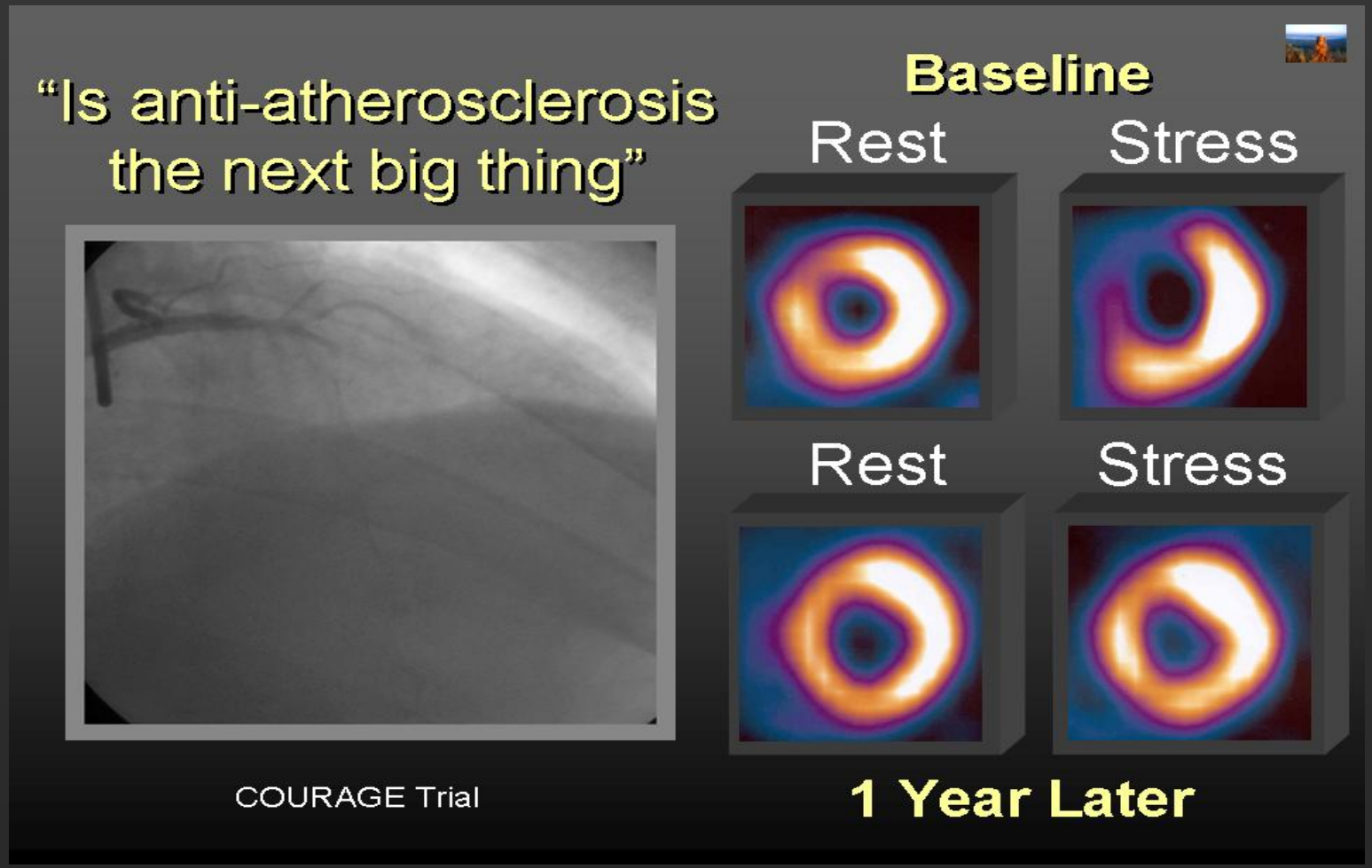
Novel HDL Targeted Therapies: The Search Continues

Assoc. Prof. K.Kostner, Univ. of Qld, Brisbane



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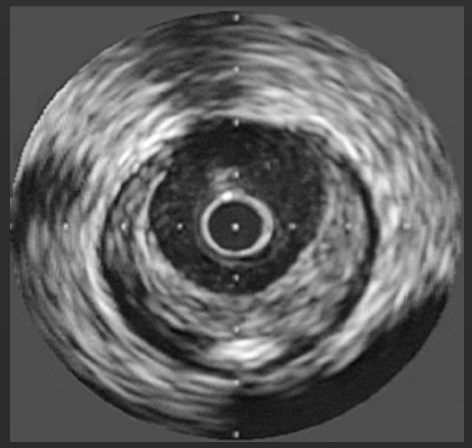
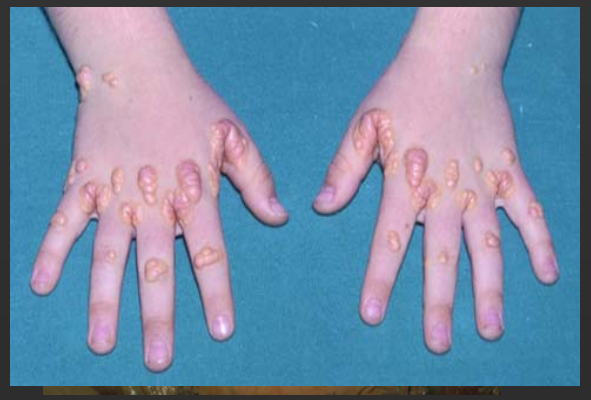
LDL Target depends on your level of Risk

Acute Plaque Rupture ACS (UA/NSTEMI/STEMI)

Stable CAD



Familial HL



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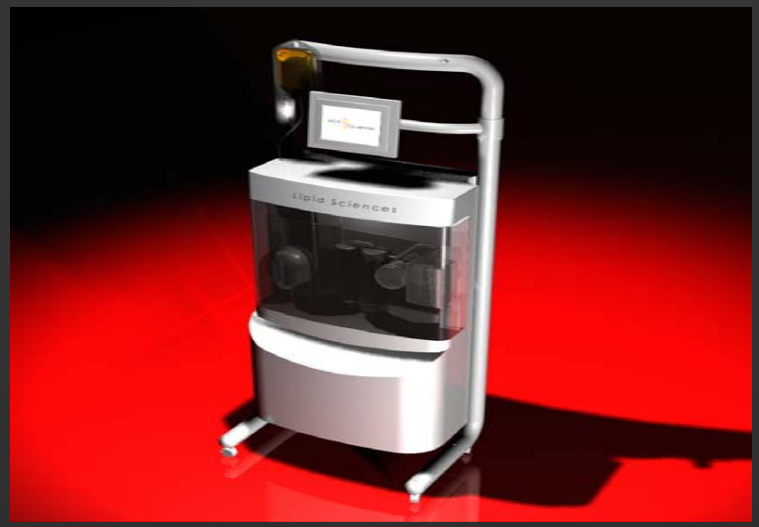
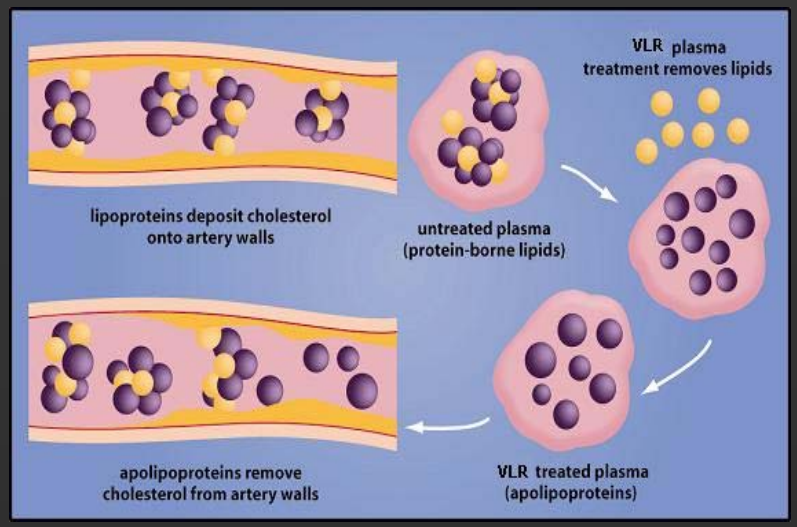
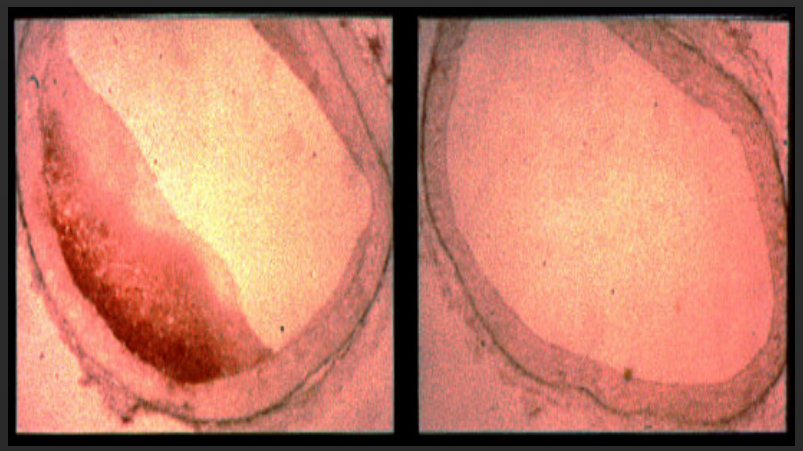
How low can we go?
Cholesterol and TG can be reduced by 99%







Kostner K et al.
JCA. 2005 Oct;20(3):143-53.

