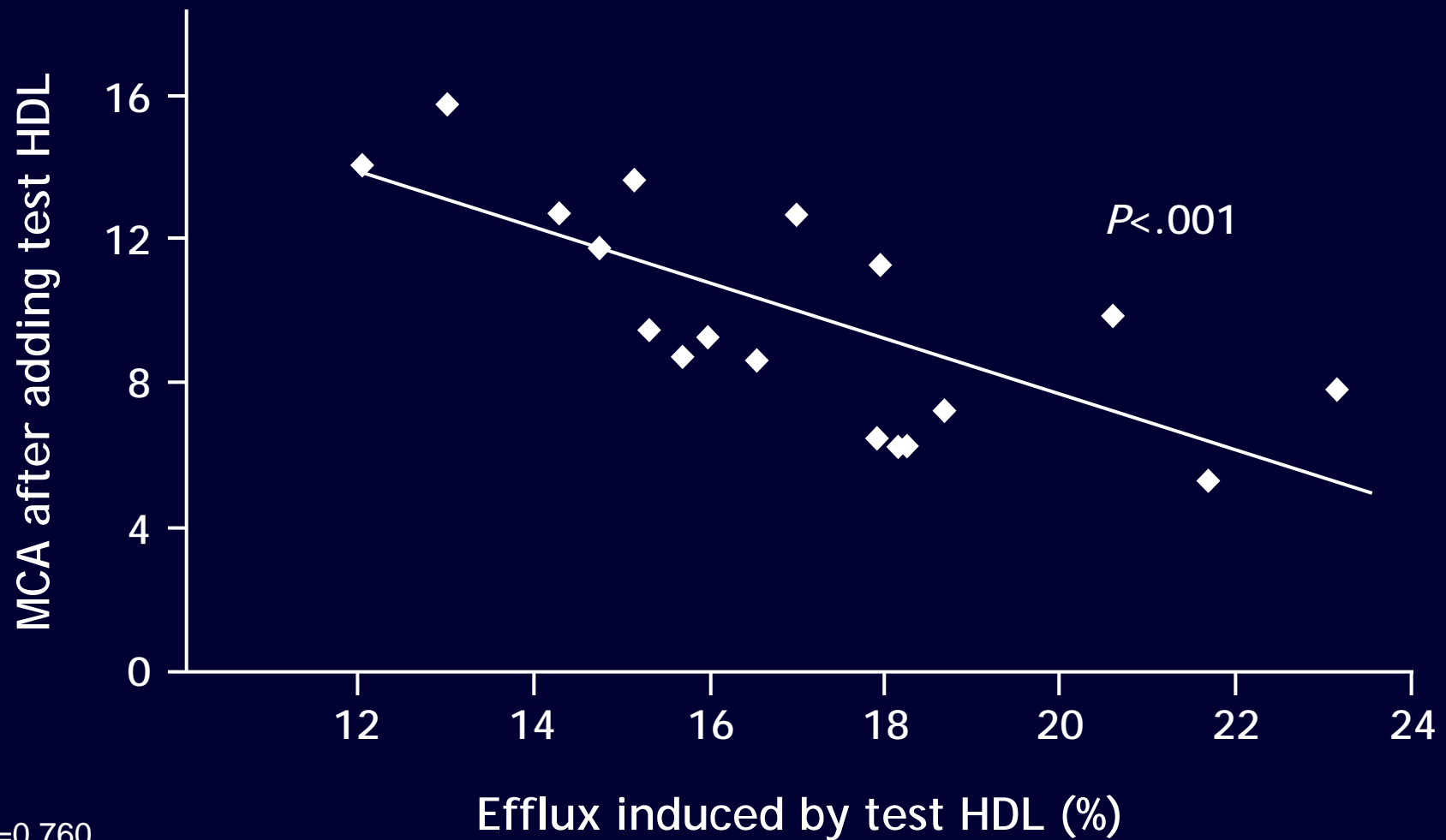
Possible Therapies

Recombinant HDL
Delipidated HDL

Assays of HDL Function

Assay class	Assay	Advantages/limitations	Human studies
HDL subpopulations and size	2D PAGE (27)	Identifies particles that may relate to HDL function and outcomes; low throughput, semiquantitative, surrogate of true function	Yes, small- to intermediate sized studies
	NMR (28)	Identifies HDL particle size and number; high throughput, but limited evidence for CVD risk prediction beyond HDL-C	Yes, epidemiological and clinical trials
RCT	Macrophage cholesterol efflux (12)	Analyzes ex vivo capacity of isolated HDL to efflux cholesterol from macrophages; low throughput	Yes, small scale; relationship to atherosclerosis is lacking
	Fecal sterol excretion (29)	Estimates total body excretion of cholesterol; may lack sensitivity for macrophage RCT and be confounded by bowel cholesterol metabolism	
	HDL tracer kinetic studies (30)	Trace HDL lipid fluxes and excretion from body; do not assay macrophage RCT; hepatic and bowel activity confounds tracer kinetics	Yes, proof of concept; needs validation
	Activity and mass assays of CEPT, LCAT, lipases etc.	Estimate mass or activity of HDL proteins involved in RCT; activity assays require standardization	Yes, greater evidence of relationship to RCT and atherosclerosis is required
HDL antiinflammatory	Monocyte chemotactic assay (7,31); cell-free assay (7,31)	Analyzes ex vivo capacity of HDL to suppress LDL-induced chemotaxis; low throughput, lacks standardization	
	Vascular adhesion molecular expression or levels	Requires vascular tissue or plasma; plasma assays are not specific to HDL function	Yes, plasma assays
HDL antioxidant	HDL-associated paraoxonase or Lp-PLA ₂ mass or activity	Assays HDL antioxidant enzymes; single dimension of HDL function, lacks standardization	Yes, limited proof of concept

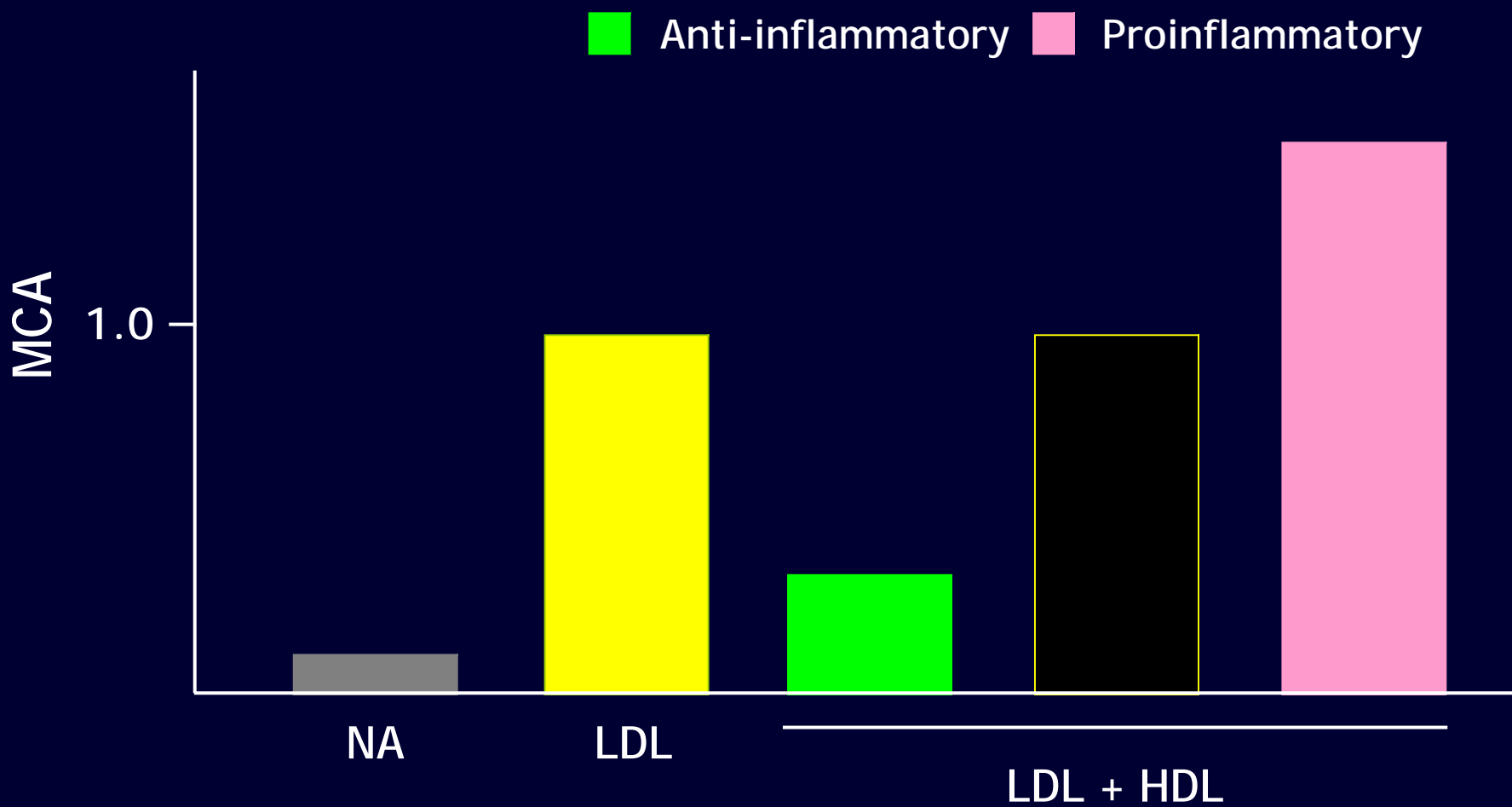
Correlation Between Monocyte Chemotaxis Assay and Cholesterol Efflux



Corr.=0.760.

