Diabetes and Dyslipidemia

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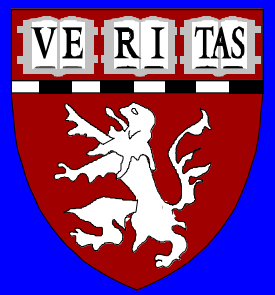


Lipid Abnormalities Associated with Type 2 Diabetes

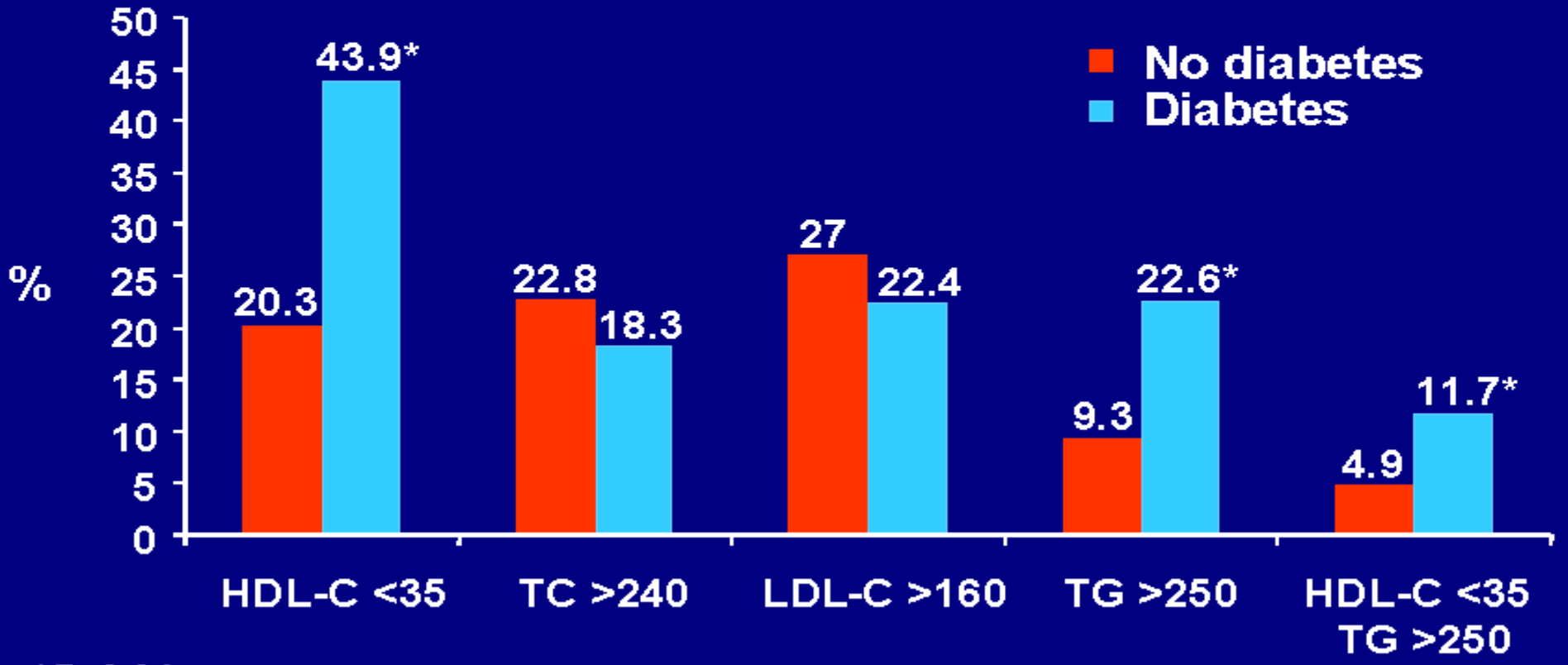
Quantitative

- ↑ Triglycerides
- ↓ HDL-Cholesterol
- * LDL-Cholesterol (Hyper-Apo B)
- ↑ LP (a)

Qualitative

- Remnant-particle accumulation
- Small dense LDL
- Cholesterol-enriched VLDL
- Triglyceride-enriched HDL
  - ↑ **cholesterol-ester transfer protein (CETP) activity**
- Glycosylated apoproteins and phospholipids