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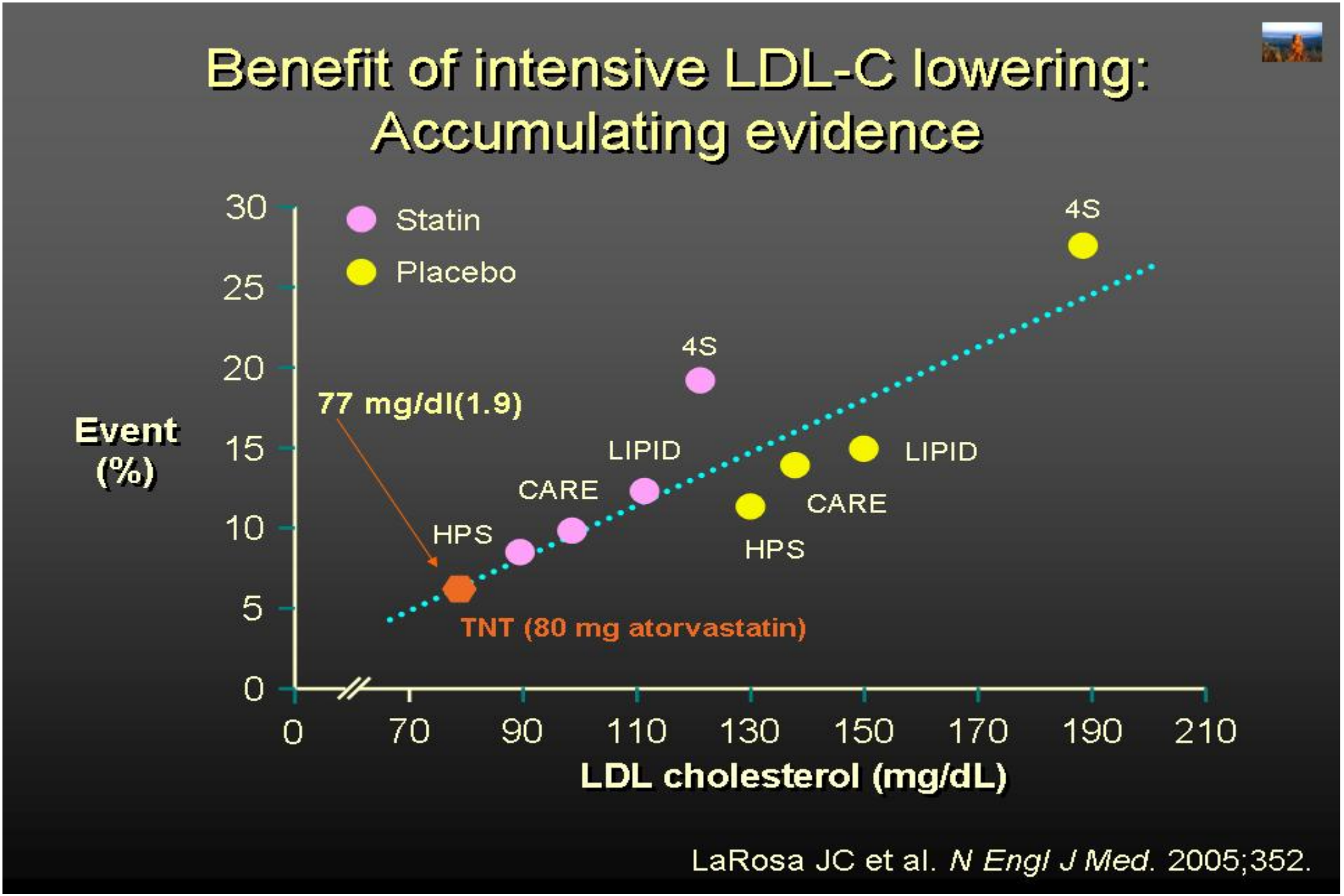
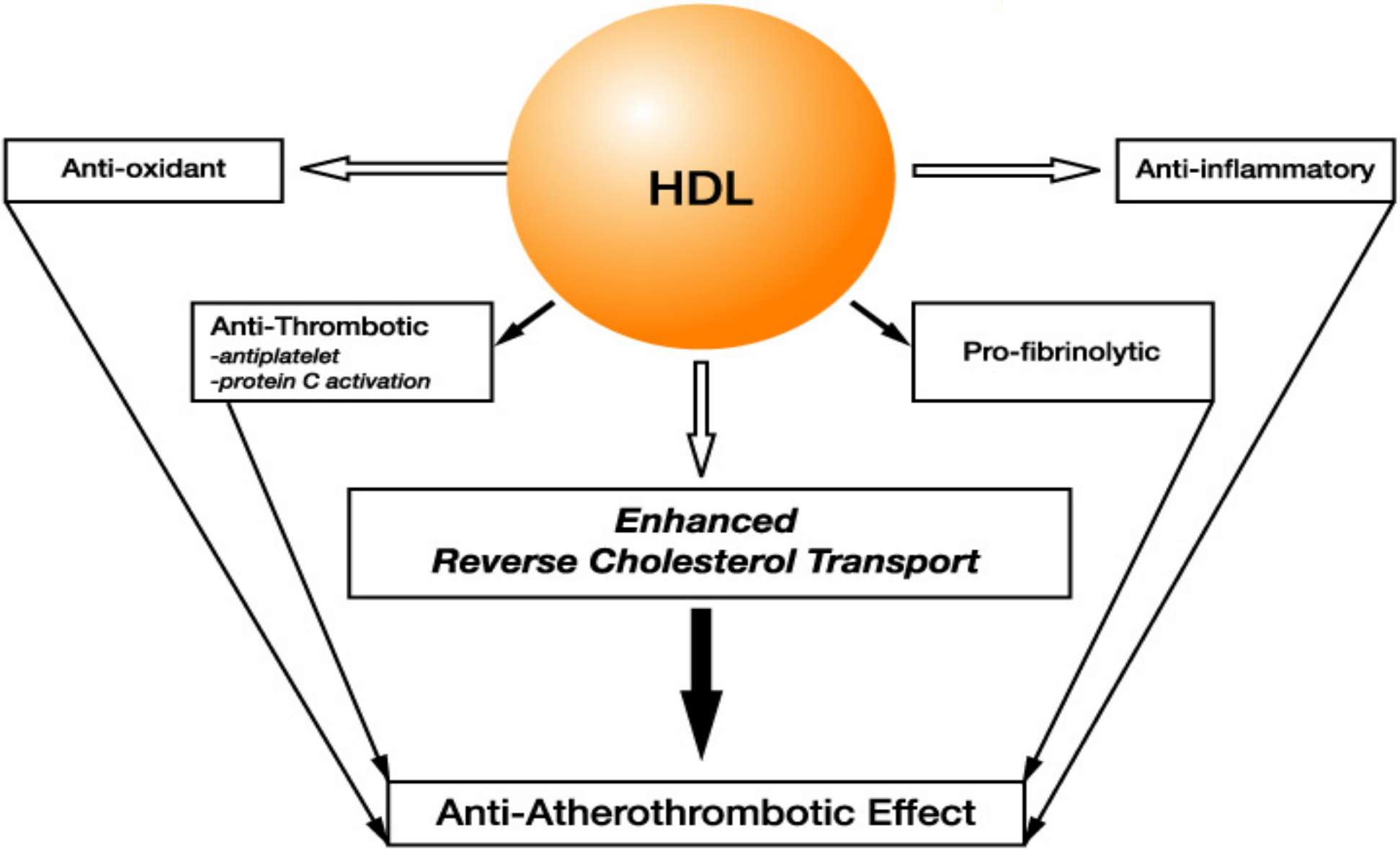
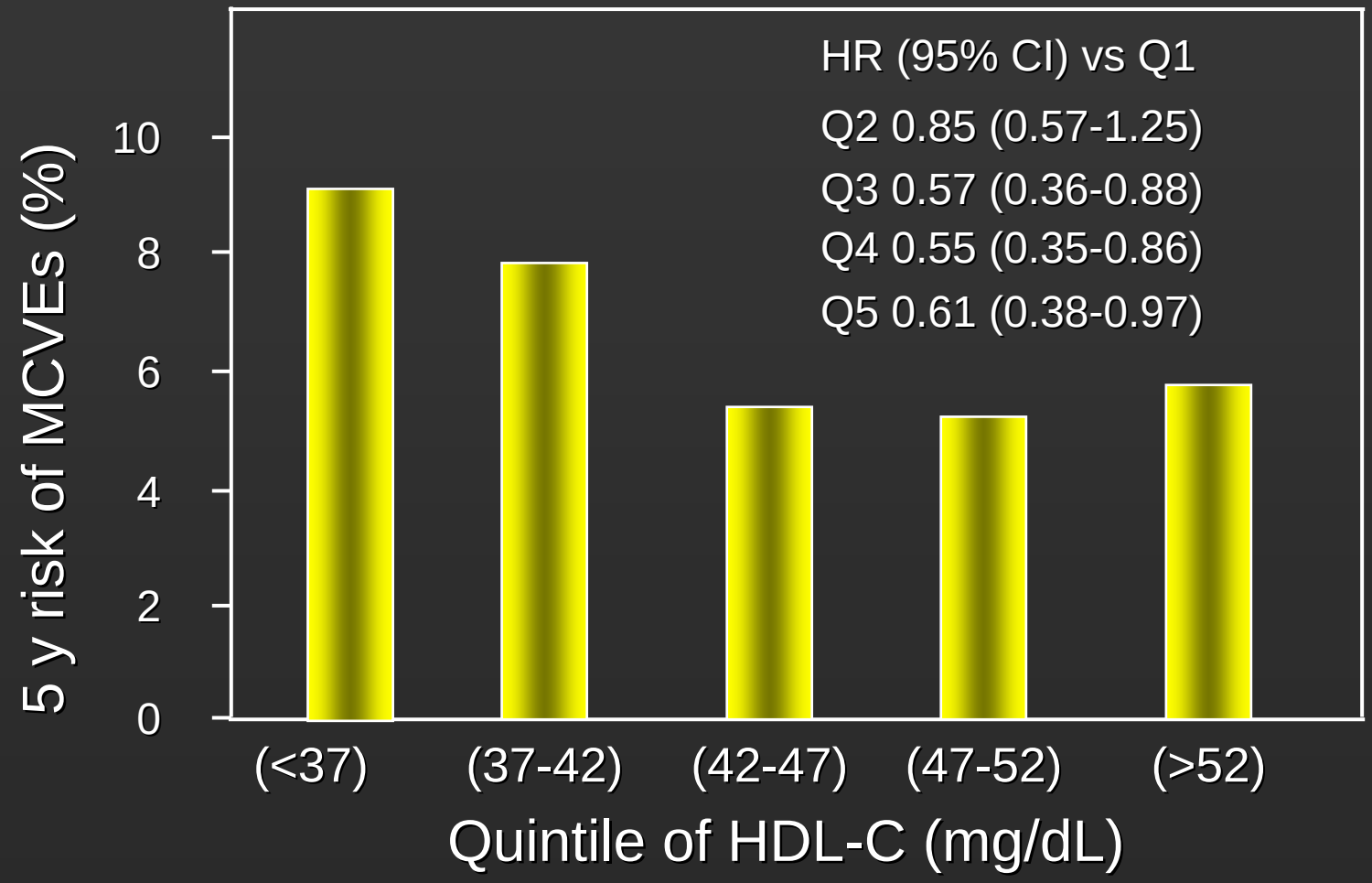
Benefit of intensive LDL-C lowering: Accumulating evidence



LaRosa JC et al. *N Engl J Med*. 2005;352.


HDL
Anti-oxidant
Anti-inflammatory
Anti-Thrombotic
-antiplatelet
-protein C activation
Pro-fibrinolytic
Enhanced
Reverse Cholesterol Transport
Anti-Atherothrombotic Effect

TNT:MCVE Frequency by HDL level in group with LDL-C < 70 mg/dL (Adjusted for baseline LDL)



No of Events	57	50	34	34	35
No of Patients	473	525	550	569	544

Barter et al, NEJM 2007; 357; 13, 1301-1310.

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Primary (Genetic) Causes of Low HDL-C

- ApoA-I
  - Complete apoA-I deficiency
  - ApoA-I mutations (eg, ApoA-I_{Milano})
- LCAT
  - Complete LCAT deficiency
  - Partial LCAT deficiency (fish-eye disease)
- ABC1
  - Tangier disease
    - Homozygous
    - Heterozygous
  - Familial hypoalphalipoproteinemia
  - Familial combined hyperlipidemia with low HDL-C
  - Metabolic syndrome

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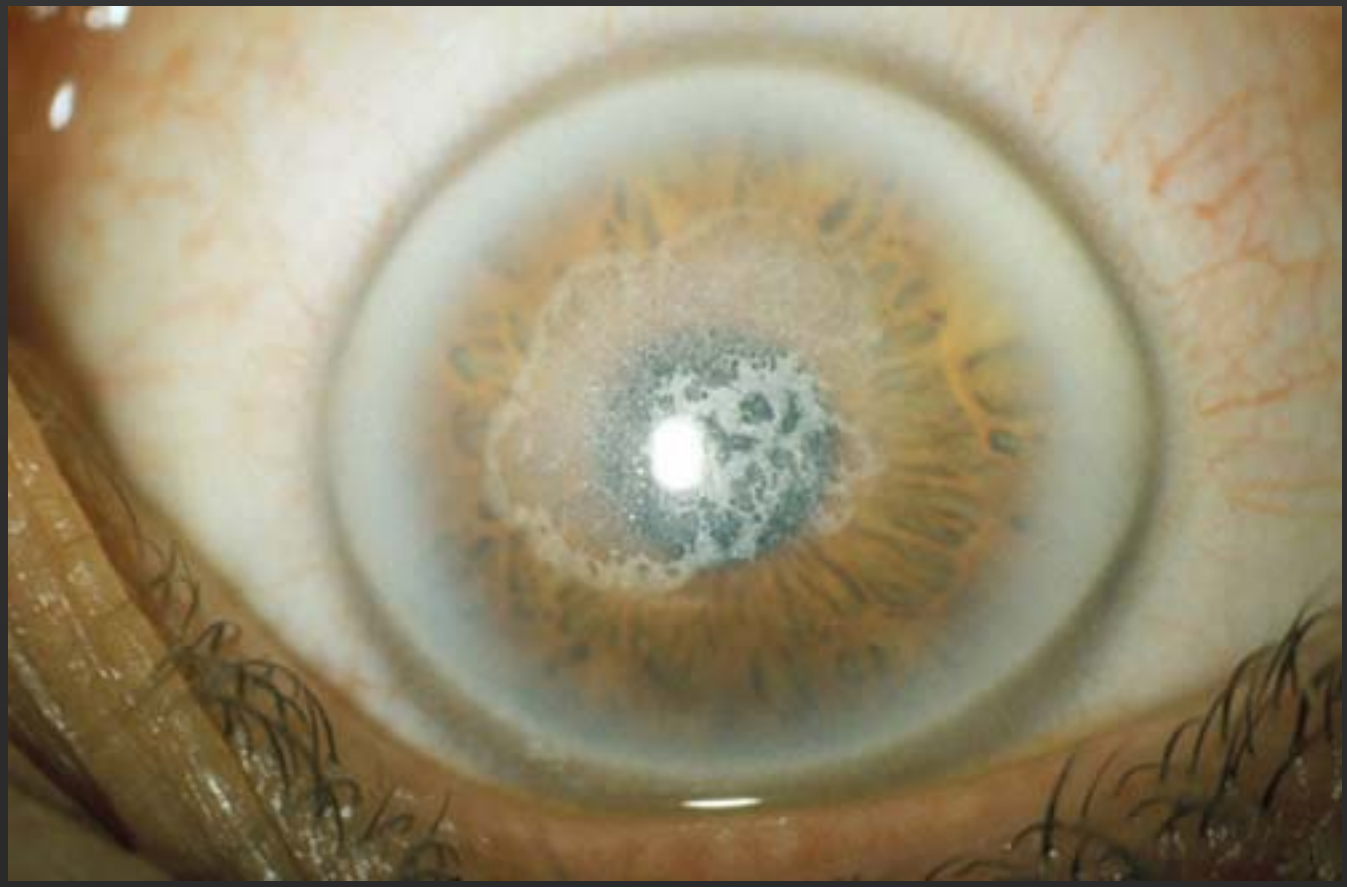

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STRATEGIES FOR RAISING HDL IN HUMANS