Navab M et al. *Ann Med.* 2005;37:173-178.

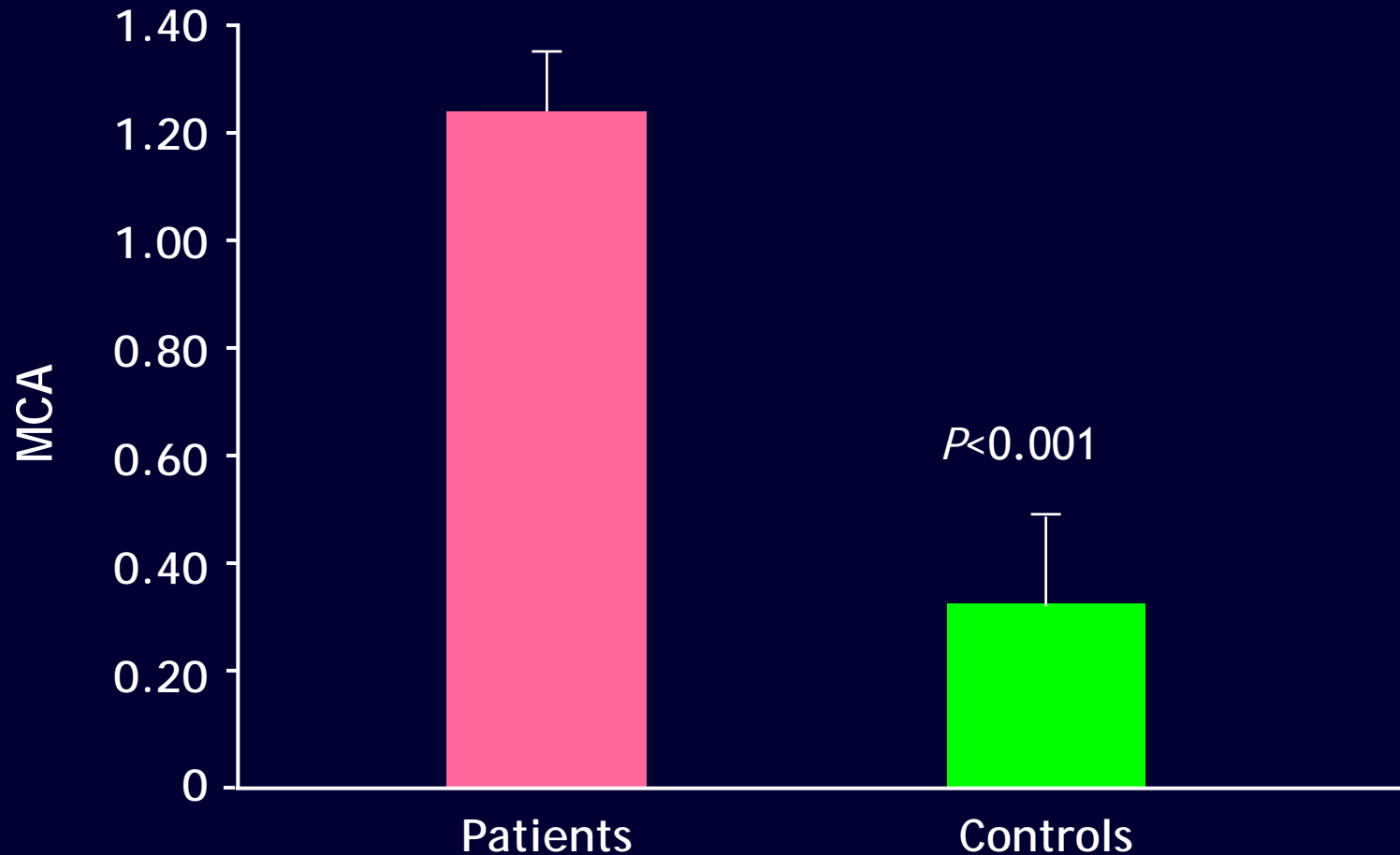
Inflammatory/Anti-inflammatory HDL-C Results: Characterization



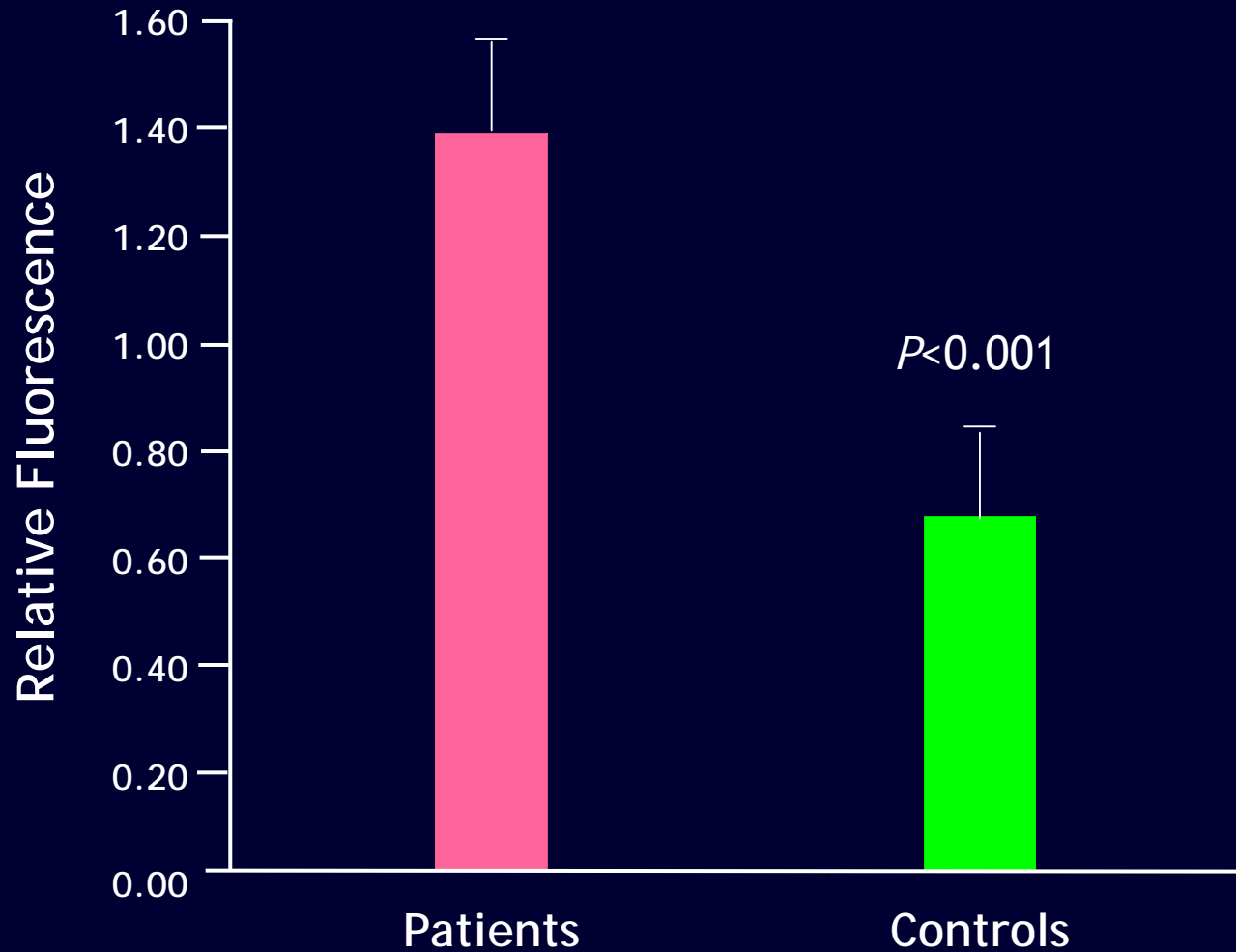
CHD Despite High HDL Study: Design

- Subjects:
 - 20 adults with stable CHD, HDL-C \geq 84 mg/dL
 - No hypolipidemic medication, smoking, or diabetes at entry
- Controls:
 - Healthy age and gender-matched controls for each subject
- Assessment of HDL function:
 - Monocyte chemotactic assay (MCA)
 - Cell-free assay (CFA)

CHD Despite High HDL Study: Monocyte Chemotaxis Assay (MCA)