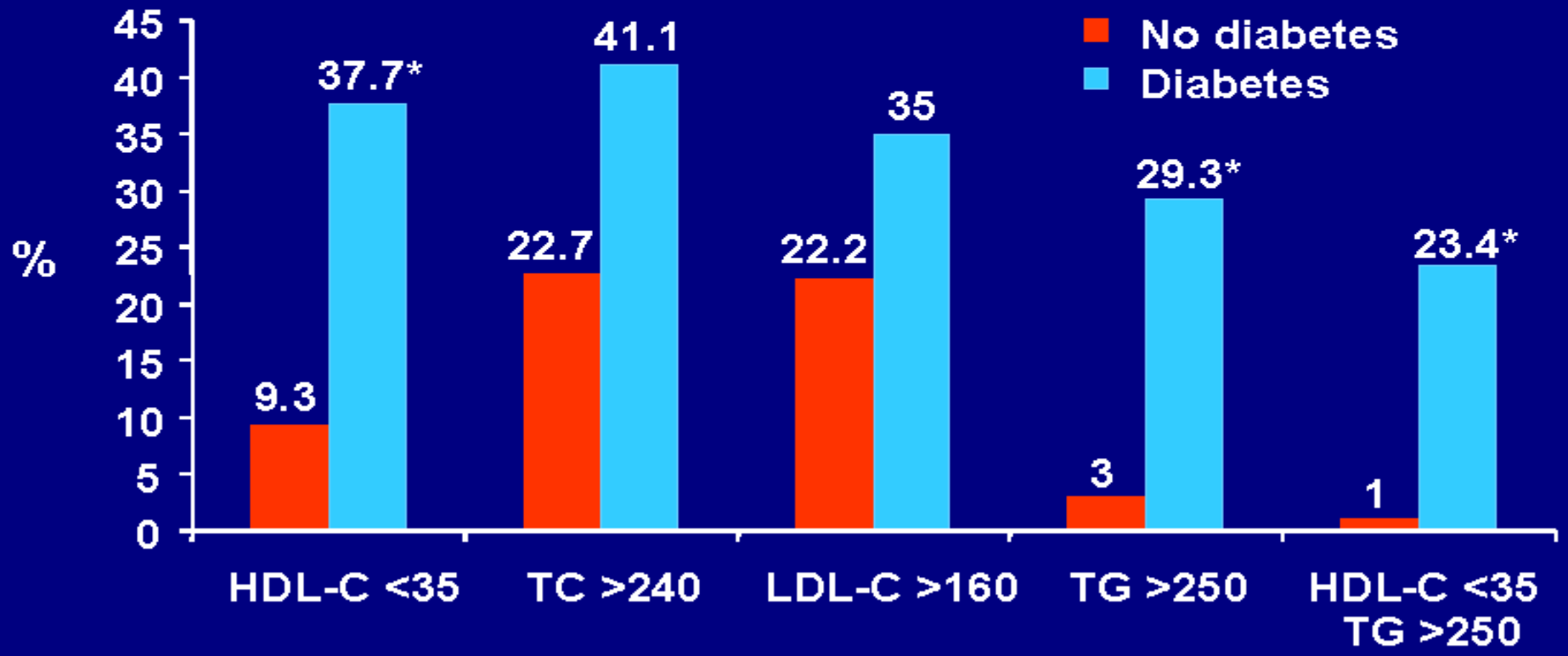
Lipid Levels in Men With and Without Diabetes: Framingham Offspring Study



*P<0.01.

Siegel RD et al. *Metabolism*. 1996;45:1267-1272.

Lipid Levels in Women With and Without Diabetes: Framingham Offspring Study



*P<0.001.

Siegel RD et al. *Metabolism*. 1996;45:1267-1272.

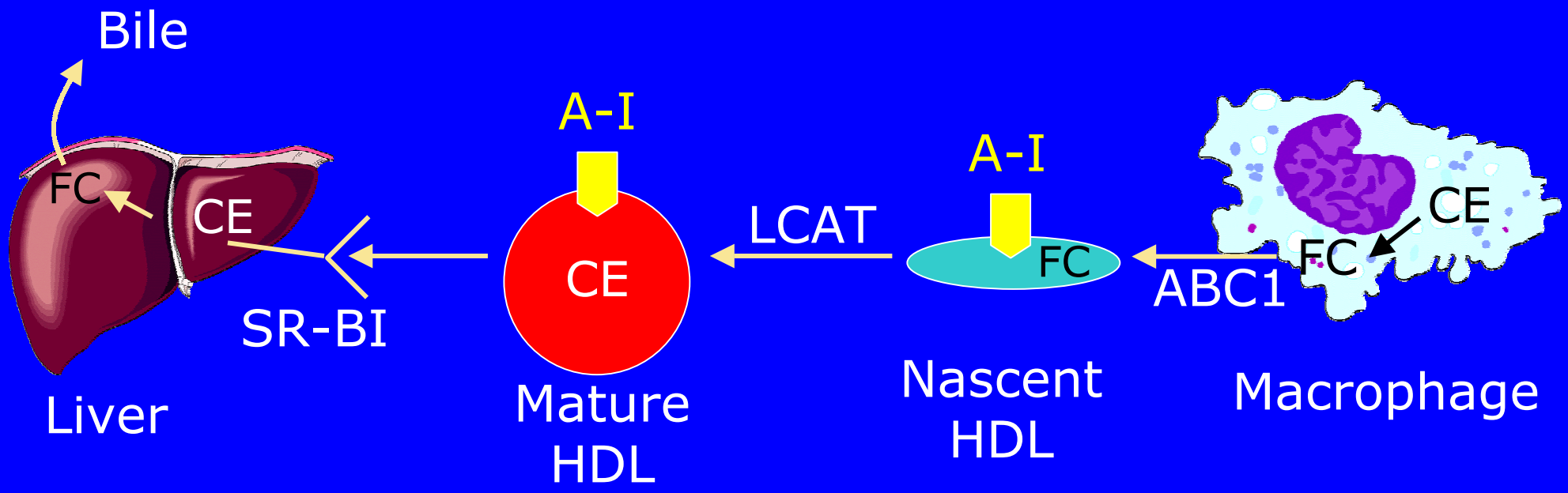
Management Challenges in Diabetic Dyslipidemia

- What is the goal for LDL-cholesterol ?
- How aggressive should we be in raising HDL-C and lowering TG ?
- Should we measure Apo-B ?
- In patients with LDL-C at goal, when to consider combination drug- therapy ?
- Do postprandial Triglyceride levels contribute in risk assessment?