Lifestyle

- Weight reduction
- Increased physical activity
- Stop smoking
- ??? alcohol

Drugs

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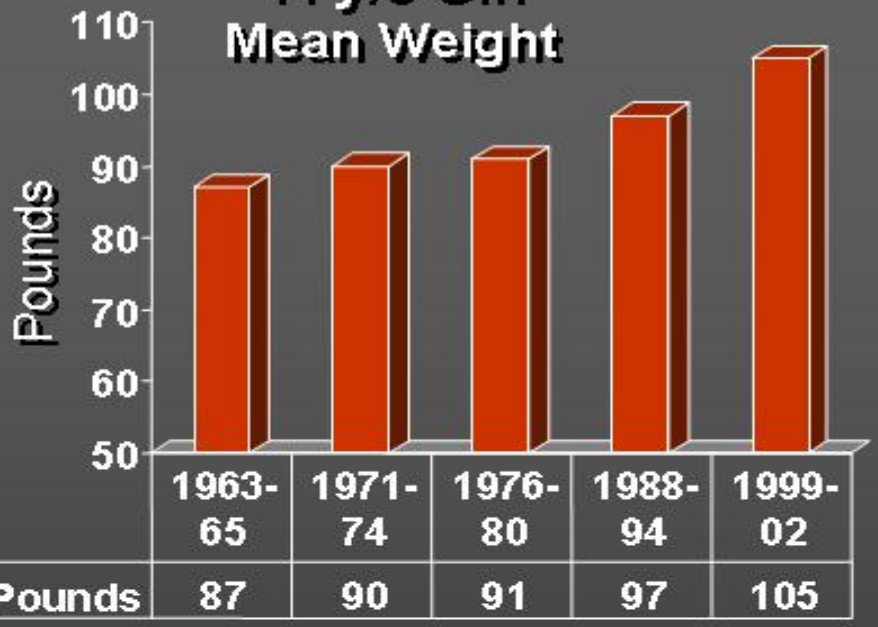
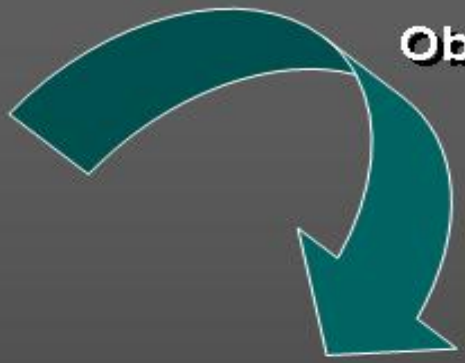
11 y/o Girl Mean Weight



	1963-65	1971-74	1976-80	1988-94	1999-02
Pounds	87	90	91	97	105



Metabolic Syndrome

CV Disease & Microvascular Disease

	Control	Pre CR	CR 1 yr
BMI	25.9	24.5	19.6
LDL	127(3.2)	122	86(2.2)
HDL	48(1.2)	43	63(1.6)
Tg	147	149	48
SBP	129	132	99
DBP	79	80	61
hsCRP	1.6	1.7	0.3

CD Advance Data No.347 + October 27,2004

PNAS April 27, 2004;101:6659

Effects of Lipid-Modifying Drugs on HDL-C Levels

Niacin	↑ 15–35%
Fibrates	↑ 10–15%
Estrogens	↑ 10–15%
Statins	↑ 5–10%

Belalcazar LM et al. *Progr Cardiovasc Dis* 1998;41:151–174

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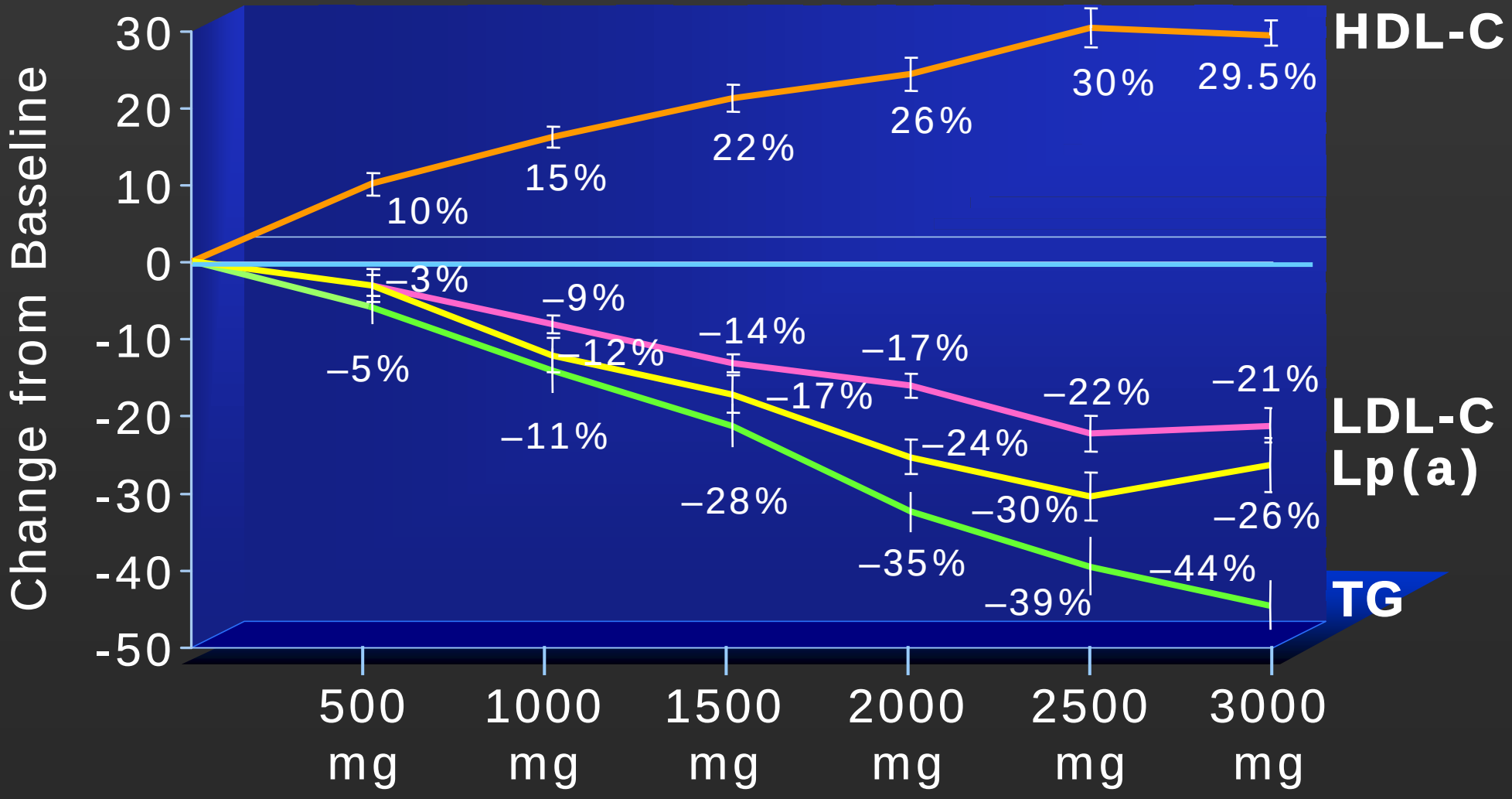
Extended-Release Niacin: The Lipid Poly Pill



Goldberg A et al. *Am J Cardiol* 2000;85:1100-1105.

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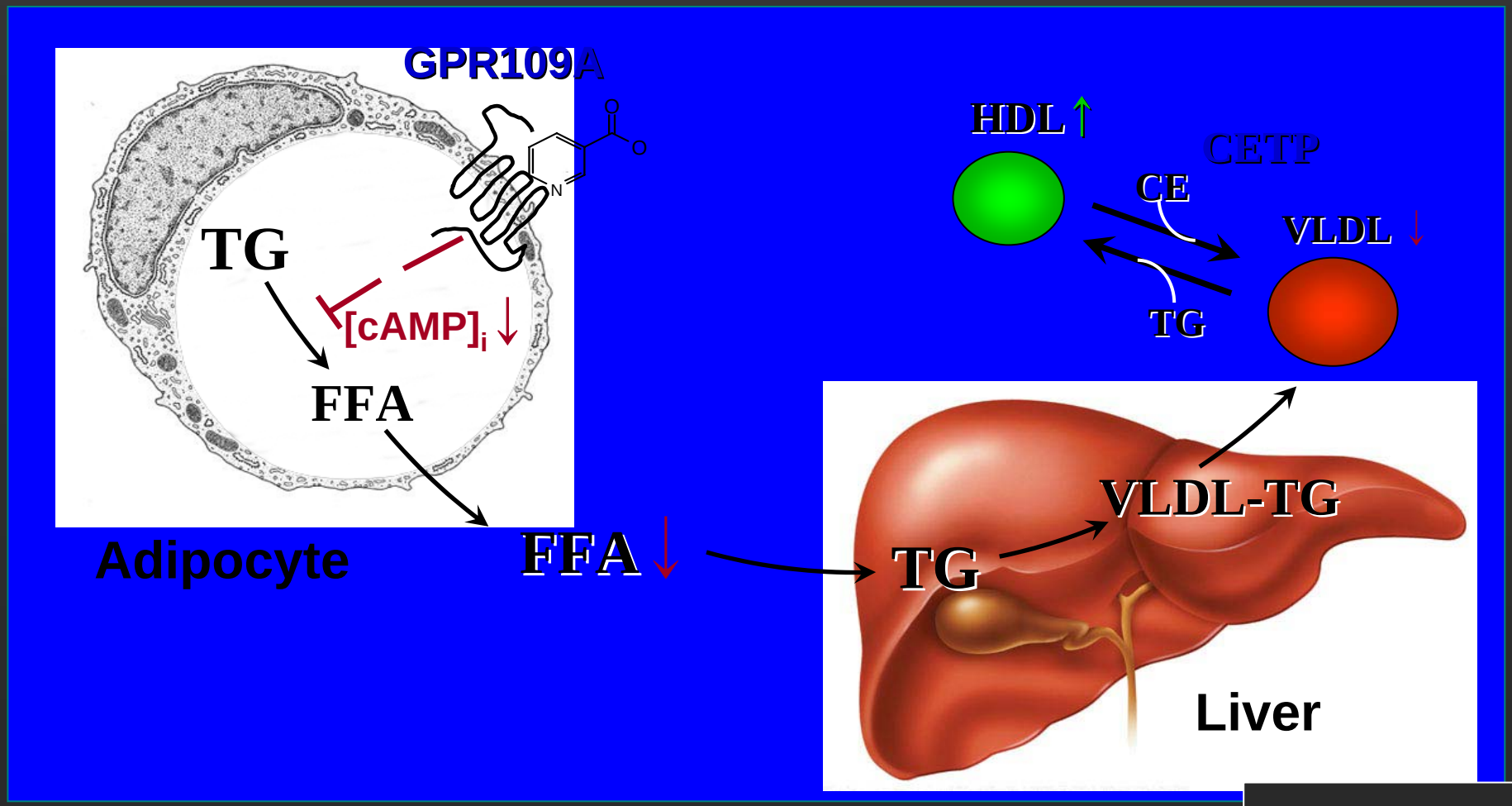
A Working Hypothesis for Niacin-Induced HDL Elevation



Adapted from Soudijn et al. Med Res Rev. 2007; 27(3):417-33.

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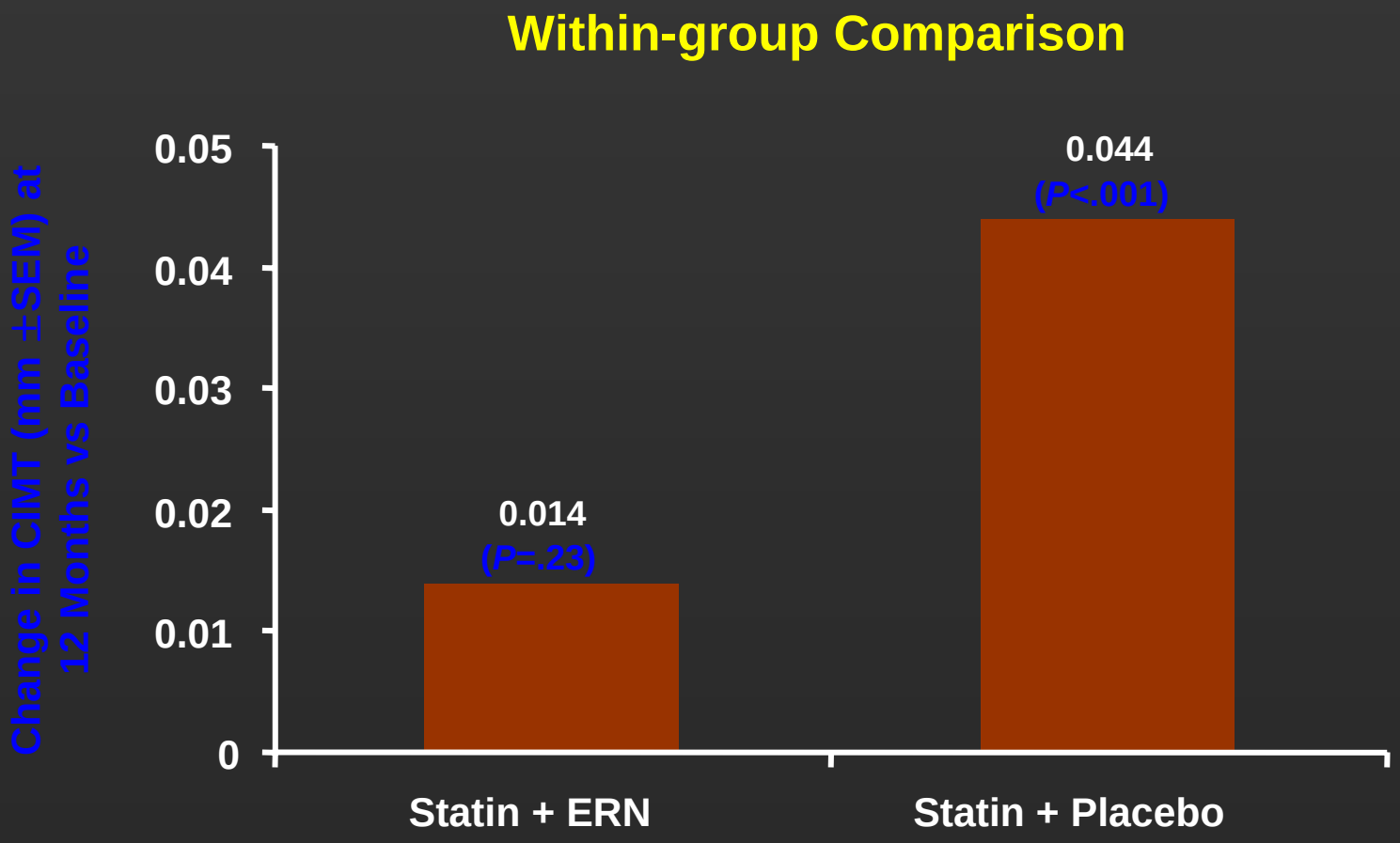
Niacin and Atherosclerosis: A Positive Effect on Clinical Outcomes