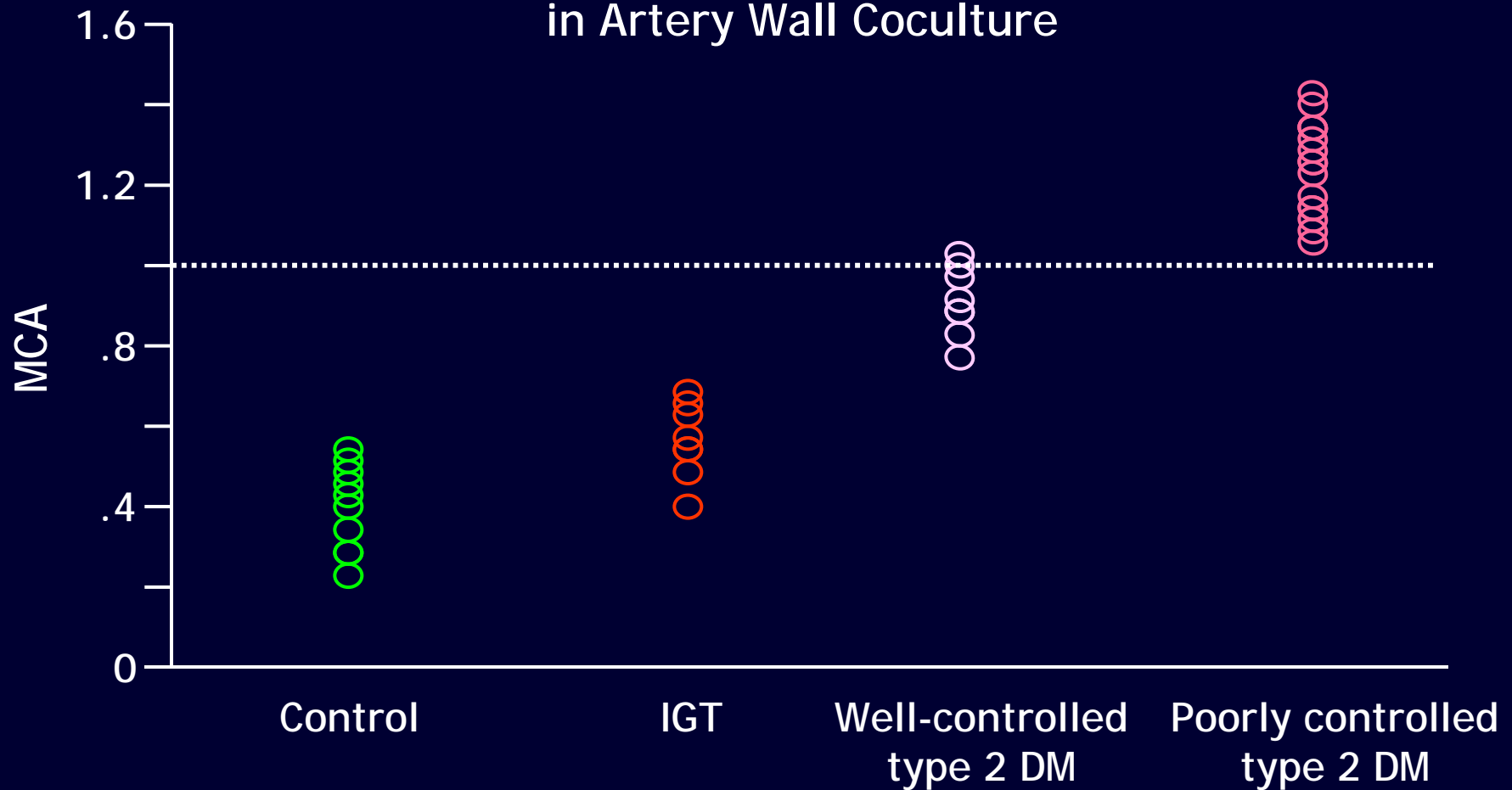


CHD Despite High HDL Study: Cell-Free Assay (CFA)



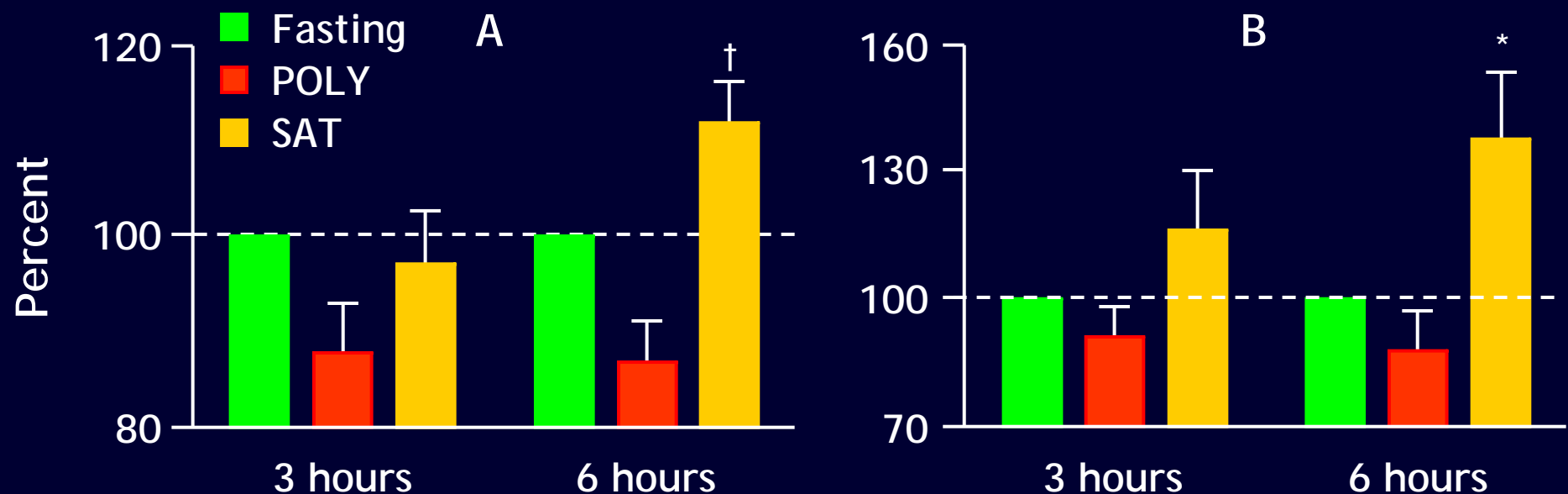
HDL Monocyte Chemotaxis Activity in Patients With Varying Degrees of Glycemia

HDL Effect on LDL-Induced Monocyte Chemotaxis in Artery Wall Coculture



Effect of Dietary Fat Type on HDL Anti-inflammatory Function

Expression of ICAM-1 (A) and VCAM-1 (B) in Human Endothelial Cells After Incubation With HDL Isolated Following Meal With Polyunsaturated (POLY) or Saturated Fat (SAT)



* $P=.007$; $^{\dagger}P=.005$.

Nicholls SJ et al. *J Am Coll Cardiol.* 2006;48:715-720.

HDL-C-Based Therapeutics: Clinical Strategies on the Horizon

Effects of Approved Lipid-Modifying Drugs on HDL-C Levels

Ezetimibe	↑ 1%-3%
Statins	↑ 5%-15%
Fibrates	↑ 10%-20%
Niacin	↑ 15%-35%

Adapted from Belalcazar LM, Ballantyne CM. *Prog Cardiovasc Dis*. 1998;41:151-174; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497; McKenney JM, Sica D. *Pharmacotherapy*. 2007;27:715-728.

Evolution of Lipid Management Guidelines

ATP I – 1988	ATP II – 1993	ATP III –2001	ATP III Update – 2004
Exclusive focus on LDL-C	Risk assessment guides therapy	Lower LDL-C threshold for therapy initiation in high-risk patients	Lower LDL-C threshold for therapy initiation in very high-risk patients
Strong support for resins, niacin	Goal LDL-C reduced for CHD (≤ 100 mg/dL)	LDL-C goal < 100 mg/dL for CHD equivalent	Optional LDL-C goal < 70 mg/dL for CVD + multiple/severe risk or ACS
Statins, fibrates not first-line option	Statins included in "major drugs," fibrates for mixed hyperlipidemia	Non-HDL-C and metabolic syndrome as secondary targets	Optional LDL-C goal < 100 mg/dL for moderately high-risk primary prevention