HDL Metabolism as a Therapeutic Target: Potential Strategies

- Increase apo A-I production
- Promote reverse cholesterol transport
- Delay catabolism of HDL

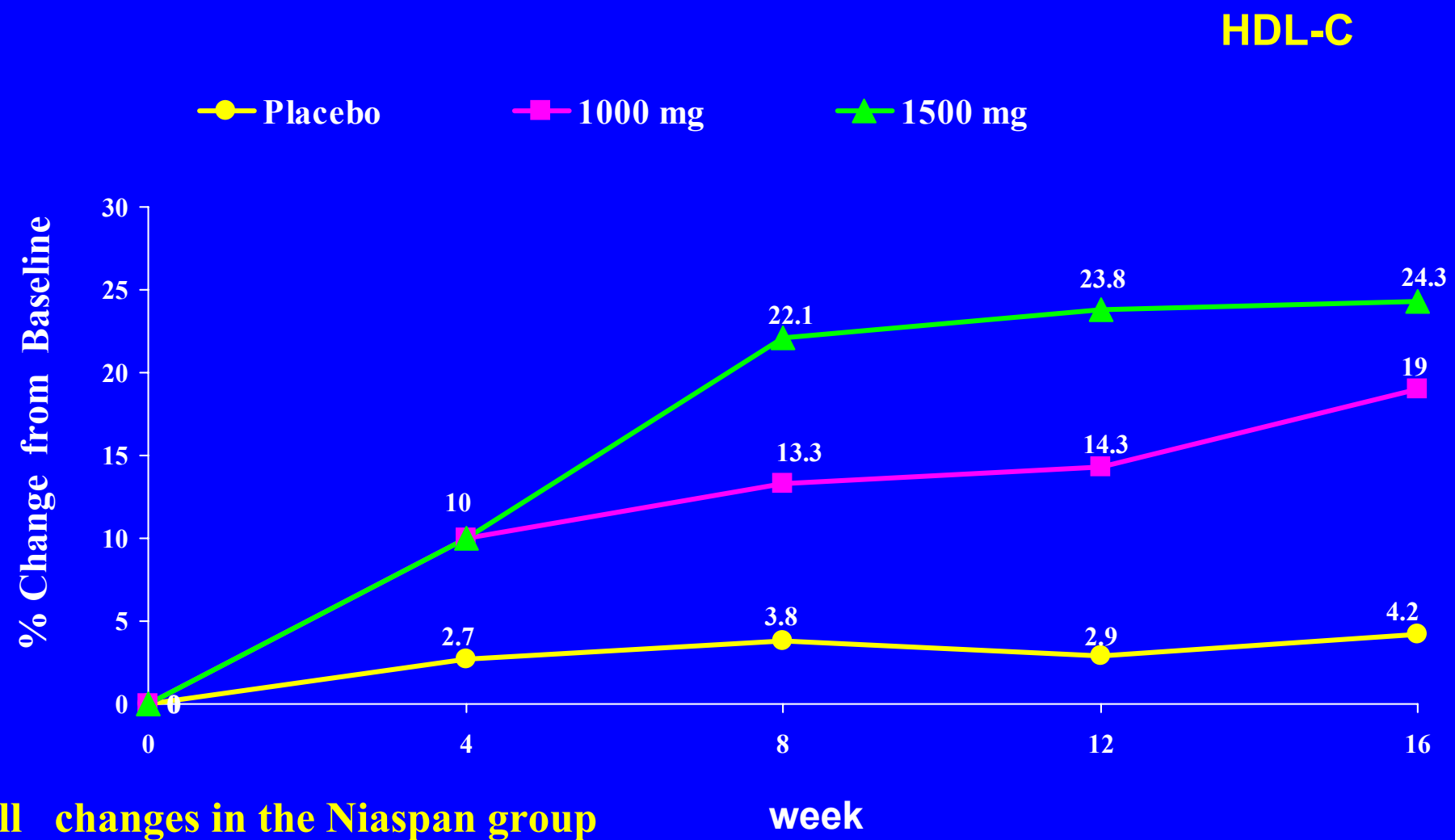
HDL Metabolism and Reverse Cholesterol Transport



ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I;
CE = cholesteryl ester; FC = free cholesterol;
LCAT = lecithin:cholesterol acyltransferase;
SR-BI = scavenger receptor class BI

Effect of Niaspan on Lipids and Glycemic Control in Patients with Diabetes Mellitus: The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT)