Trial (reference)	Treatment (mean dose)	Number of participants		Change in lipids in treatment group				Findings
		Treatment	Placebo	T-C	TG	LDL-C	HDL-C	
CLAS [17]	Niacin (4.3 g/day) + colestipol (30 g/day)	80	82	↓26%	↓21%	↓43%	↑37%	Significant angiographic regression No differences in clinical events
FATS [18]	Niacin (4 g/day) + colestipol (30 g/day)	48	52	↓23%	↓29%	↓32%	↑43%	Significant angiographic regression ↓80% Clinical events[a] ($P < 0.01$)
HATS [19]	Niacin (2.4 g/day) + simvastatin (13 mg/day)	73	73	↓29%	↓34%	↓40%	↑18%	Significant angiographic regression ↓60% Clinical events[a] ($P = 0.02$)
Stockholm [23]	Niacin (4.5 g/day) + clofibrate (1.5 g/day)	279	276	↓13%	↓19%	NR	NR	↓36% ischemic heart disease mortality ($P < 0.01$) ↓26% Total mortality ($P < 0.05$)
CDP [2,3]	Niacin (3 g/day)	1119	2789	↓10%	↓26%	NR	NR	↓27% Non-fatal myocardial infarction ($z = -2.88$) ↓11% Total mortality ($P = 0.0004$)

T-C, total cholesterol; TG, triglyceride; CLAS, Cholesterol-Lowering Atherosclerosis Study; FATS, Familial Atherosclerosis Treatment Study; HATS, HDL Atherosclerosis Treatment Study; CDP, Coronary Drug Project; NR, not recorded. [a]Coronary death, stroke, revascularization, myocardial infarction, worsening ischemia.

ARBITER 2:
Carotid Intima Media Thickness



Between-group comparison *P*=.08.
Intent-to-treat analysis of placebo > extended-release niacin, *P*=.048.

Taylor AJ et al. *Circulation*. 2004;110:3512-3517.

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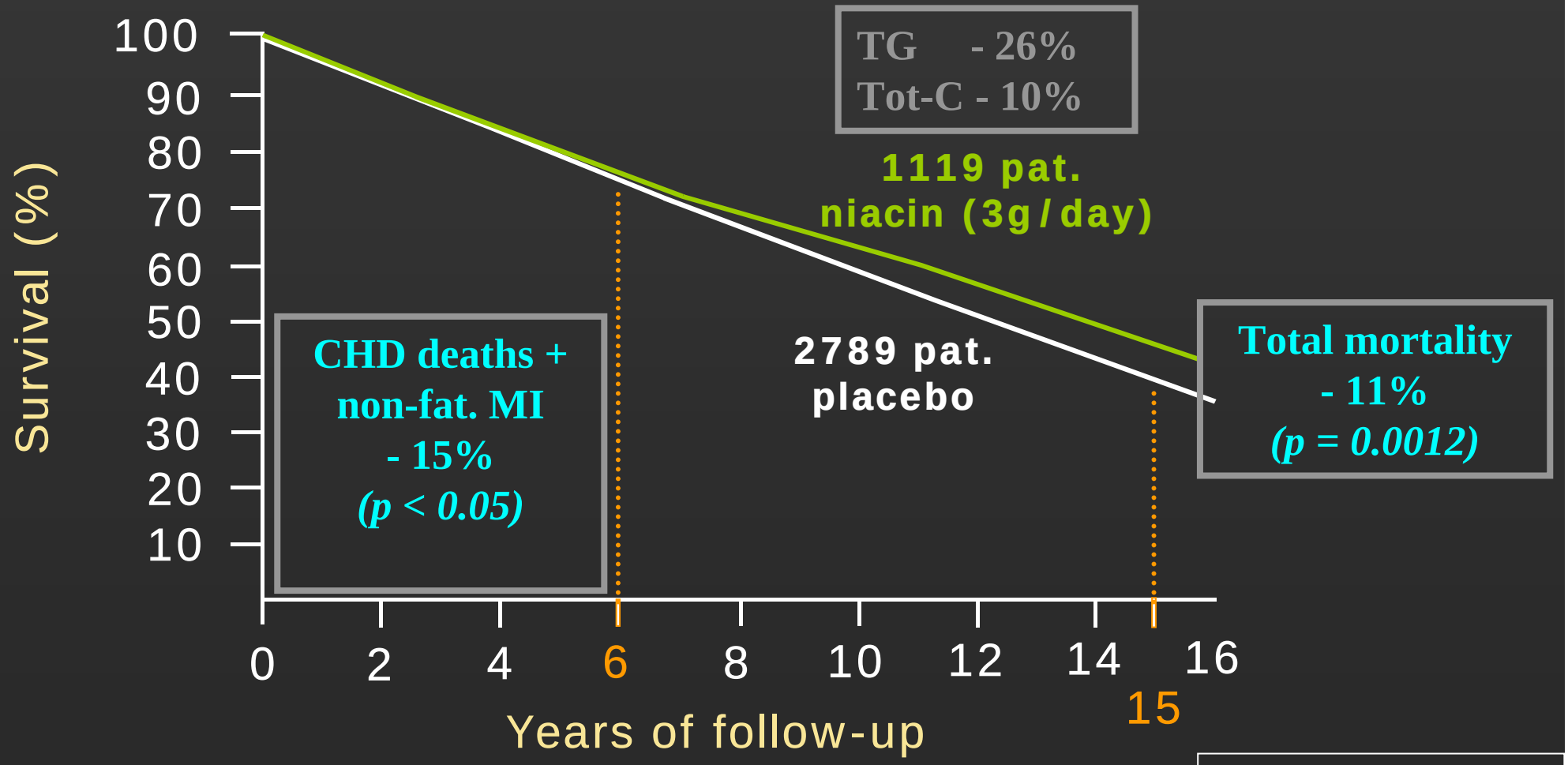
Coronary Drug Project

Long-Term Mortality Benefit of Niacin in Post-MI Patients (8341 men)



Canner PL et al. J Am Coll Cardiol 1986;8:1245–1255

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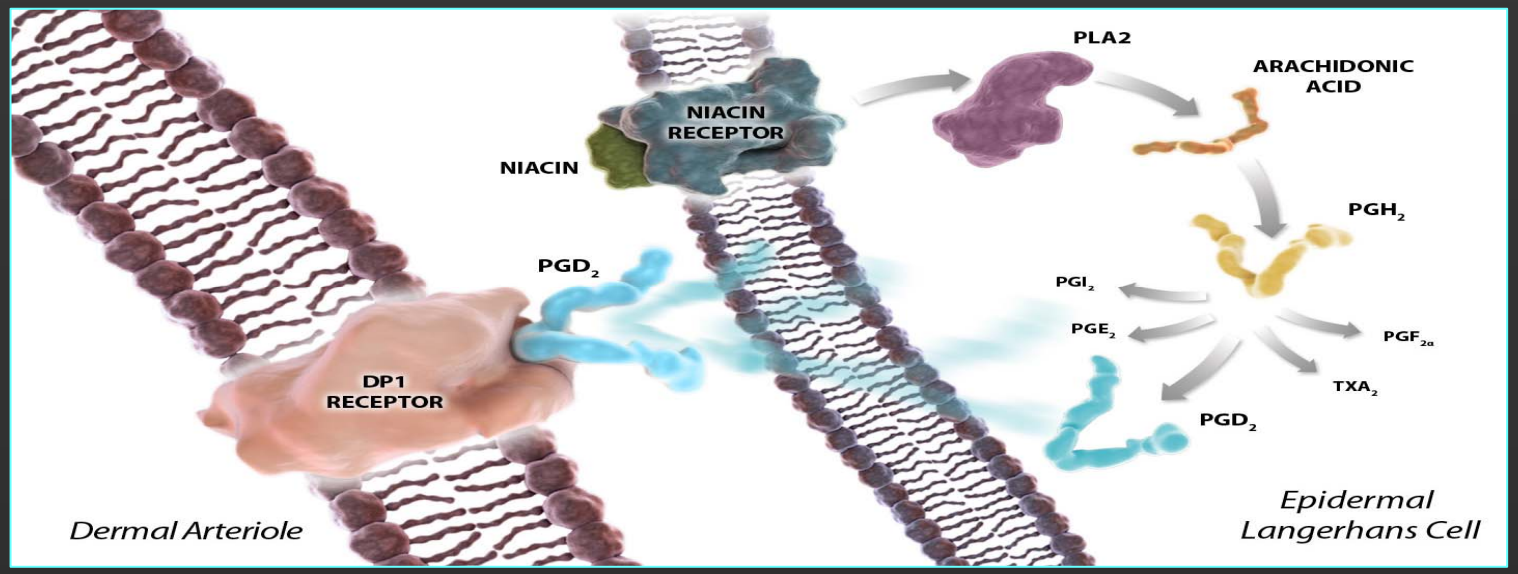
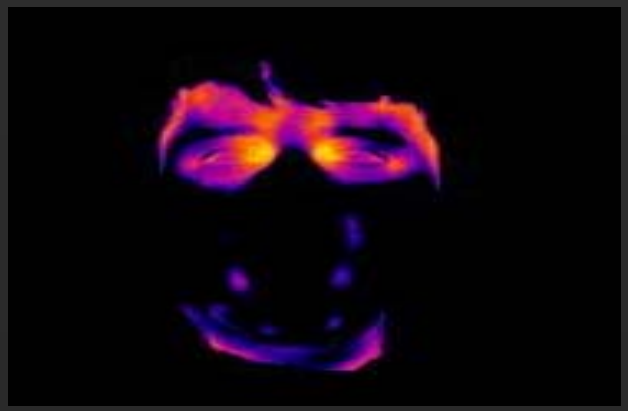
Nicotinic Acid Receptor (GPR109A): Locations and Effects





+ 300 mg niacin

1. Cheng K et al. *Proc Natl Acad Sci U S A.* 2006;103:6682–6687.
2. Narumiya S et al. *Physiol Rev.* 1999;79:1193–1226.
3. Maciejewski-Lenoir D et al. *J Invest Dermatol.* 2006;126:2637–2646.

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Properties of Laropiprant (MK-0524)

- Potent antagonist of DP_1 (not DP_2).
- Blocks PGD_2 binding without inhibiting PGD_2 synthesis
  - Functional potency at the platelet thromboxane A_2 receptor (TP) IC_{50} 770 nM; at 40 mg dose no evidence of meaningful inhibition of platelet aggregation.
- At relevant systemic exposures, preclinical program did not reveal significant toxicities attributable to laropiprant
- In phase I and II studies, tested at doses up to 900 in single and 450 mg in multiple dose studies and up to 150 mg with niacin for up to 11 months and was well-tolerated

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Phase III Data: ESC 9-07

- Purpose:
  - To evaluate the lipid-altering efficacy and flushing profile of ERN/LRPT administered as monotherapy
  - or added to ongoing statin therapy in patients with primary hypercholesterolemia or mixed dyslipidemia.