Low- to Moderate-Dose Monotherapy

Moderate- to High-Dose Statin

High-Dose Statin; Increased Combination Therapy



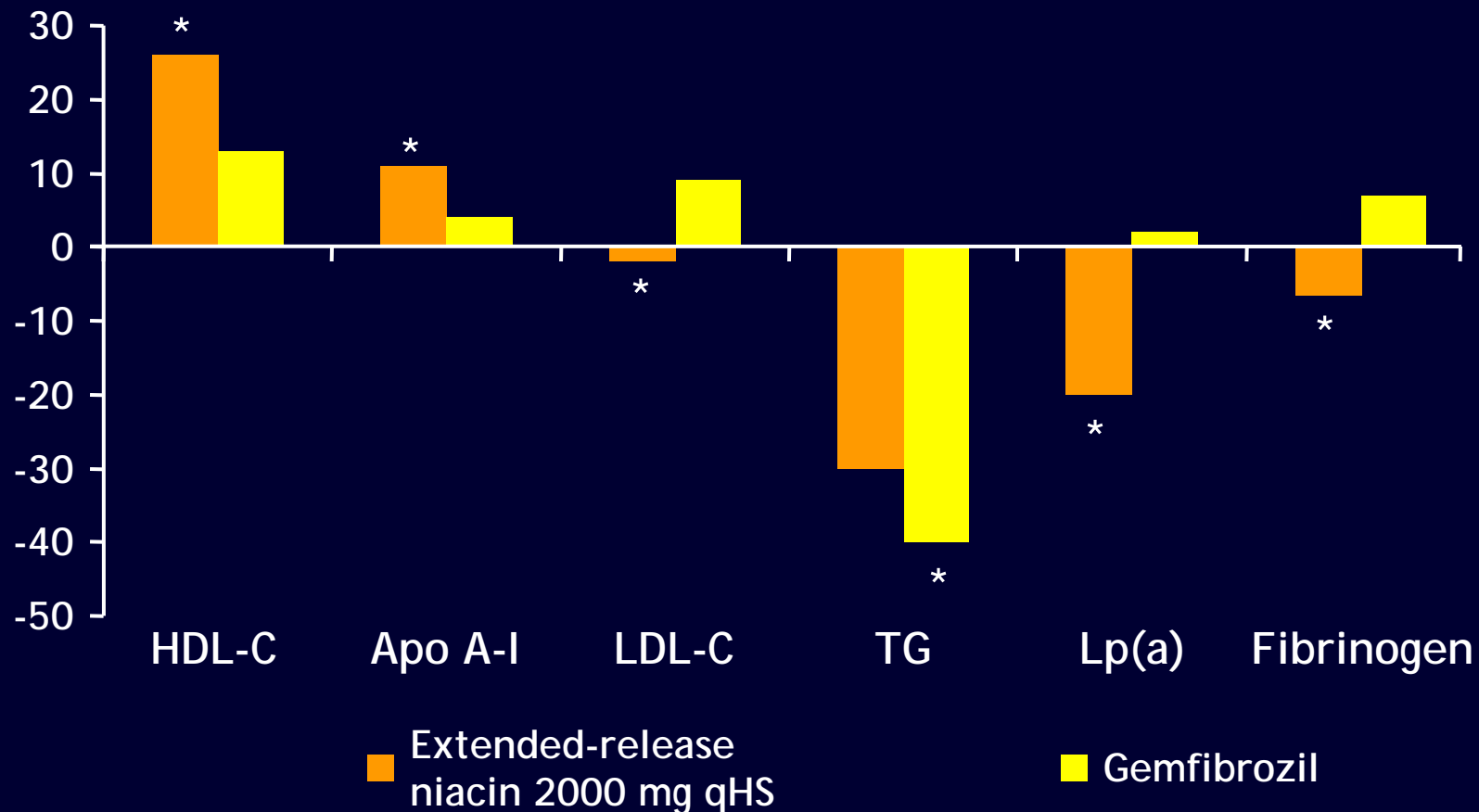
ATP=Adult Treatment Panel.

Effects of Lifestyle Modifications on HDL-C Levels

- Caloric restriction
 - Caloric restriction acutely lowers HDL-C
 - For every 3 kg (7 lb) of weight loss, HDL-C levels increase by 1 mg/dL
- Total fat intake
 - Low-fat diets lower HDL-C in all patients, HDL inflammatory index however is reduced es in obese men
- Smoking cessation
 - HDL-C levels in smokers are reduced by 7% to 20% than those in nonsmokers
 - HDL-C levels return to normal within 30 to 60 days after smoking cessation
- Exercise
 - Aerobic exercise (eg, running) increases HDL-C in a dose-dependent manner
- Alcohol
 - Alcohol increases HDL-C in a dose-dependent manner (not recommended)

Niacin Raises HDL-C by 20% to 30%

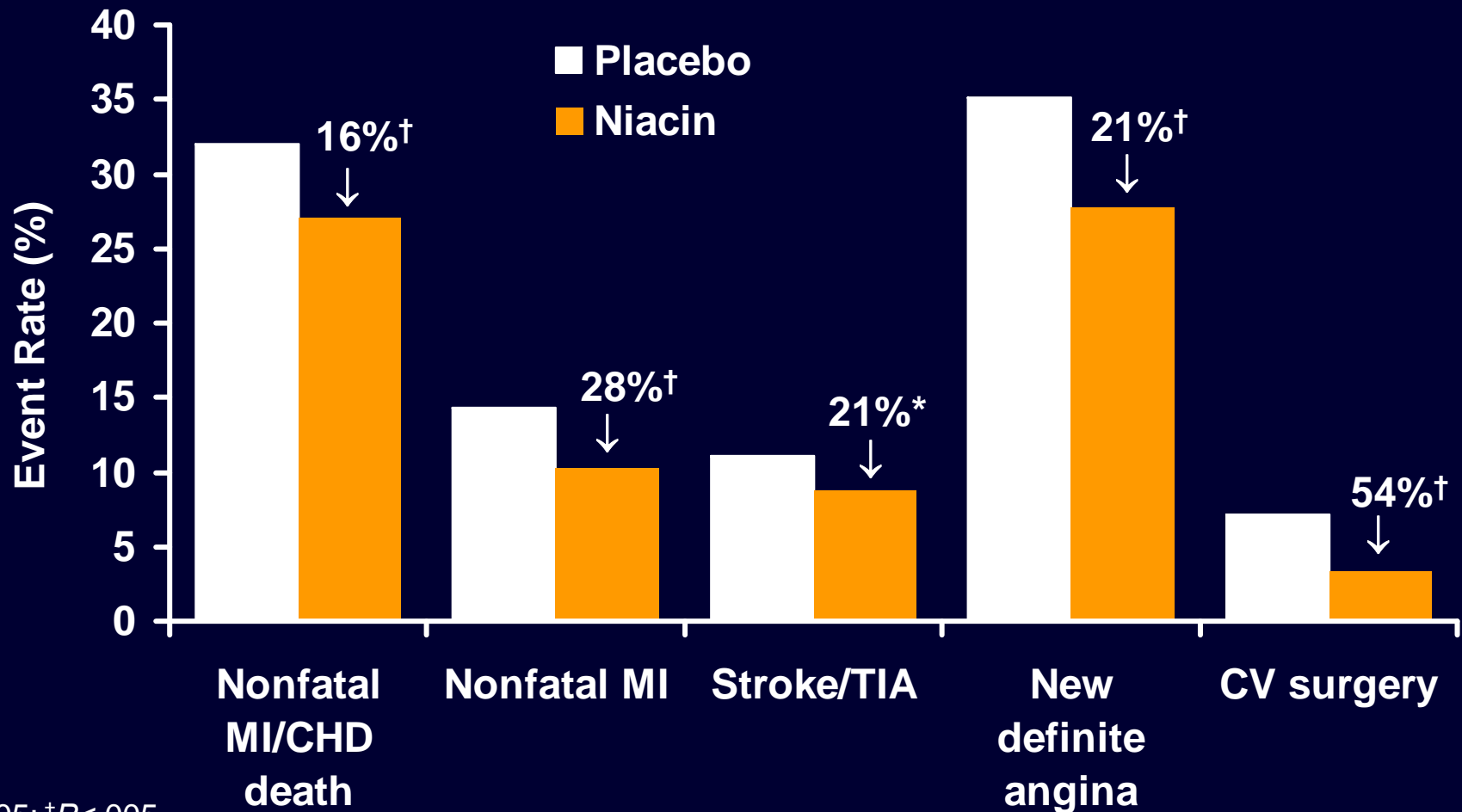
N=173, HDL-C <40 (mean 31 mg/dL, TG 190 mg/dL)



* $P \leq .02$.

Adapted from Guyton JR et al. *Arch Intern Med.* 2000;160:1177-1184.