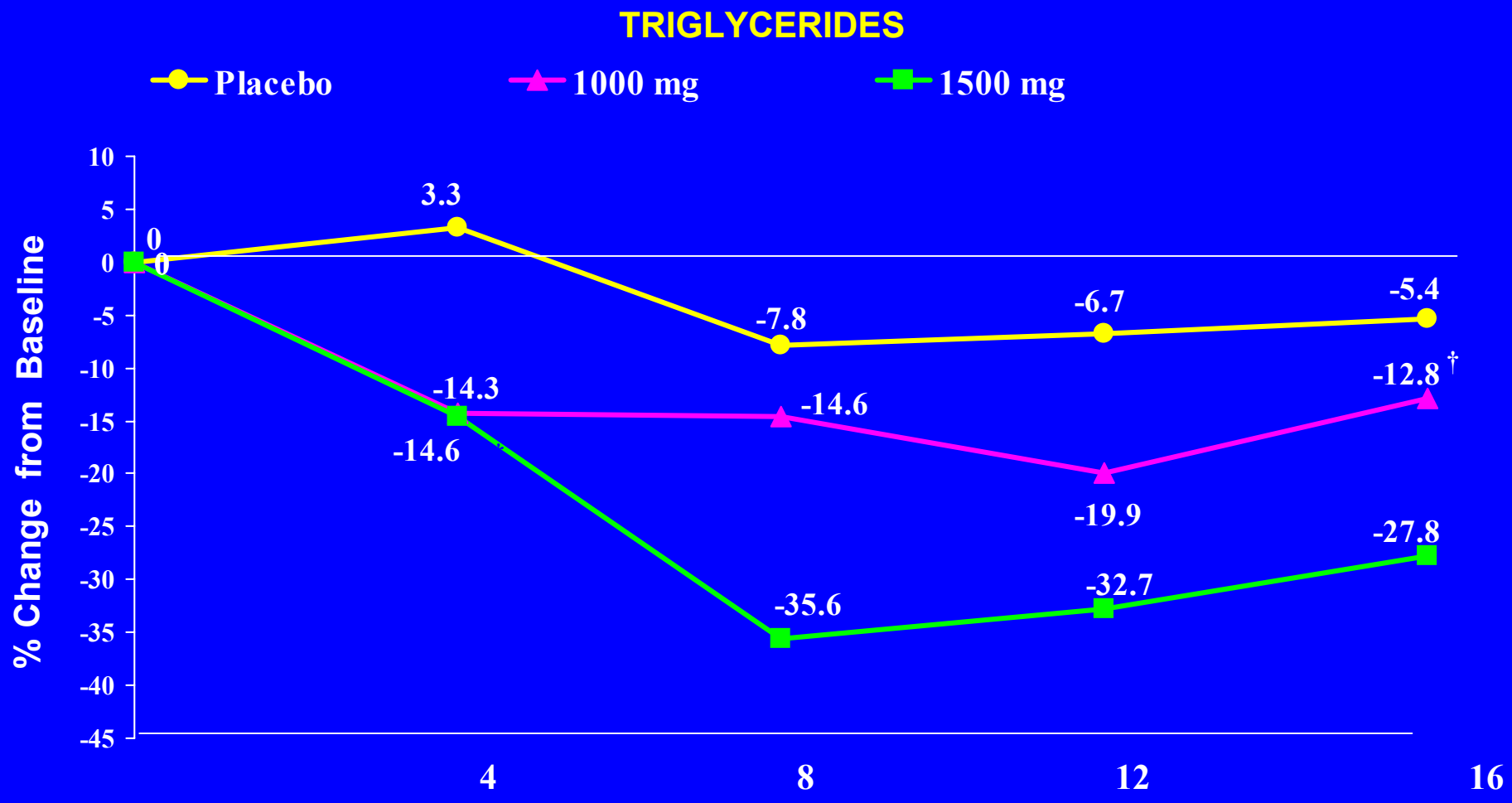
ADVENT



All changes in the Niaspan group

$P < 0.05$ vs. placebo

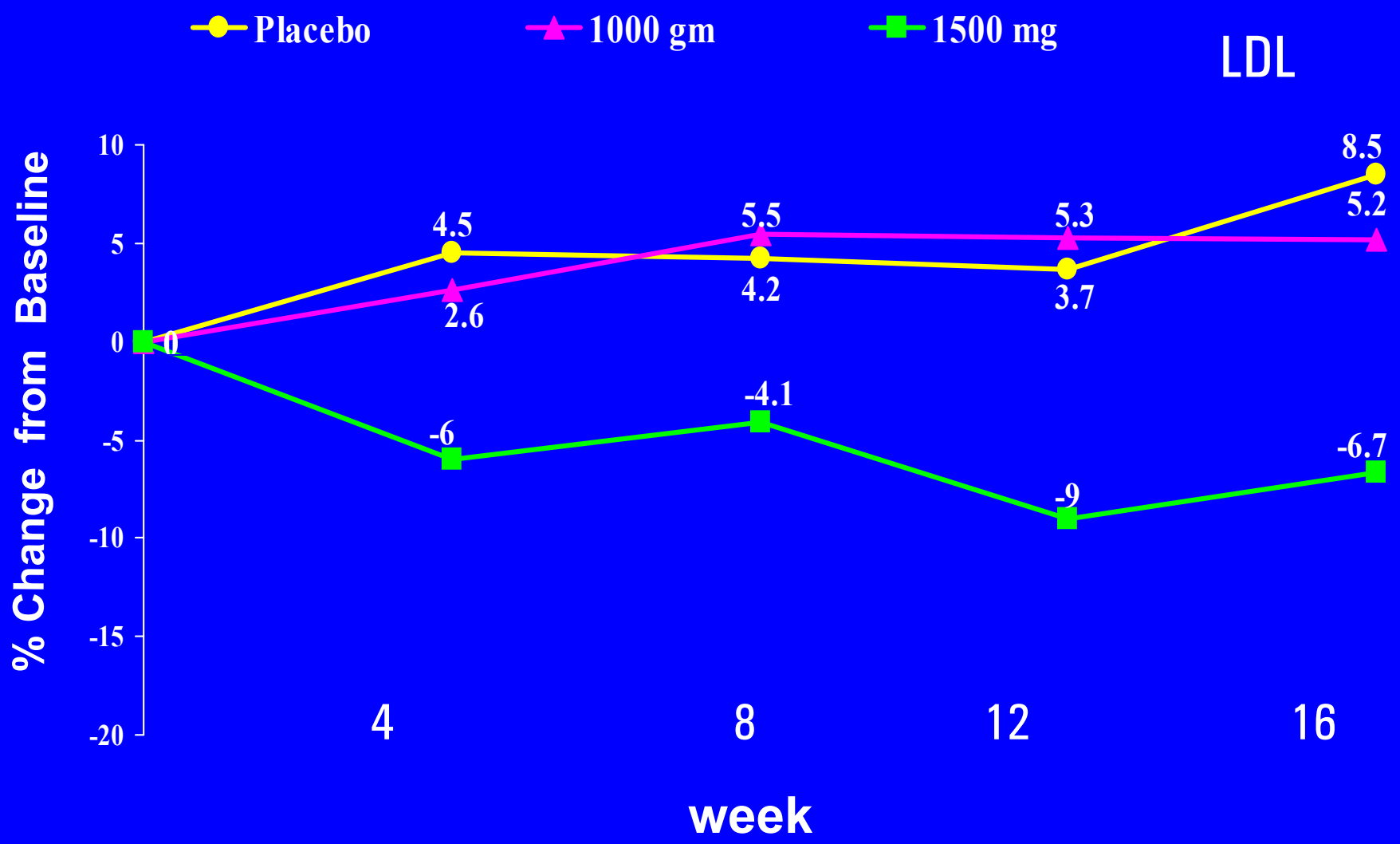
ADVENT



*P< 0.05 vs. placebo

†P<0.05 vs. 1500 mg

ADVENT


Placebo
1000 gm
1500 mg
LDL
% Change from Baseline
10
5
0
-5
-10
-15
-20
4.5
5.5
5.3
8.5
5.2
4.2
3.7
2.6
0
-4.1
-6
-6.7
-9
4
8
12
16
week

ADVENT

	Placebo N = 49	1000 mg N = 47	1500 mg N = 52	*p*
% Completing Study	86%	87%	81%	NS
Global Assessment *				
Improved or Same	88%	80%	71%	NS
Worse	12%	18%	29%	NS
Added Drug or ↑ Dose	16%	24%	29%	NS

*of diabetes status (by investigator)

Combination Therapy in Mixed Hyperlipidemia :

Evidence from Clinical Trials

HDL Atherosclerosis Treatment Study (HATS)

RANDOMIZED TREATMENT ASSIGNMENT
(double-dummy technique):

1. Niacin (2-4 grams/day) + Simvastatin (10-20 mg/day)
2. Niacin (2-4 grams/day) + Simvastatin (10-20mg/day) plus Antioxidant Vitamins
3. Antioxidant Vitamins
4. Double placebos

Antioxidant Vitamins = Vitamin E 800 IU, Vitamin C 1,000 mg, Beta Carotene 25 mg, Selenium 100 mcg