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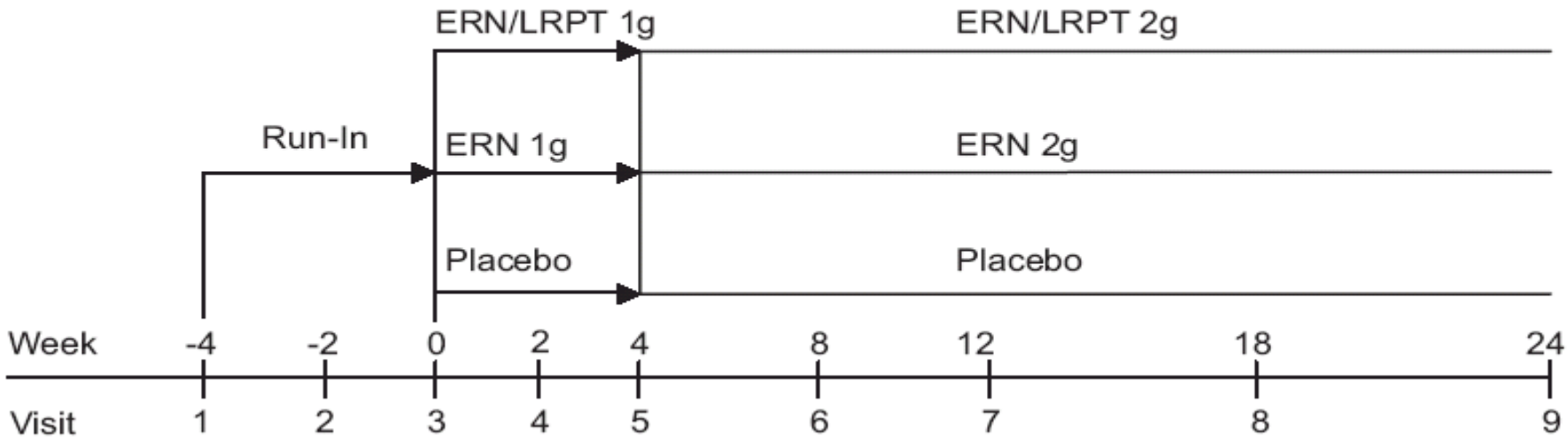
Study Design

This was a worldwide, multicenter, double-blind, randomized, placebo-controlled, parallel study with a 24-week double-blind treatment period. Endpoints: lipids, flushing and safety

Figure 1. Study Design



- Patients were randomized to ERN/LRPT 1g, ERN 1g or placebo in a 3:2:1 ratio (stratified by on-going statin use and study site).
- After 4 weeks, the active treatment doses were doubled, increasing the ERN/LRPT doses to 2g/40 mg (designated ERN/LRPT 2g) and ERN dose to 2g

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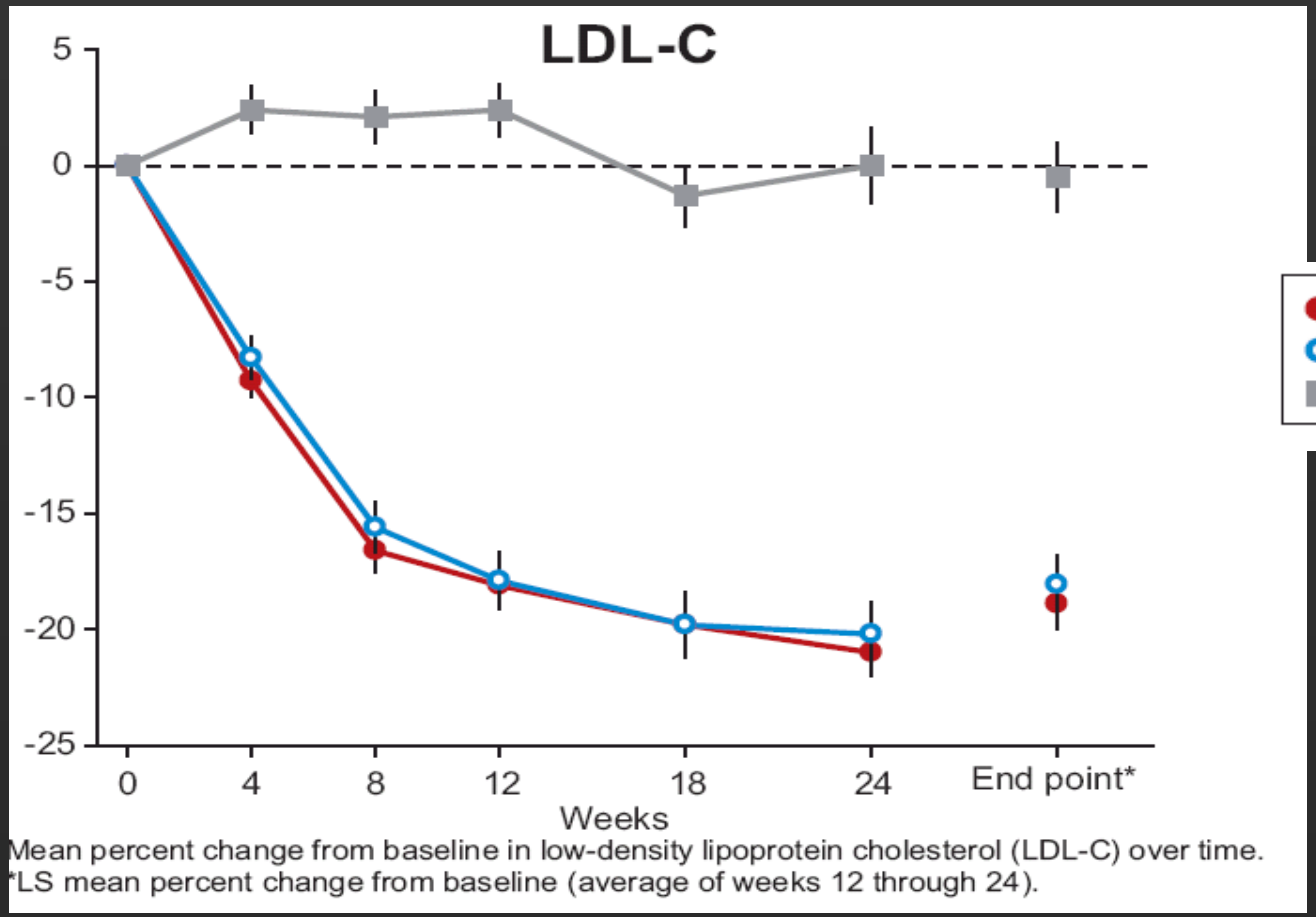
Results (Lipid Efficacy)

- ERN/LRPT 2g produced significantly ($p<0.001$) greater % reductions from baseline in LDL-C relative to placebo across weeks 12 to 24



Mean percent change from baseline in low-density lipoprotein cholesterol (LDL-C) over time.
*LS mean percent change from baseline (average of weeks 12 through 24).

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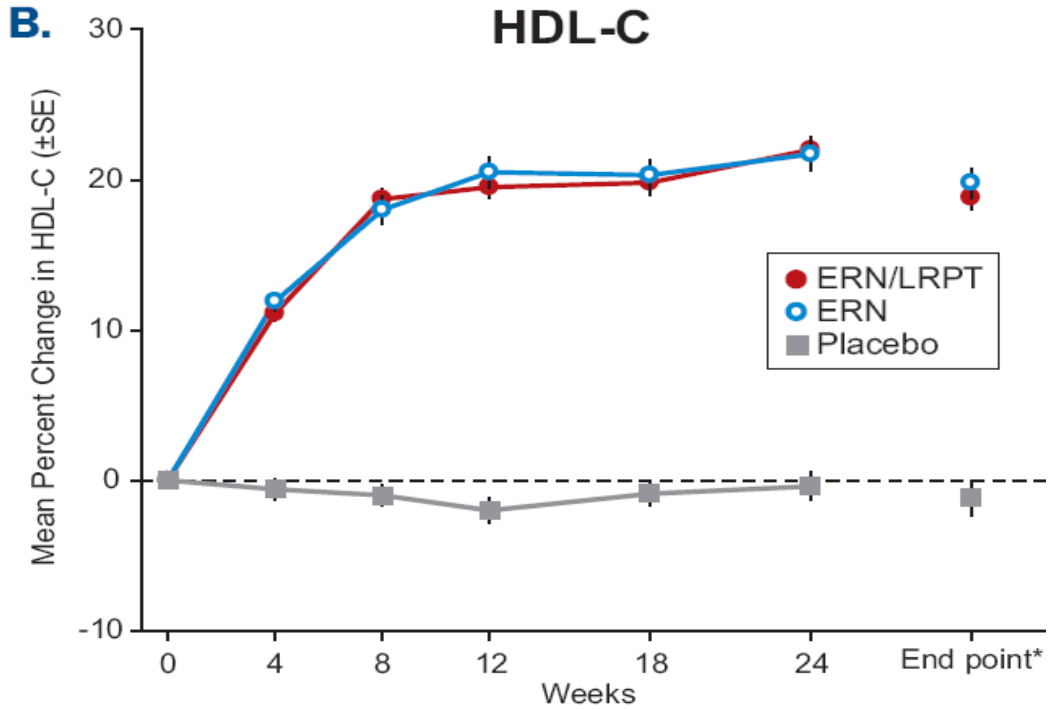
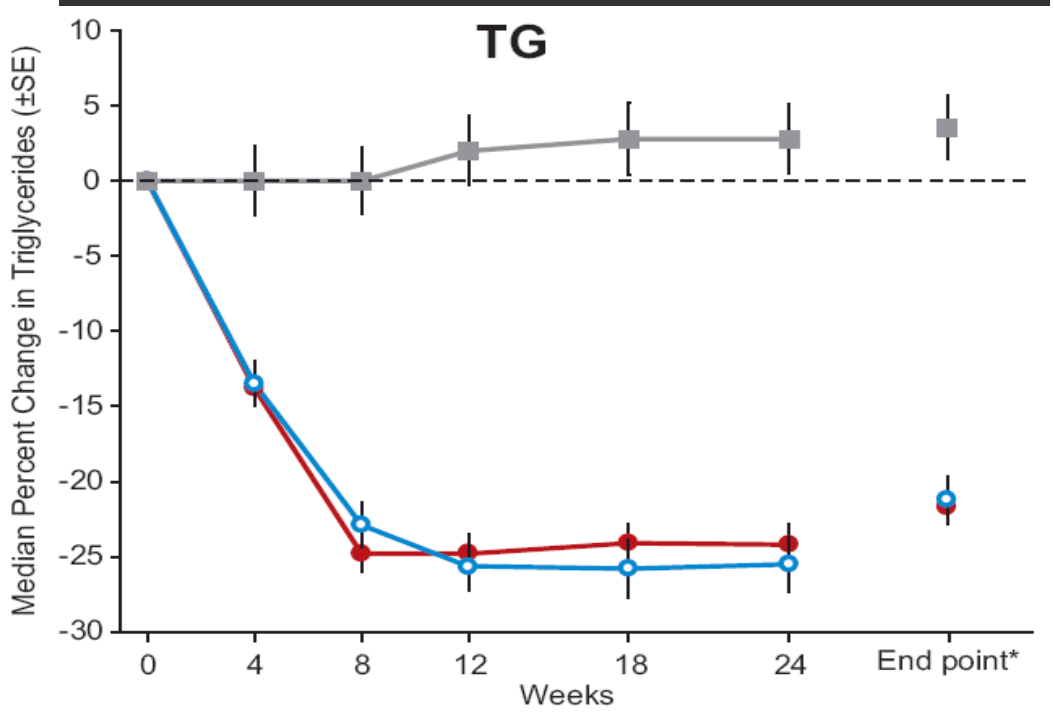
Results (Lipid Efficacy)

ERN/LRPT 2g produced significantly ($p<0.001$) greater % changes from baseline in HDL-C & TG.



Mean percent change from baseline in high-density lipoprotein cholesterol (HDL-C)
*LS mean percent change from baseline (average of weeks 12 through 24).



Median percent change from baseline in triglycerides (TG) over time.
*Median percent change from baseline (average of weeks 12 through 24).

Efficacy of ERN/LRPT 2g was similar when administered alone or when added to ongoing statin therapy.