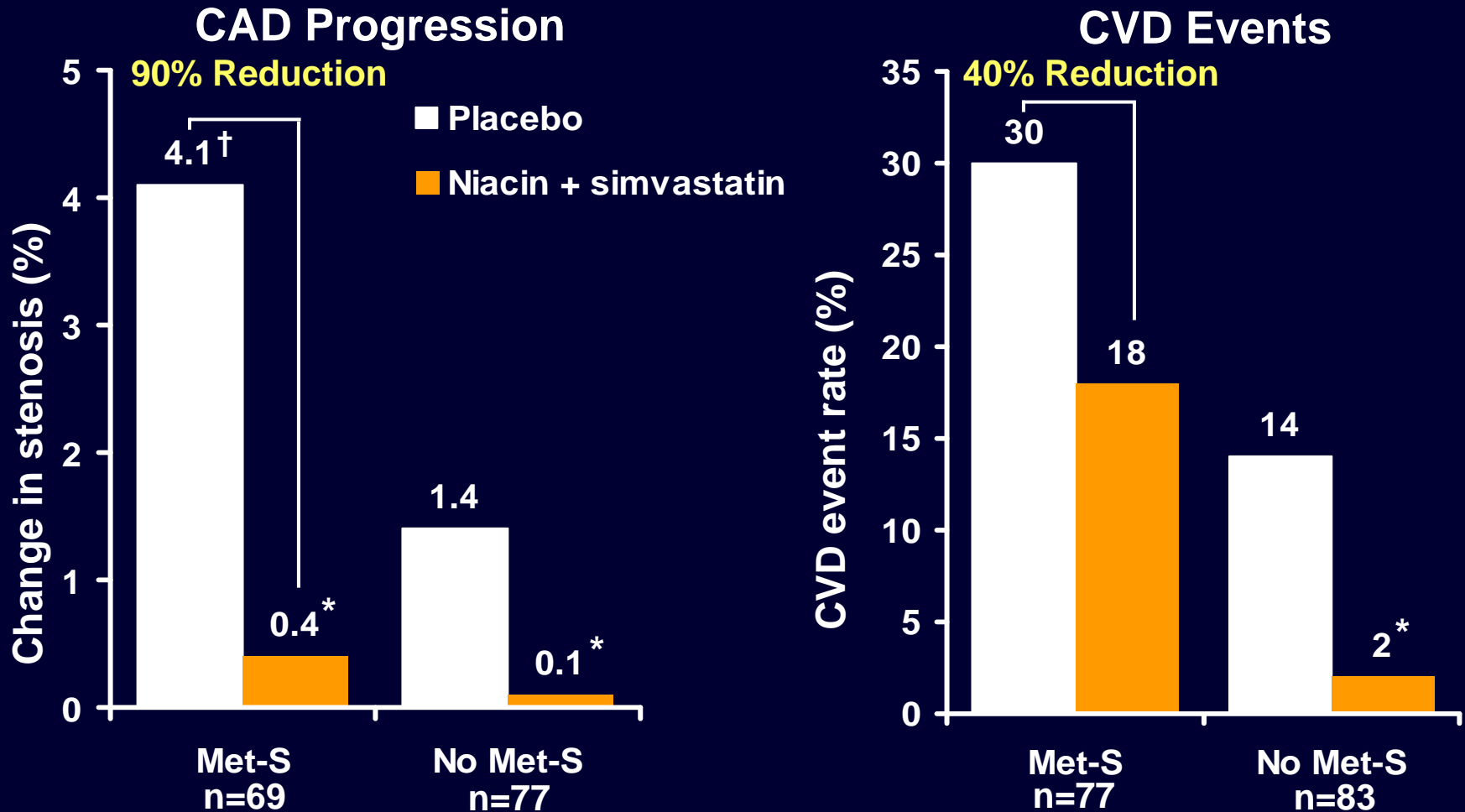
Coronary Drug Project: Complete Treatment Follow-up (Mean 6.2 Years)



* $P < .05$; † $P < .005$.

Brown BG et al. Nicotinic Acid. In: Ballantyne CM, ed. *Clinical Lipidology: A Companion to Braunwald's Heart Disease*. Philadelphia, PA: WB Saunders. In press.

HATS: Clinical End Points in Patients With and Without the Metabolic Syndrome

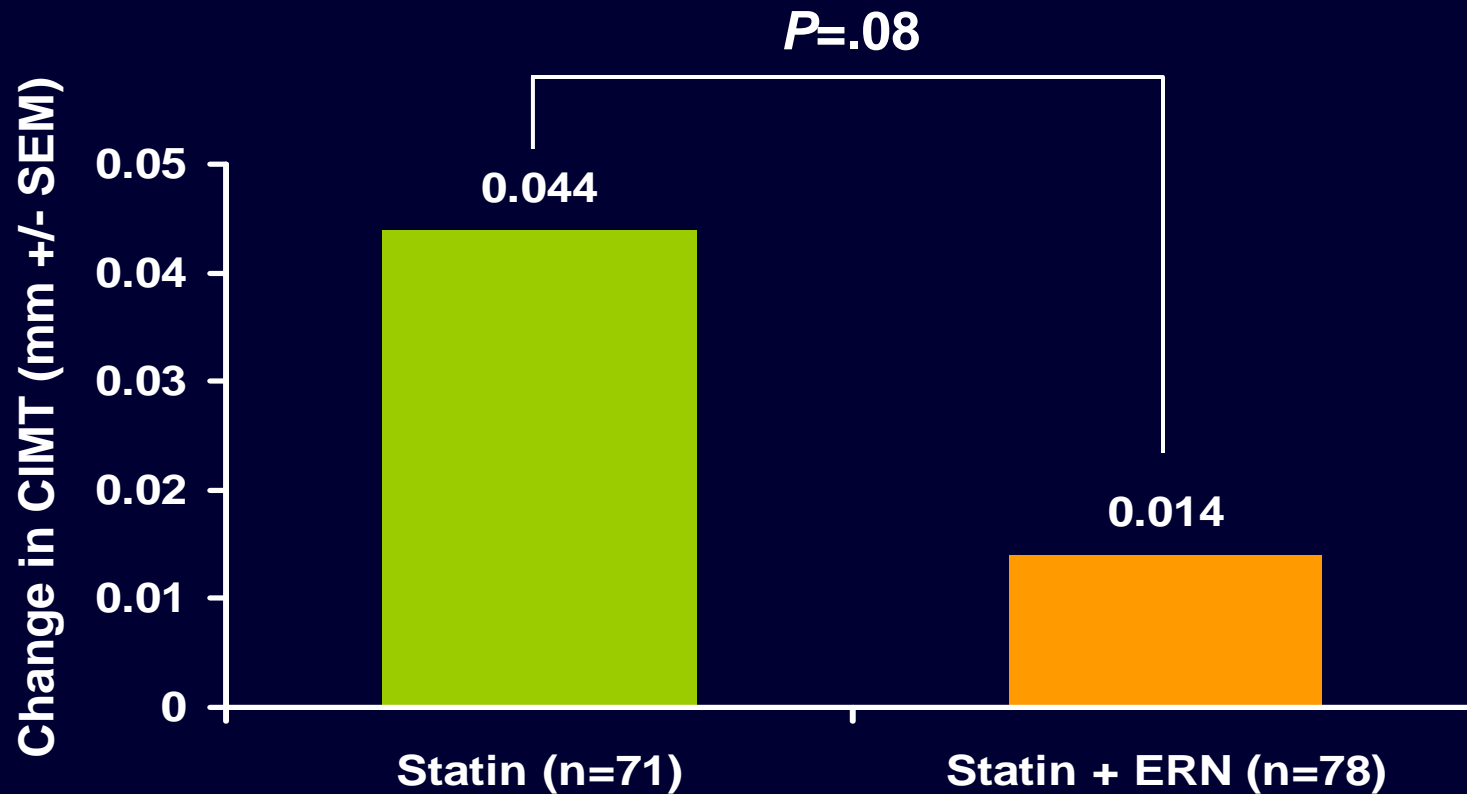


* $P < .05$ vs placebo; $†P = .02$ vs no Met-S.

HATS= HDL Atherosclerosis Treatment Study; Met-S=metabolic syndrome.

Zhao X-Q et al. *J Am Coll Cardiol.* 2002;39(suppl A):242A. Abstract 1130-73.

ARBITER 2: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: 12-Month Study



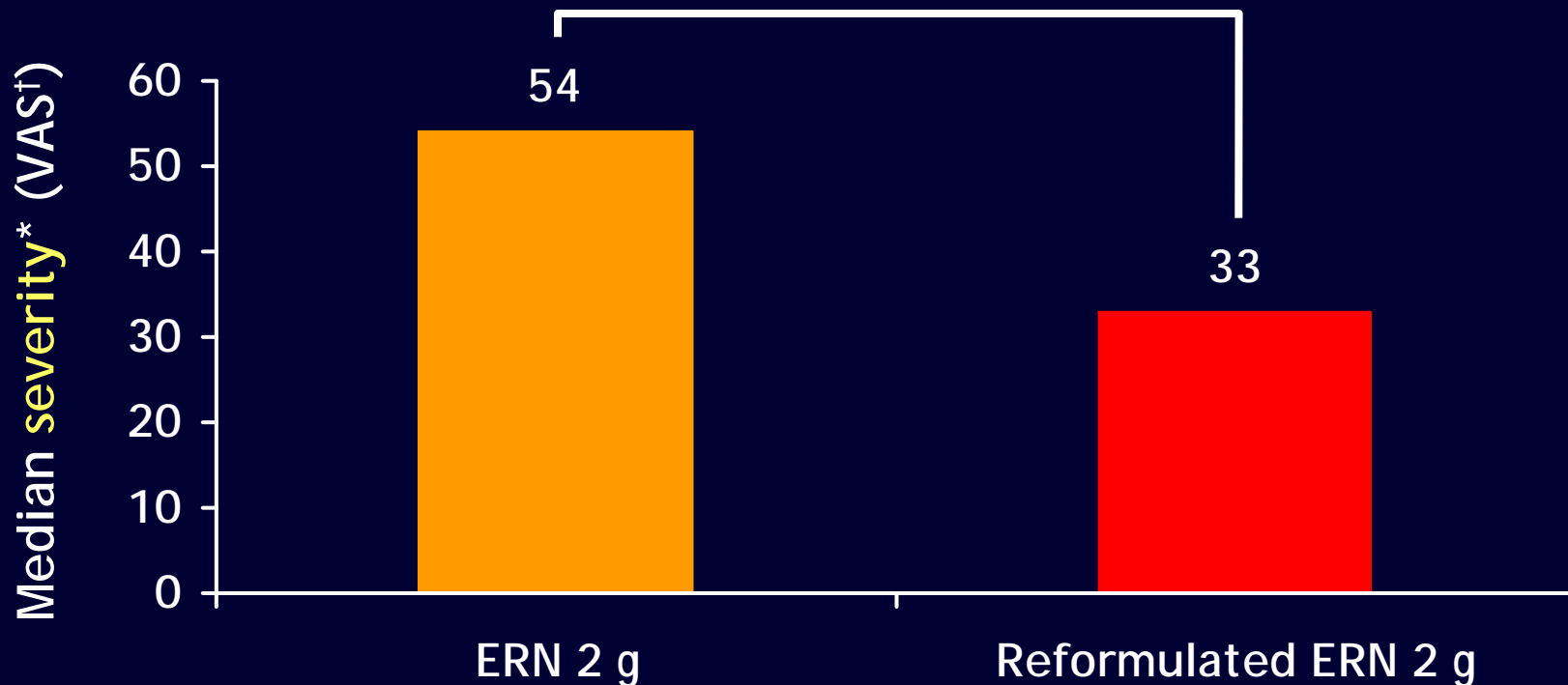
CIMT=carotid intima-media thickness; ERN=extended-release niacin; SEM=standard error of mean.
Taylor AJ et al. *Circulation*. 2004;110:3512-3517.