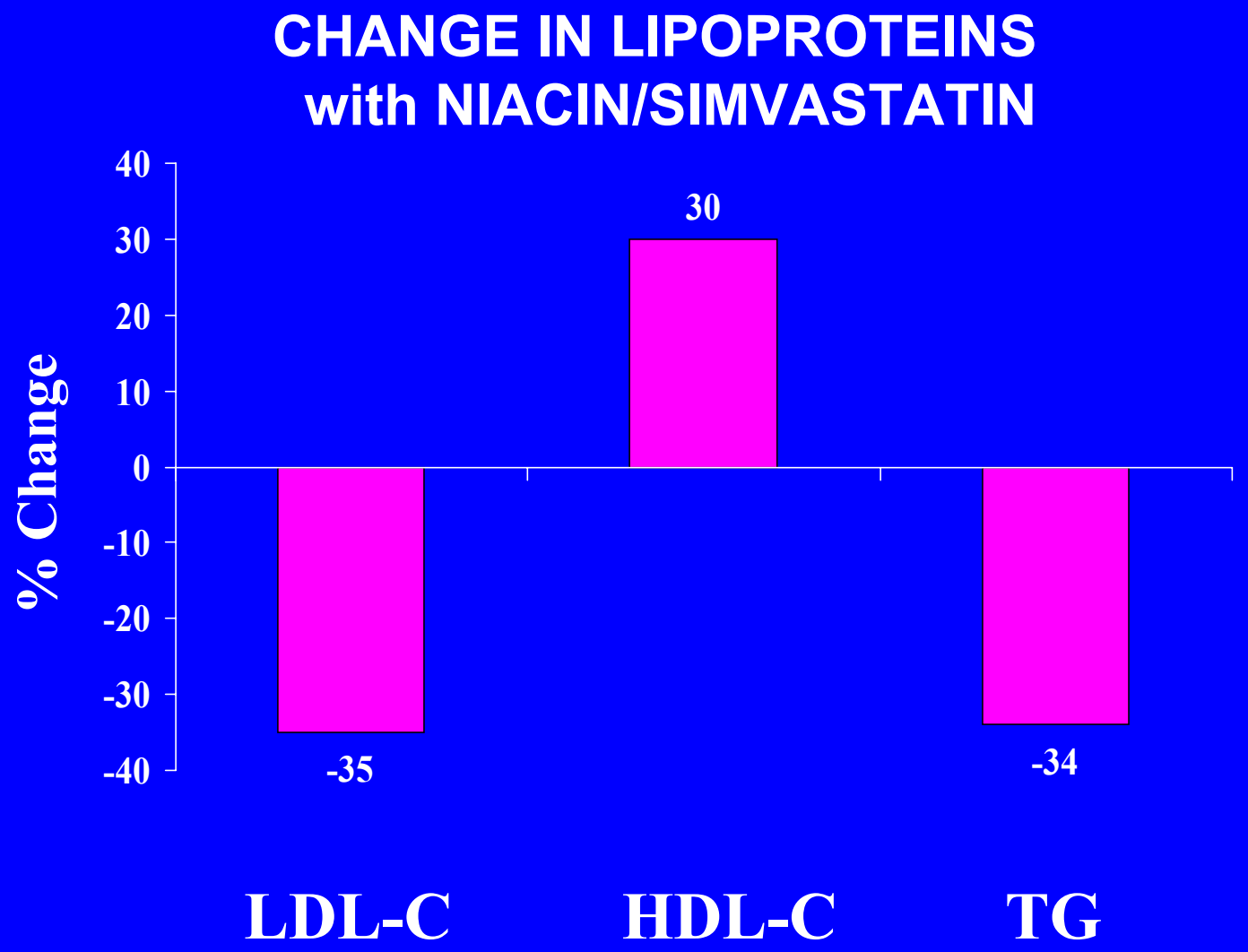
HDL Atherosclerosis Treatment Study (HATS)

BASELINE CHARACTERISTICS

LDL-C	126 mg/dl
HDL-C	31 mg/dl
Triglycerides	212 mg/dl

15% with Diabetes Mellitus (DM)
10% with Impaired Glucose Tolerance (IGT)
85% men/15% women
50% prior MI

HDL Atherosclerosis Treatment Study (HATS)



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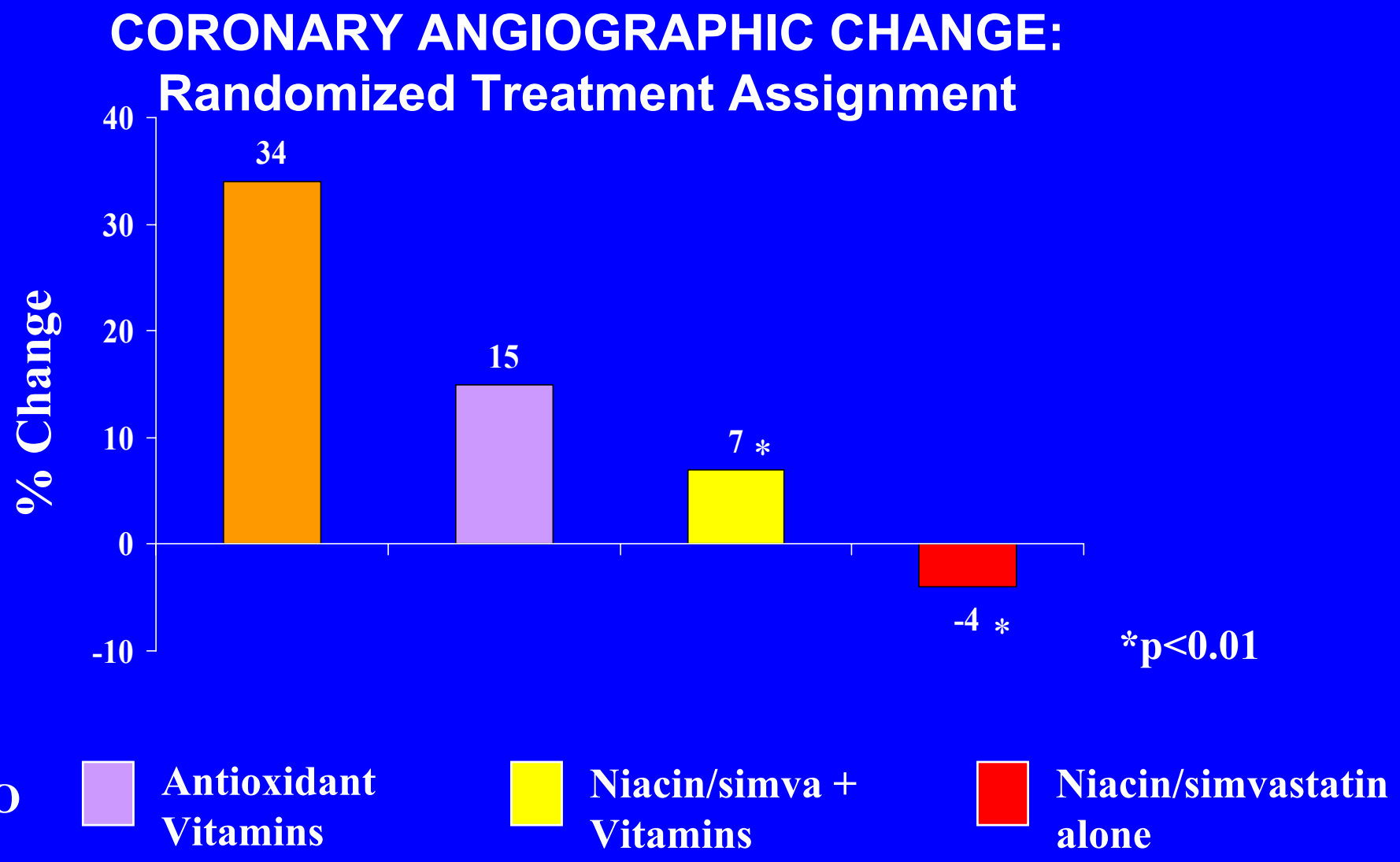