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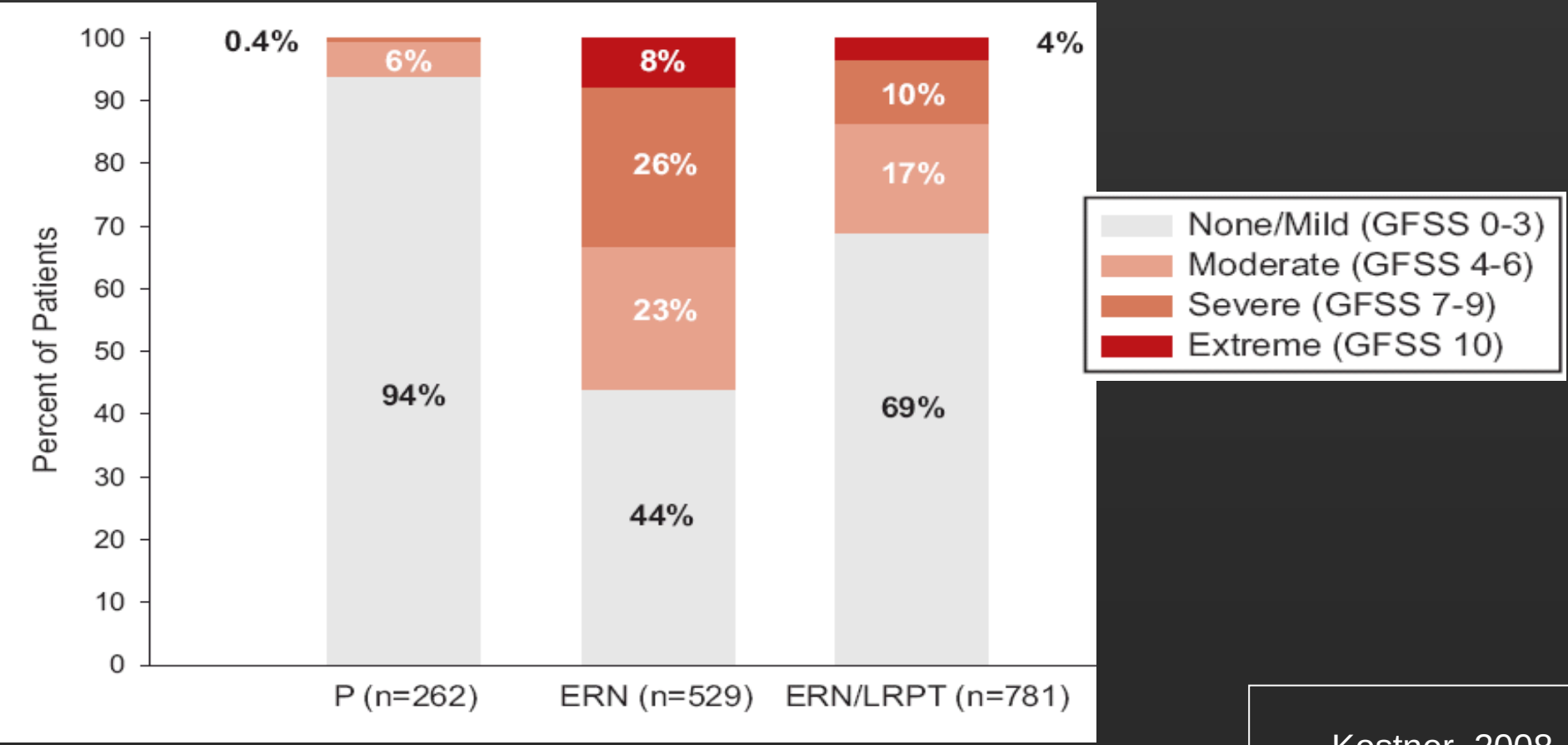
Results (Flushing Endpoints)

Initiation Phase of Therapy (Week 1):

• Patients treated with ERN/LRPT 1g experienced significantly ($p<0.001$) less flushing compared with patients treated with ERN 1g, as measured by maximum GFSS



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Pooled Safety Profile

- **Methods**
  - Pooled data from 3 active or placebo controlled Phase 3 and 3 phase 2 one year extension studies
  - 4747 patients exposed: ERN/LRPT (n=2548), ERN (1268) Simv/Pbo(931)

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Pooled Safety Profile

Safety Parameter	SIMVA/Pbo N=931	ERN N=1268	ERN/LRPT N=2548
Drug-related* AEs (n [%])	156 (16.8)	501 (39.5)	901 (35.4)[1,2]
Drug-related* serious AEs (n [%])	1 (0.1)	1 (0.1)	8 (0.3)[3,4]
Discontinuations due to drug-related* AEs (n [%])	28 (3.0)	204 (16.1)	328 (12.9)[1,2]
Pre-specified parameters of interest:			
Confirmed adjudicated cardiovascular events (n/N [%])	3/931 (0.3)	5/1268 (0.4)	8/2548 (0.3)[5,6]
Consecutive or presumed consecutive ALT/AST elevations ≥3 x ULN (n/N [%])	8/920 (0.9)	6/1221 (0.5)	25/2465 (1.0)[5,6]
Drug-related hepatitis (n)	0	0	0
Myopathy** (n/N [%])	0	1/1221 (0.08)	1/2465 (0.04)[5,6]
CK elevations ≥10 x ULN (n/N [%])	2/920 (0.2)	2/1221 (0.2)	7/2465 (0.3)[5,6]
New onset diabetes§ (n/N [%])	1/888 (0.1)	3/1094 (0.3)	12/2276 (0.5)[5,6]

AE=adverse events; SIMVA=simvastatin; Pbo=placebo; ERN=extended-release niacin; ERN/LRPT=extended-release niacin/laropiprant; ALT/AST=alanine aminotransferase and/or aspartate aminotransferase; ULN=upper limit of normal; CK=creatine kinase

*Determined to be possibly, probably, or definitely drug-related by the investigator.

**Defined as CK ≥10 x ULN with muscle symptoms and considered drug-related by the investigator.

§Based on clinical AEs and/or change in medication.

[1]95% CI for difference with ERN does not include 0.

[2]95% CI for difference with SIMVA/Pbo does not include 0.

[3]95% CI for difference with ERN includes 0.

[4]95% CI for difference with SIMVA/Pbo includes 0.

[5]Not significantly different from ERN based on exposure-adjusted analysis.

[6]Not significantly different from SIMVA/Pbo based on exposure-adjusted analysis.

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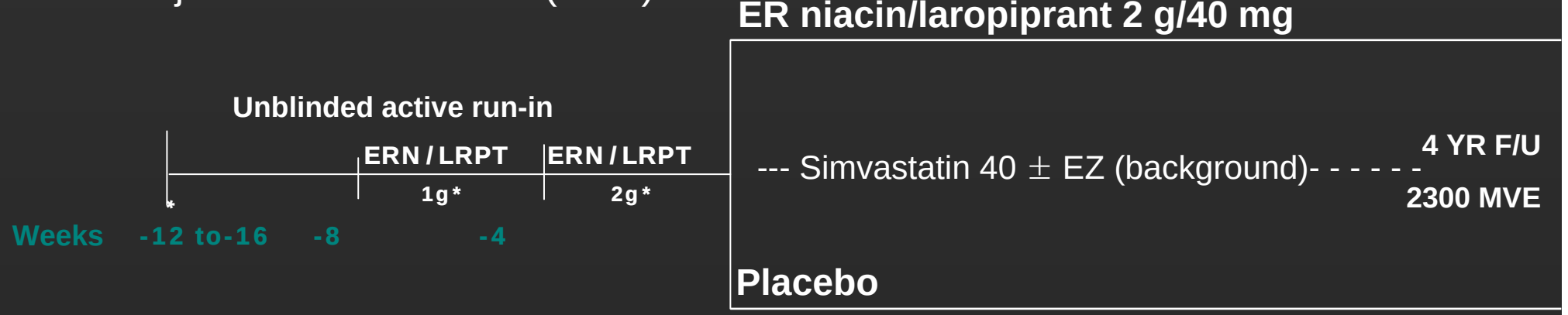
HPS2- THRIVE Study Overview

- Objective:
  - To assess the effect of ER niacin/laropiprant 2 g/40 mg vs placebo on CV events, on a background of simvastatin 40 mg
- Patient Population:
  - 20,000 high risk atherosclerosis patients (a) MI, (b) peripheral or cerebrovascular disease, (c) diabetes + atherosclerotic vascular disease. One third in category (c)
- Primary Study Endpoints:
  - Major vascular events (MVE)



*Patients enter on a background of either simvastatin 40 mg or ezetimibe (EZ)/simvastatin 10/40 mg. ezetimibe/simvastatin 10/40 mg initiated at week -8 if TC levels >3.5 mmol/L (LDL-C 76 mg/dL)

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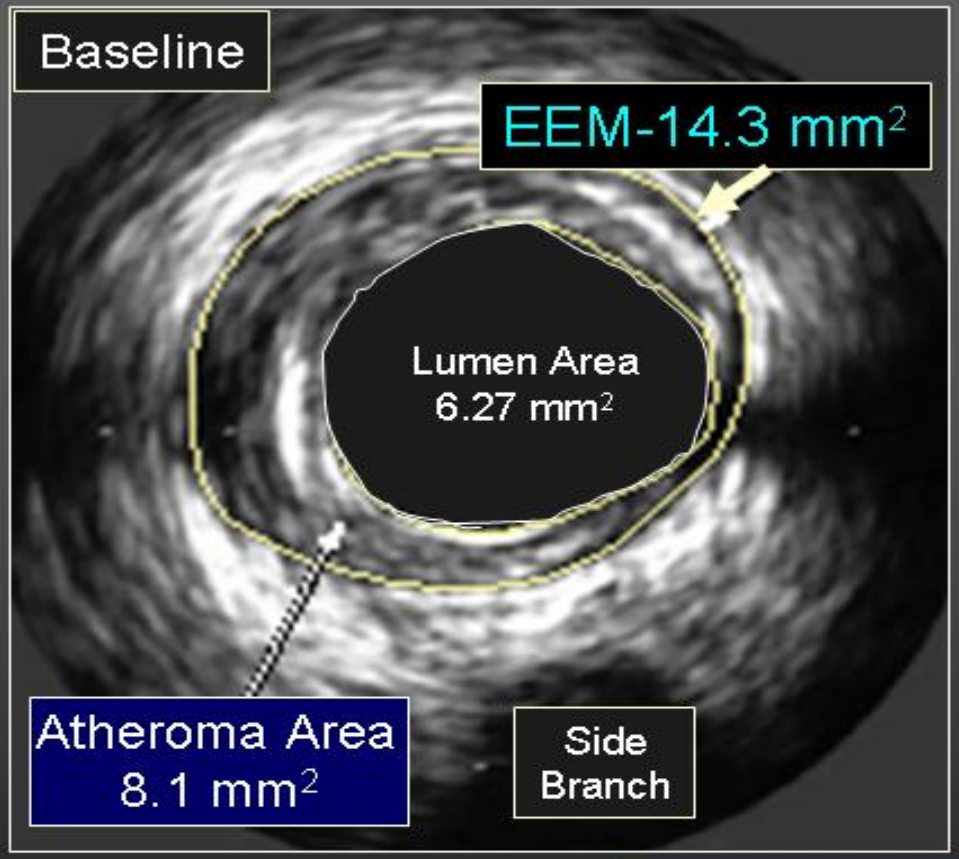
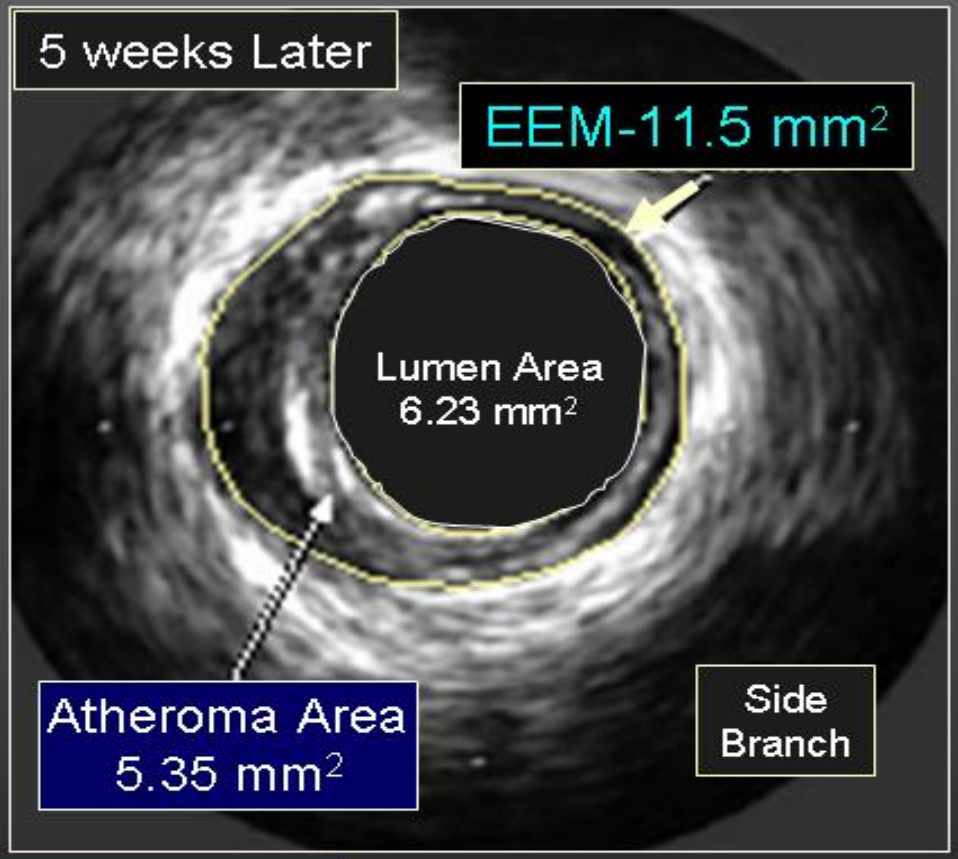
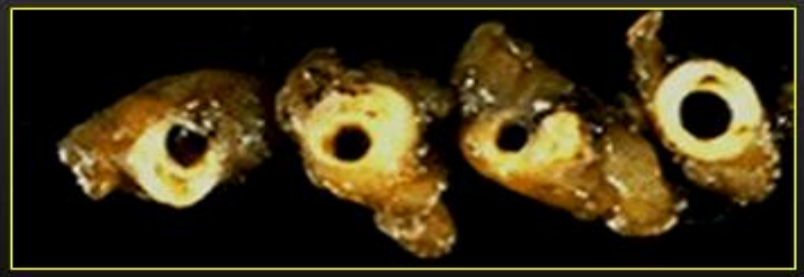
ACS Patients







Apo A-1 Milano
Phospholipid complex

JAMA Nov 5, 2003;290:2292

Anacetrapib

- Anacetrapib is an orally active, potent and selective CETP inhibitor.
- In preclinical models, anacetrapib consistently increased HDL-C concentrations with no observed effects on either blood pressure or heart rate and was well tolerated up to the maximal feasible dose.
- Preliminary studies in healthy subjects showed that single and multiple doses of anacetrapib for 2 weeks produced CETP inhibition and favorable HDL-C,
  LDL-C and apolipoprotein effects, and was generally well tolerated without an effect on blood pressure.