Niacin-Induced Flushing

- Dose-dependent; occurs in almost all patients
- Contributes to decreased adherence and subtherapeutic dosing
- Mediated by PGD_2 acting through DP1 receptor

Efficacy of Reformulated ERN on Acute Flushing Severity

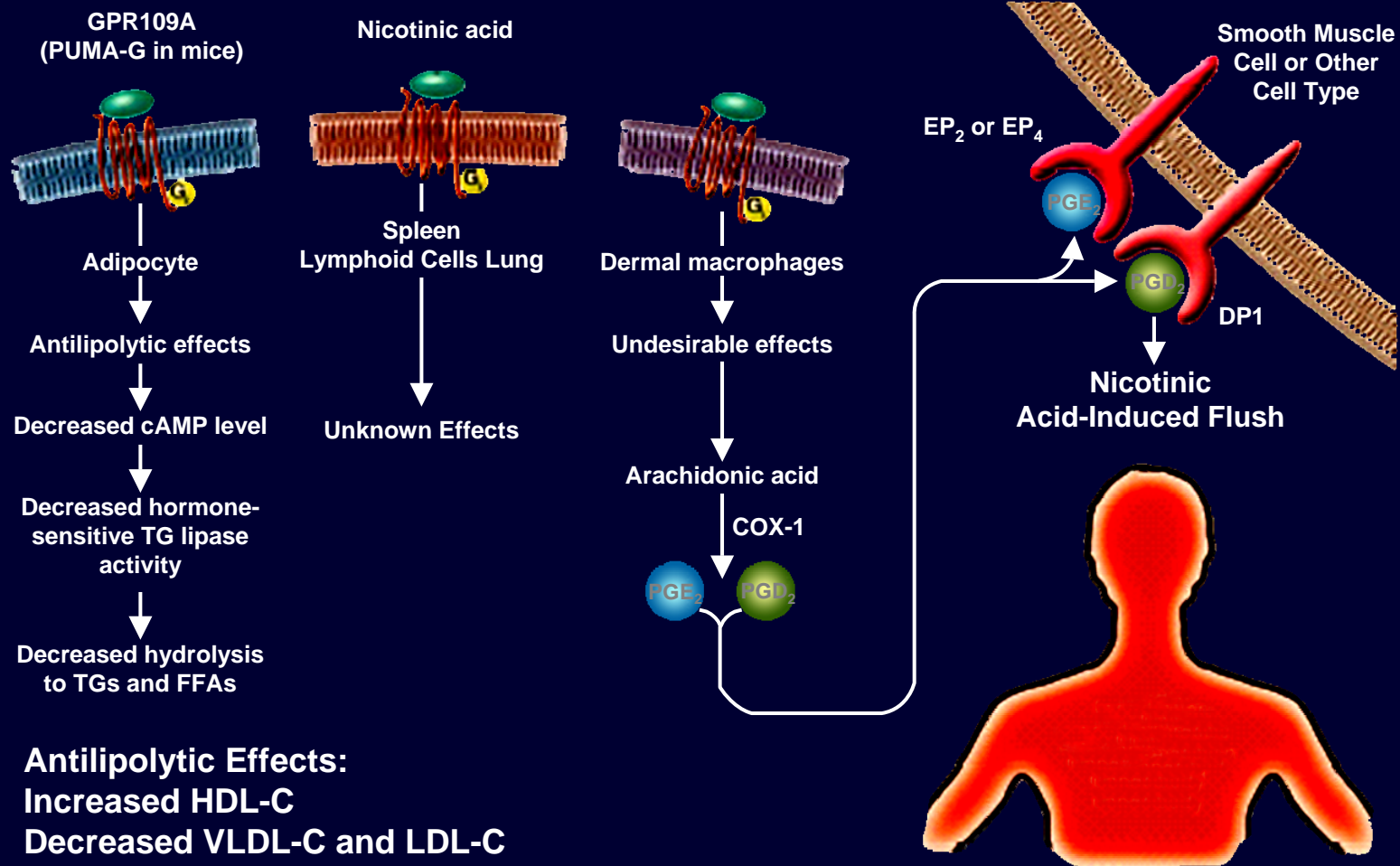
89% of subjects experienced flushing during treatment with reformulated ERN



*First flushing event; † visual analog scale: 0=none; 100=intolerable.

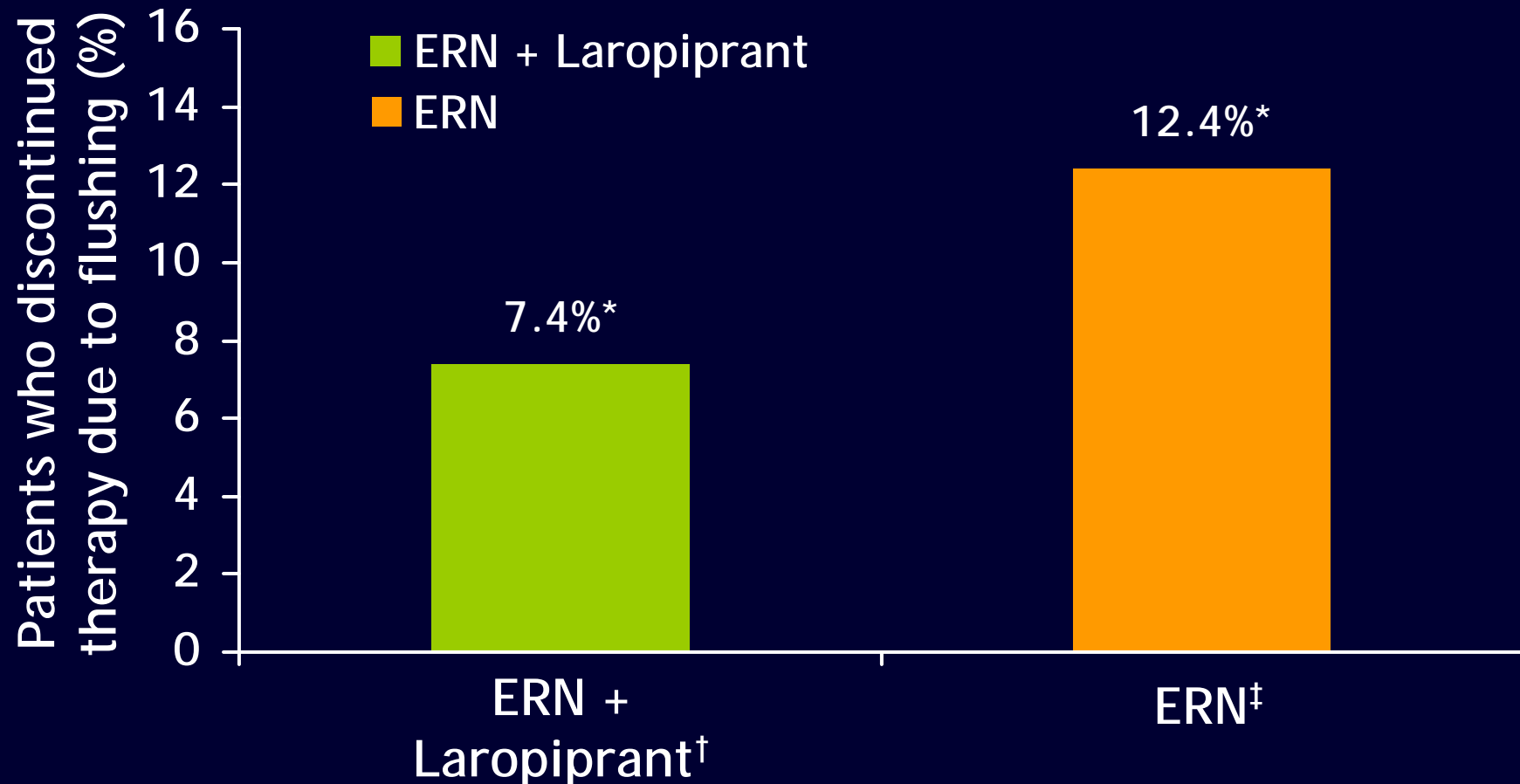
Cefali EA et al. *Int J Clin Pharmacol Ther.* 2006;44:633-640.