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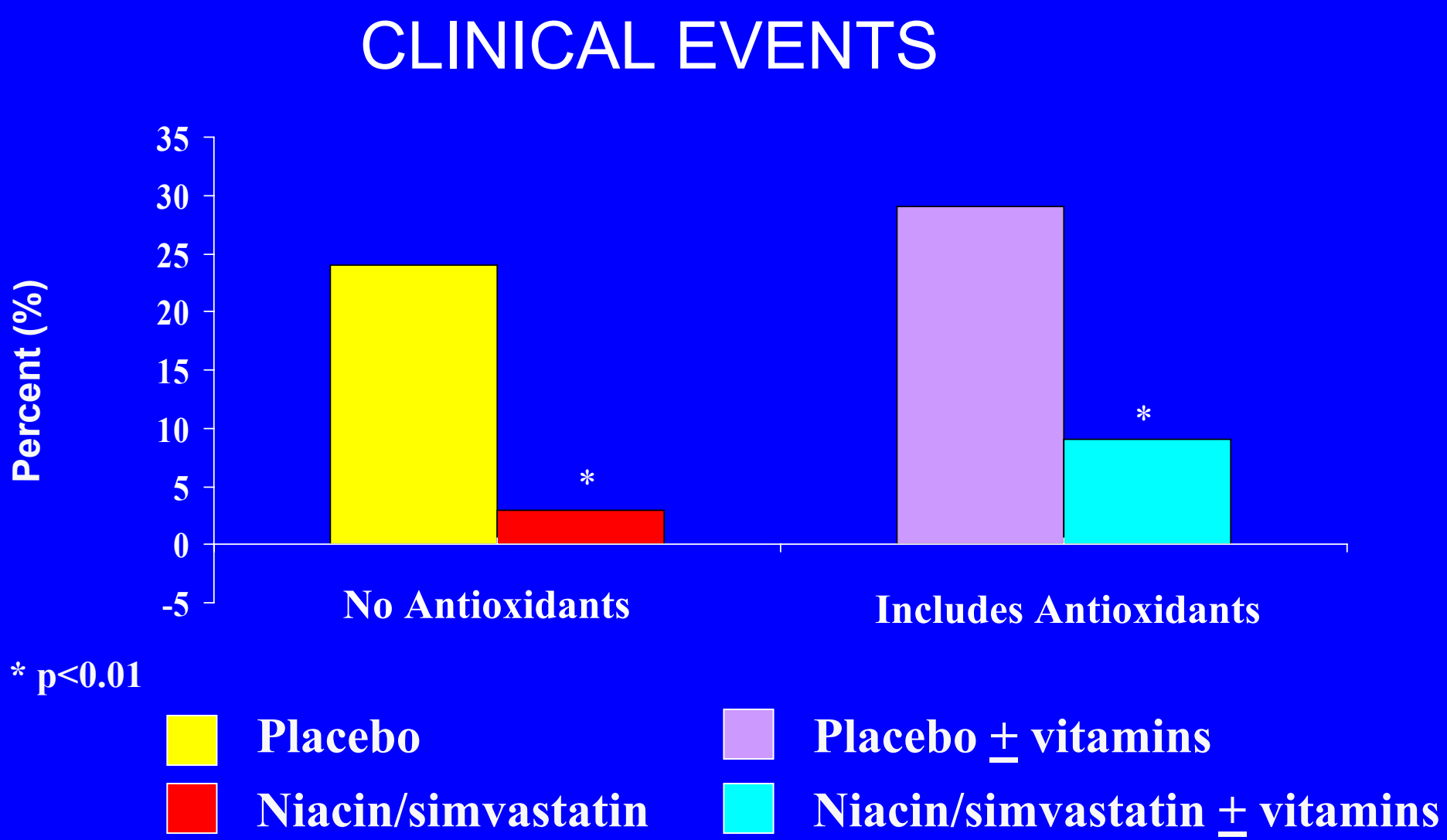