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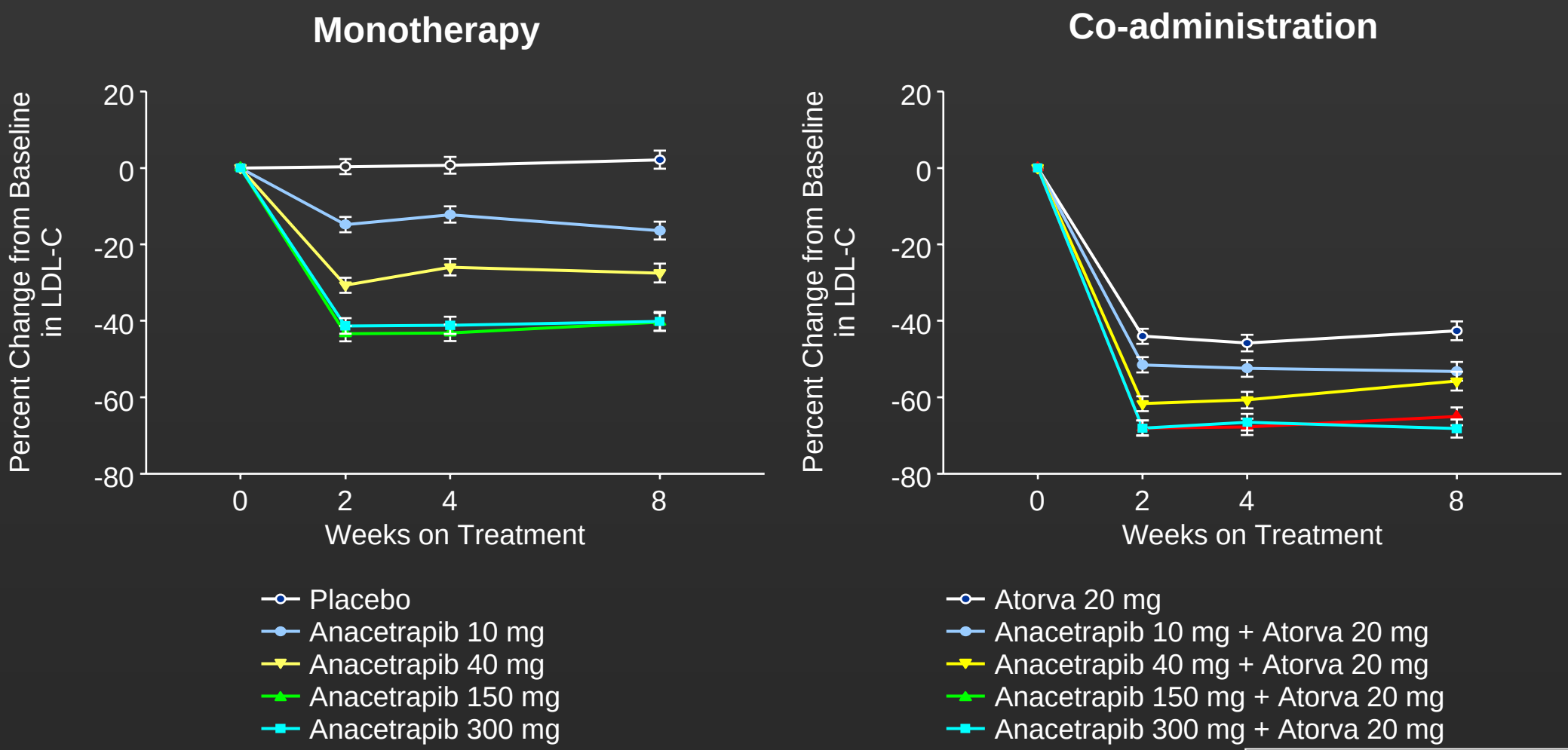
Percent Changes from Baseline in LDL-C



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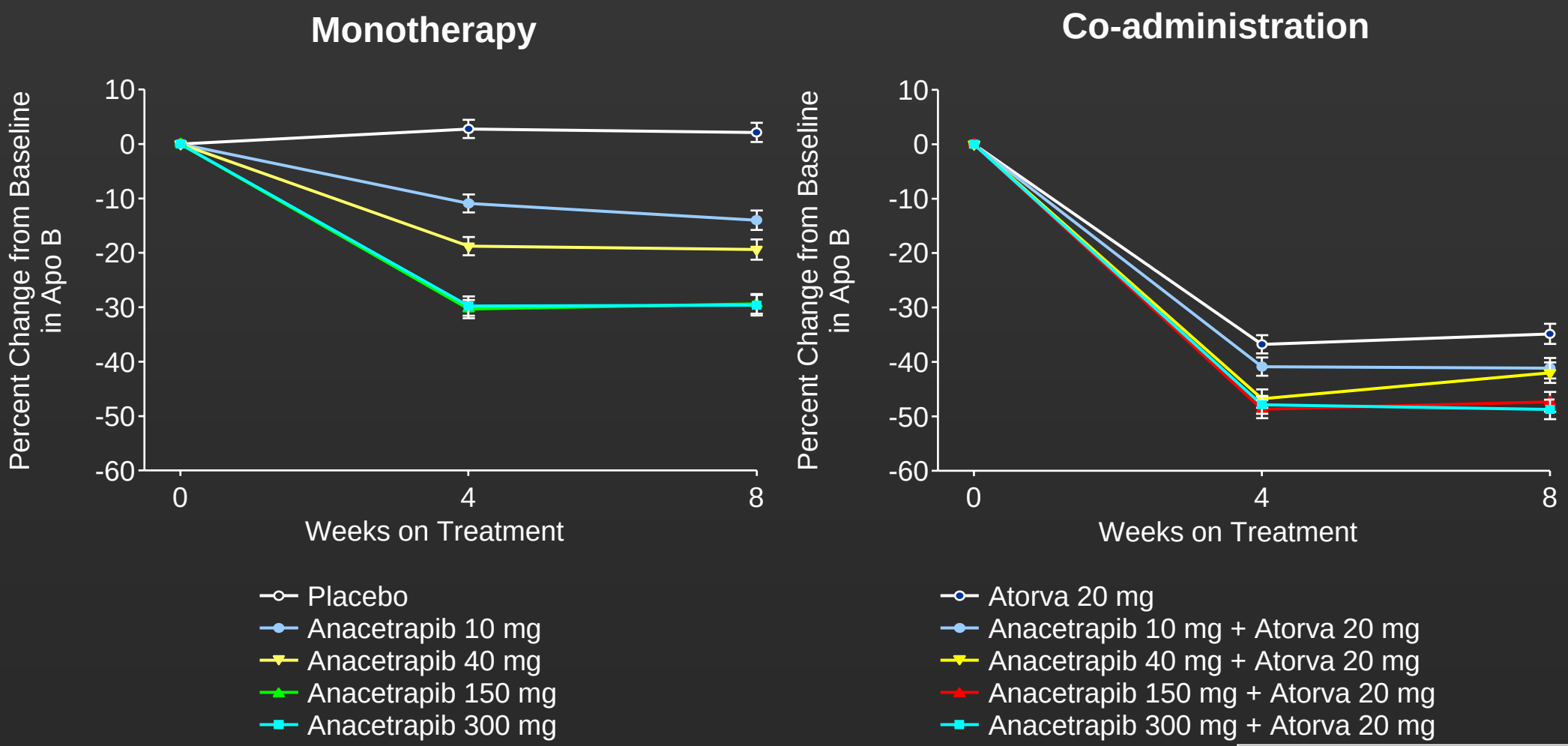
Percent Change from Baseline in Apo B



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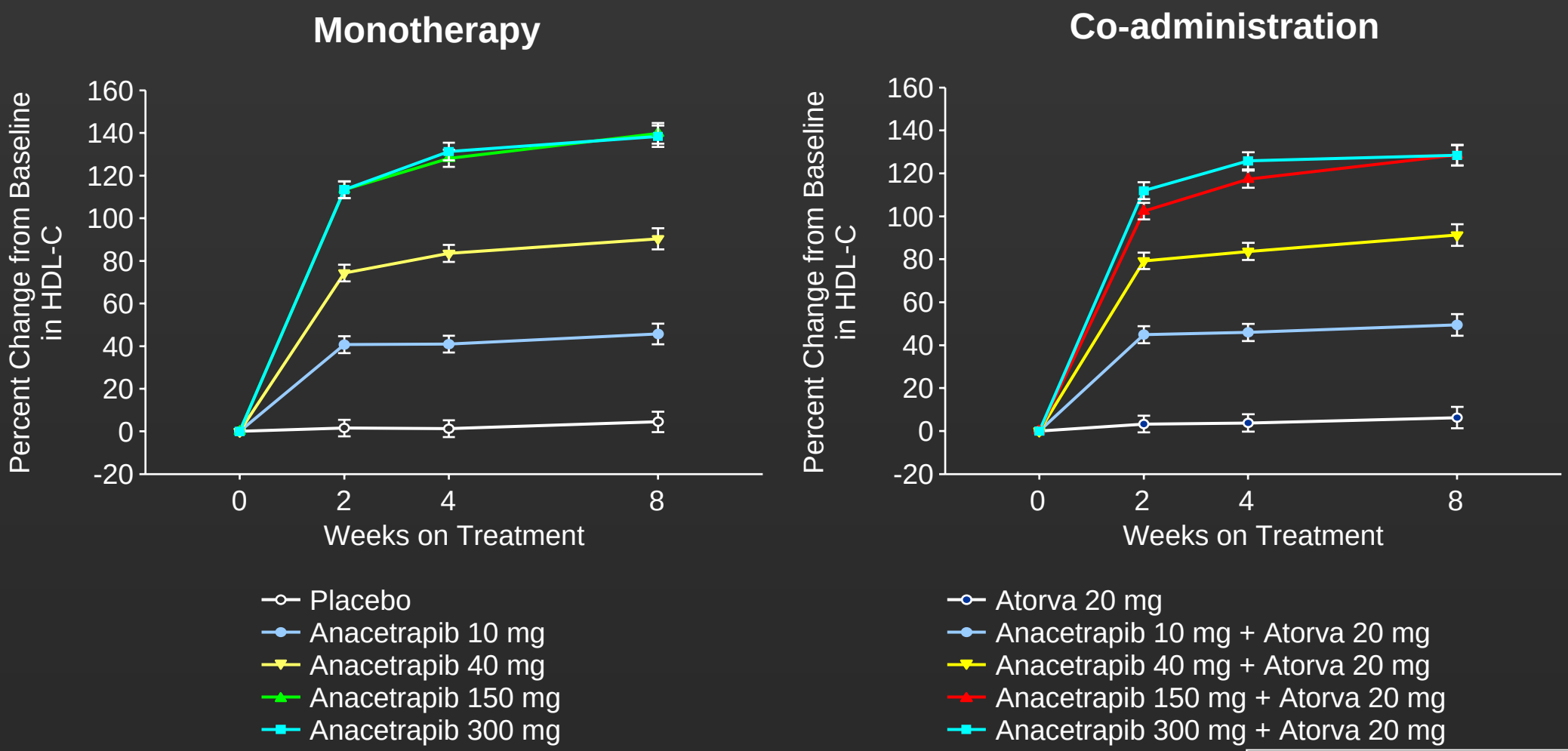
Percent Changes from Baseline in HDL-C