Nicotinic Acid Receptor HM74A



Adapted from Pike NB. *J Clin Invest.* 2005;115:3400-3403.

Fewer Patients Discontinued ERN + Laropiprant Therapy Due to Flushing



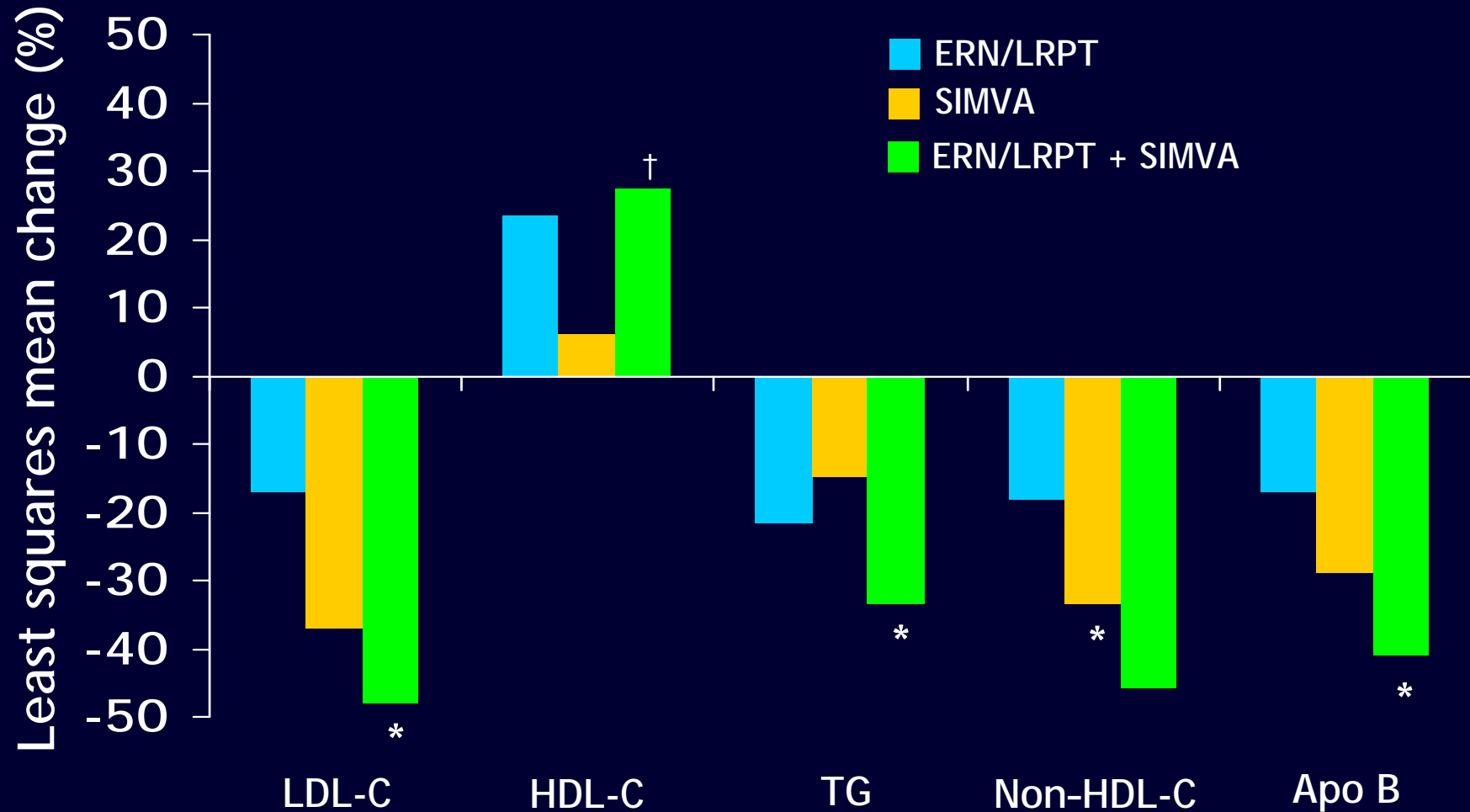
* $P=.002$; Results over 16-week treatment period.

†ERN 1 g + LRPT 20 mg for 4 weeks and increased to ERN 2 g + LRPT 40 mg for 12 weeks.

‡0.5 g for 4 weeks titrated in 0.5 g increments every 4 weeks to 2 g for last 4 weeks.

Koren MJ et al. *J Am Coll Cardiol.* 2008;51(suppl A):A324.

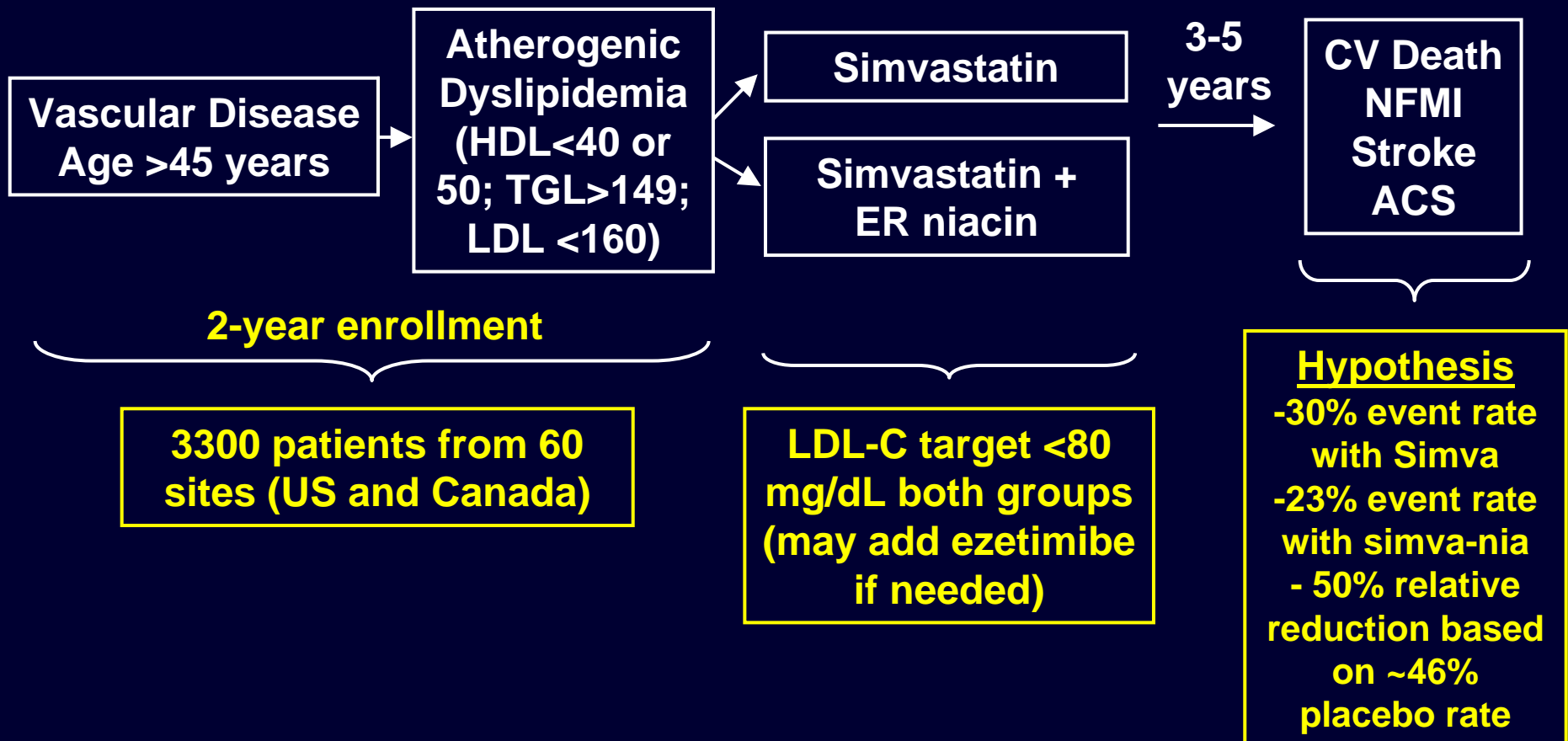
Improvement in Lipid Profile With ER Niacin Plus Laropiprant ± Simvastatin



* $P < .001$ vs ERN/LRPT and $P < .001$ vs SIMVA; † $P < .05$ vs ERN/LRPT and $P < .001$ vs SIMVA

Gleim G et al. Presented at AHA Scientific Sessions 2007; November 3-7, 2007; Orlando, Florida. Abstract.