Drug-Therapy in Combined Hyperlipidemia in Type 2 Diabetes

	Atorvastatin		Fenofibrate		Atorva+ Feno	
	BL	% δ	BL	% δ	BL	% δ
LDL-C	161	-40	163	-15	163	-46
Trig.	278	-30	281	-41	278	-50
HDL-C	35	+9	35	+16	35	+22
Fibrinogen	379	-3	382	-21	380	-19

n= 40 in each group (M+F) x 24 wk ; Atorva 20mg, Fenofibrate 200 mg/d

Athyros, VG et el Diabetes Care 2002; 25: 1198-1202

% of Patients reaching ADA Lipid Targets and probability of MI

n	Baseline 120	Atorva 40	Feno 40	A+F 40
LDL-C <100mg/dl	0	80	5	97.5
TG < 200 mg/dl	0	75	92.5	100
HDL-C >45 mg/dl	0	17.5	30	60
10 yr MI Risk (%)	21.6	7.5	10.9	4.2

Athyros,VG et al Diabetes Care 2002; 25: 1198-1202

Newer Agents in Lipid Management

- Rosuvastatin (Crestor)
- Niaspan+Lovastatin (Advicor)
- Cholesterol Absorption Inhibitors:

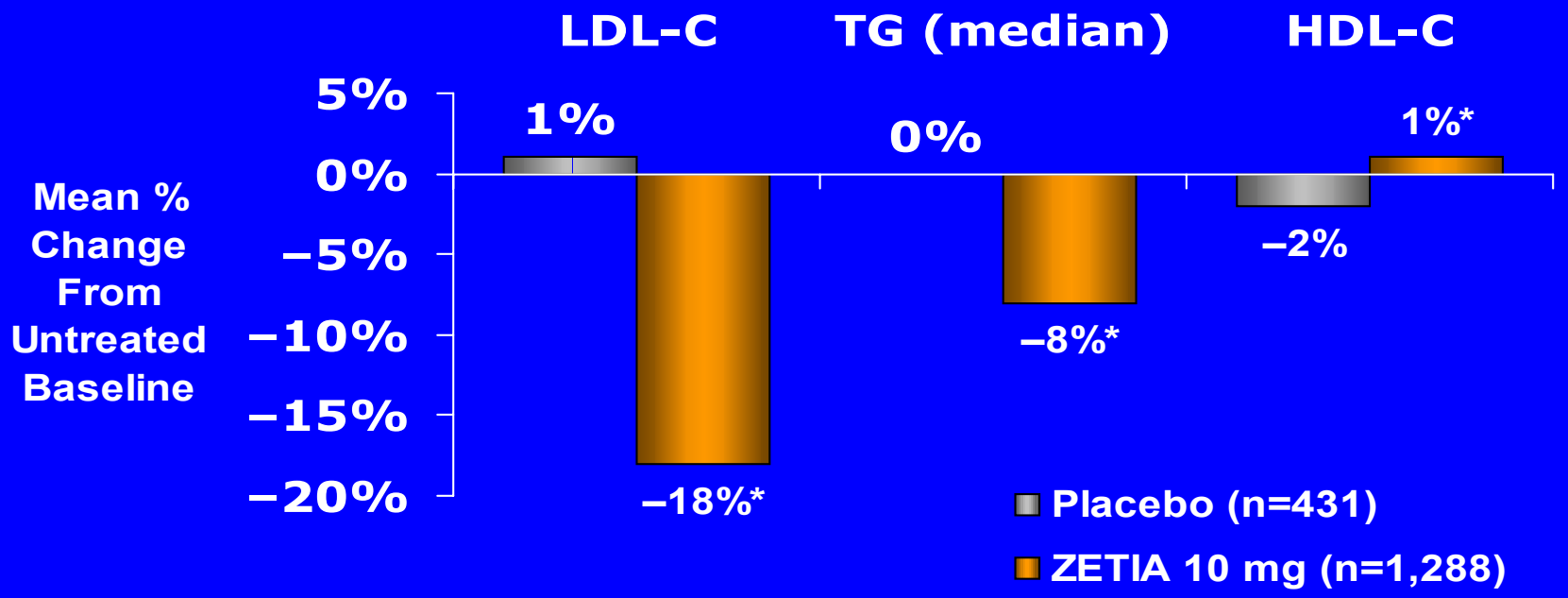
  Plant Stanol Margarine (Benecol)

  Colesevelam (Welchol)

  Ezitimibe (Zetia) **-Approved-10/02**

Clinical Studies for ZETIA™ (ezetimibe) —Monotherapy

Pooled Results From 2 Multicenter, Double-Blind, Placebo-Controlled, 12-Week Studies in 1,719 Patients With Primary Hypercholesterolemia



- Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETIA

*$P \leq 0.01$ vs placebo.

Some On-going Lipid Trials

	n	Drugs	Endpoints
TNT	>10,000	Atorva 10 or 80 mg	CAD death or non-fatal MI
SEARCH	~ 12,000	Simva 20 or 80 +/- B12+ folate	MI and CAD death
IDEAL	7600	Atorva 80 or Simva 20-40	CAD death or non-fatal MI
HPS II	10,000	Simva 20 –40 or Atorva 80 +/- B12 +folate	Major CV endpoints
ACCORD	~5000	Simva 20 +/- Fenofibrate	CAD death or non-fatal MI

TNT: Treat to New Targets; SEARCH : Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine; IDEAL : Incremental decrease in Endpoints through Aggressive Lipid Lowering; ACCORD : Action to Control Cardiovascular Risk in Diabetes