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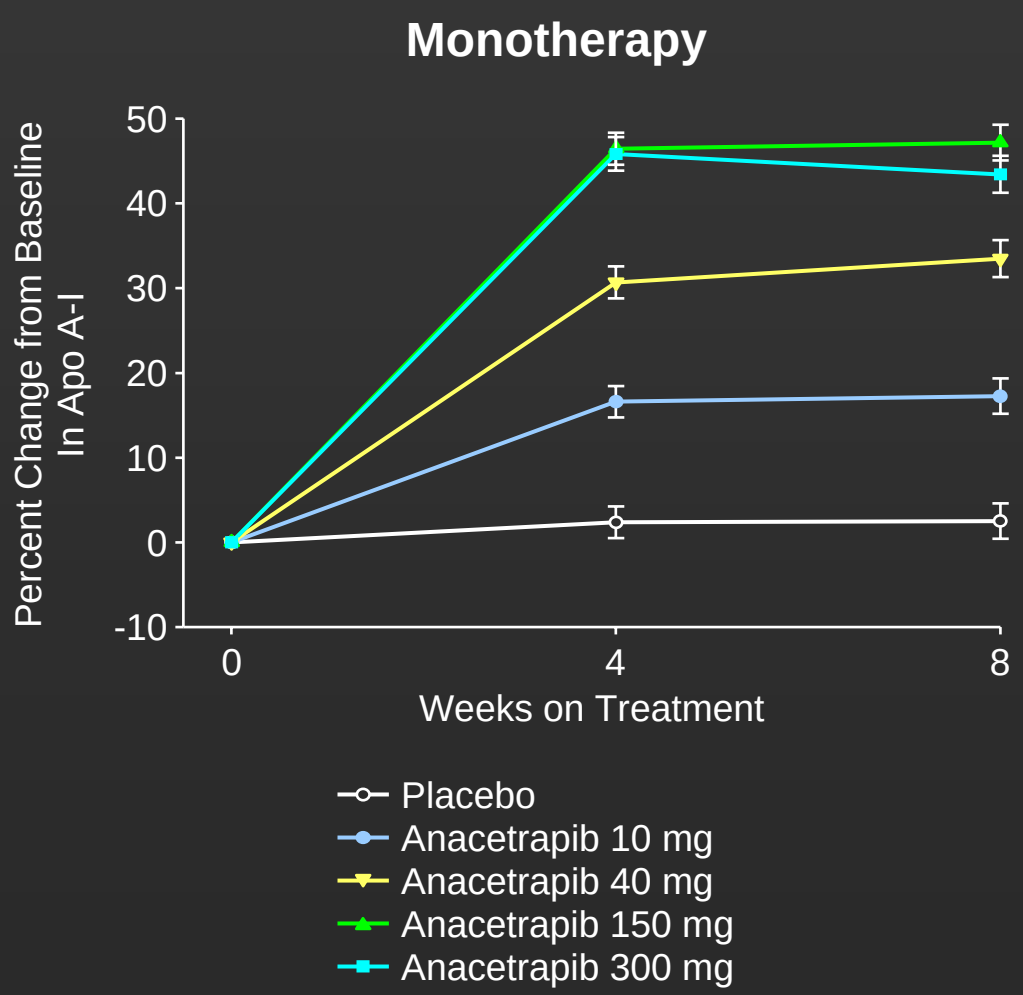
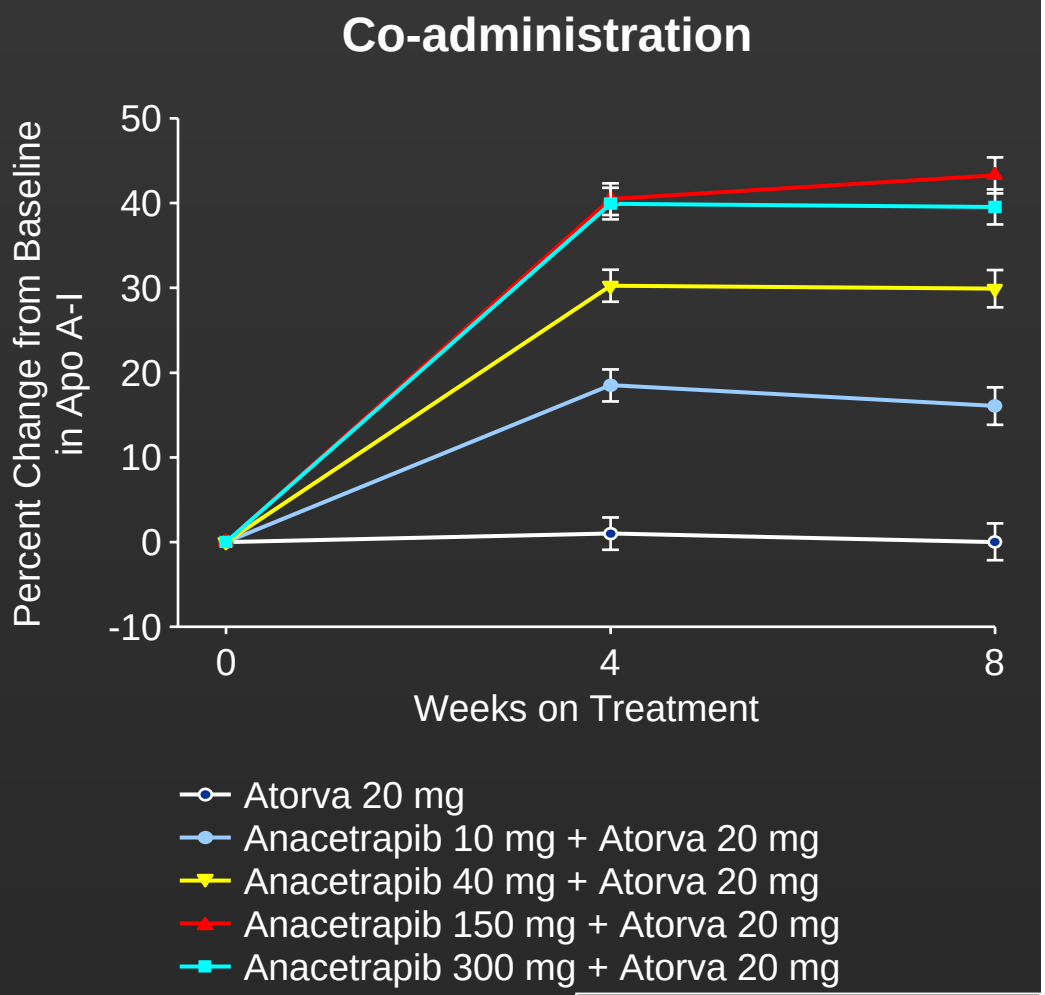
Percent Change from Baseline in Apo A-I





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Safety and Tolerability

- Anacetrapib as monotherapy and co-administered with atorvastatin was generally well tolerated.
- The incidences for all AE categories were similar across pooled treatment groups, with no dose response relationships.
- Most treatment-related AEs were mild or moderate, with constipation, diarrhea, dyspepsia and myalgia being the most common.
- There were no treatment-related serious AEs or deaths.
- Treatment-related discontinuations were rare and no patient discontinued due to serious treatment-related AEs.
- There were sparse and non-dose-related incidences of clinically important elevations in ALT, AST and CK.
- There were no hepatitis-related AEs, myopathy (unexplained muscle symptoms and CK elevations > 10 x upper limit of normal) or rhabdomyolysis.

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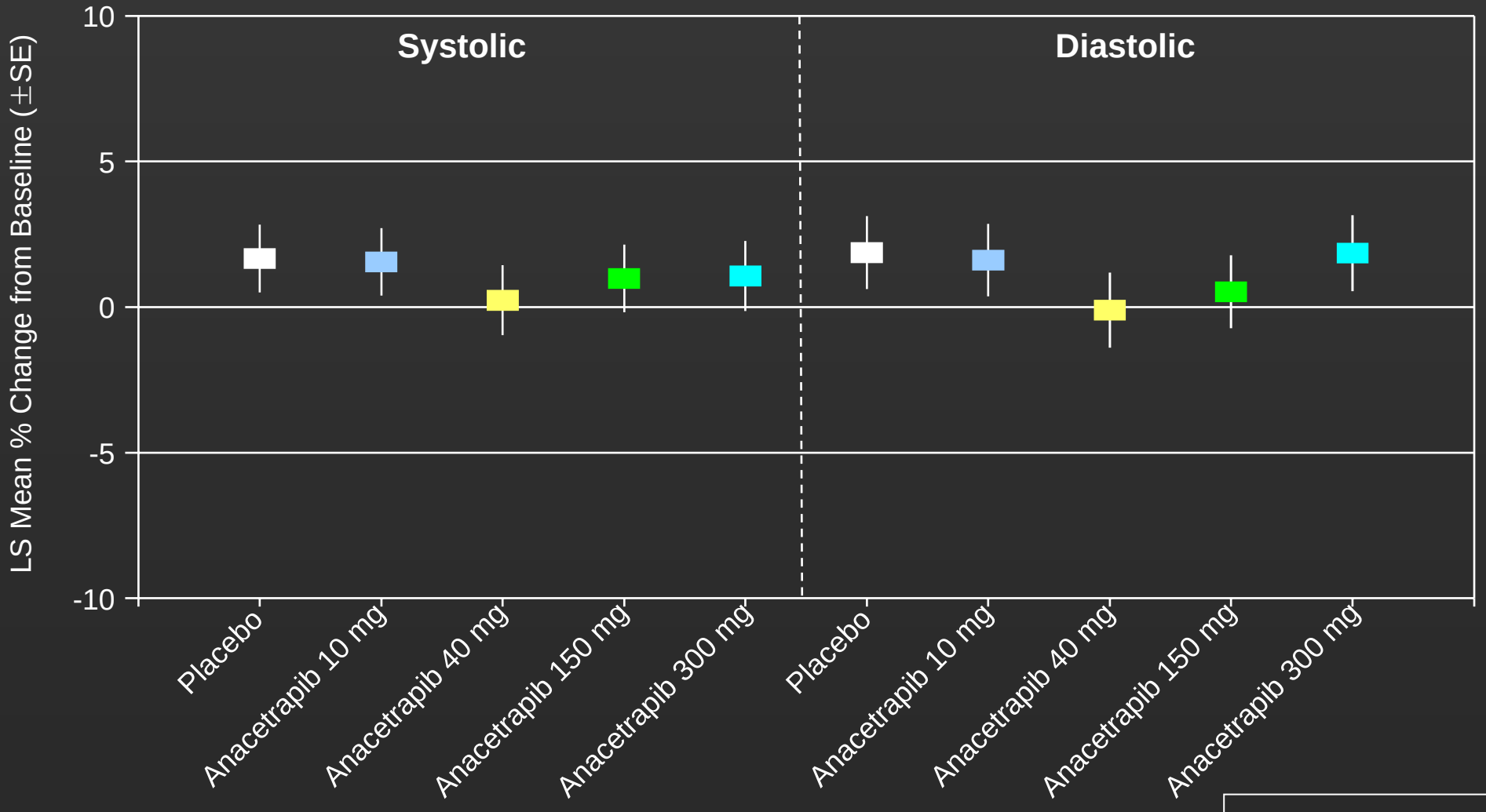
Blood Pressure



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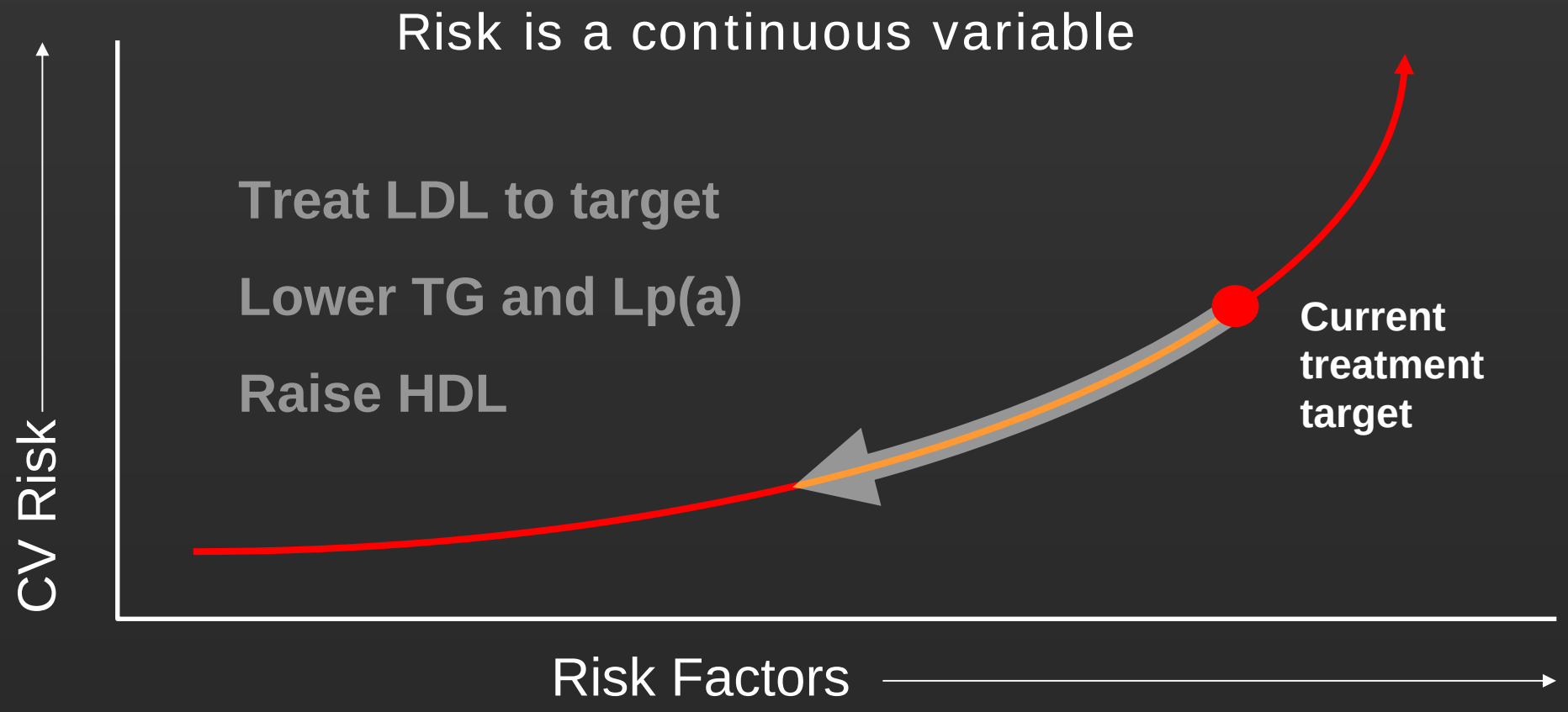
Future Paradigm:
Lower Targets, earlier and more specific Treatment (HDL, TG etc)



Kostner, 2008