AIM-HIGH Study Overview



HPS2-THRIVE: A Randomized Trial of the Long-term Clinical Effects of Raising HDL With Niacin and Laropiprant

Does niacin combined with laropiprant prevent vascular events in high-risk patients receiving intensive LDL-lowering therapy?

N=20,000

Patients aged 50-80 years with pre-existing atherosclerotic disease receiving simvastatin 40 mg qd and, if indicated, ezetimibe/simvastatin 10/40 mg qd

Randomization

Niacin 2 g +
Laropiprant 40 mg

Placebo

Follow-up visits at 3 and 6 months,
then every 6 months thereafter

An international collaboration, with a central office in Oxford and 3 regional coordinating centers in the UK, China, and Scandinavia, will conduct the trial in about 200 hospitals

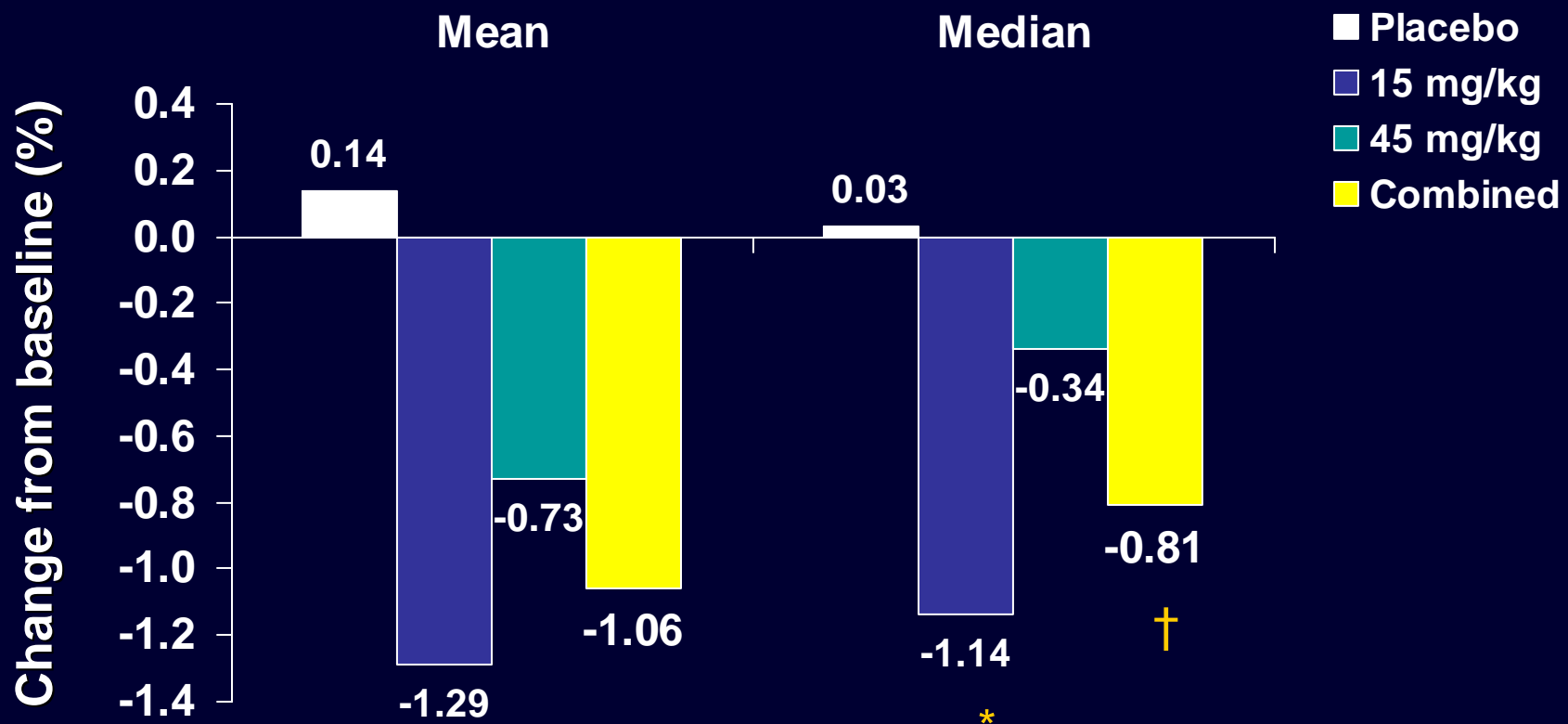
THRIVE=Treatment of HDL to Reduce the Incidence of Vascular Events.

New Approaches to Targeting the HDL Pathway

- Raising HDL-C
 - CETP inhibition by newer agents (JT 705),
 - PPAR agonists
 - Enhancing reverse cholesterol transport
 - Apo A-I Milano
 - Apo A-I mimetics, D-4F (oral peptide)
 - Large unilamellar phospholipid vesicles
- Enhancing HDL function
- LDL apheresis
- HDL remodeling mass changes (ApoE -niacin)

CETP=cholesteryl ester transfer protein.

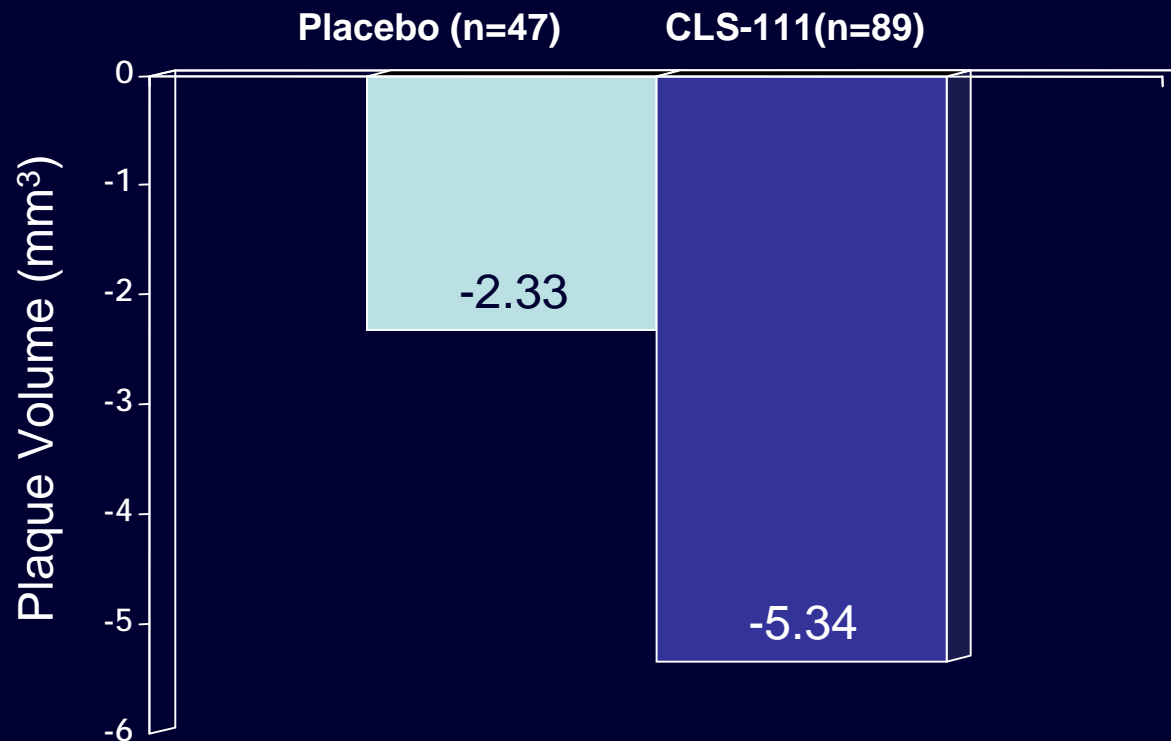
Effect of Recombinant ApoA-I Milano (ETC-216) on Change in Percentage Atheroma Volume



* $P=.03$; † $P=.02$ (1° end point).

Nissen SE et al. *JAMA*. 2003;290:2292-2300.

Effect of Reconstituted HDL on Atherosclerosis-Safety and Efficacy (ERASE)



IQR=interquartile range.

Tardiff J-C. *JAMA*. 2007;297:1675-1682.

EFFECT OF LDL APHERESIS ON HDL

LIPID	PRE	POST
LDL mg/dl	208	99*
HDL mg/dl	49	41*
INFLAMMATORY HDL (mca activity)	22	14*

*P<.05

AJC OPOLE, 2007

Conclusion

- A large number of high-risk individuals have reduced HDL-C levels and still have increased residual risk after statin therapy.
- Both experimental and clinical data suggest usually raising HDL-C may reduce CV events but practical testing of HDL functionality is needed.
- Currently, niacin is the most effective drug available to raise HDL-C, but adherence remains a clinical challenge.
- Ongoing trials will provide information on benefits/risks of HDL altering therapies + statin in high-risk patients so HDL 'targets' and guidelines can be defined; until then LDL, Non-HDL, and ApoB remain are primary targets.