Niacin's Triple Paradox and Thoughts on HDL

NLA Clinical Lipid Update

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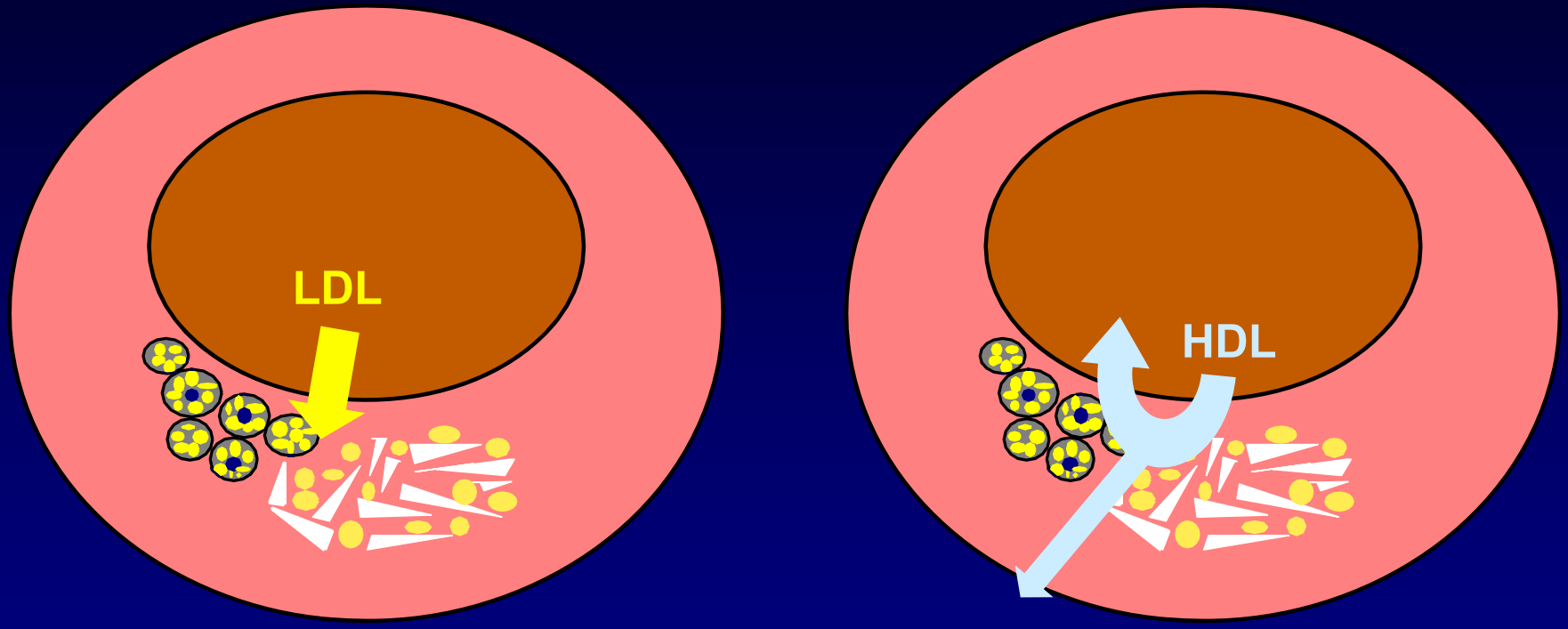
Roles of LDL and HDL in Atherosclerosis

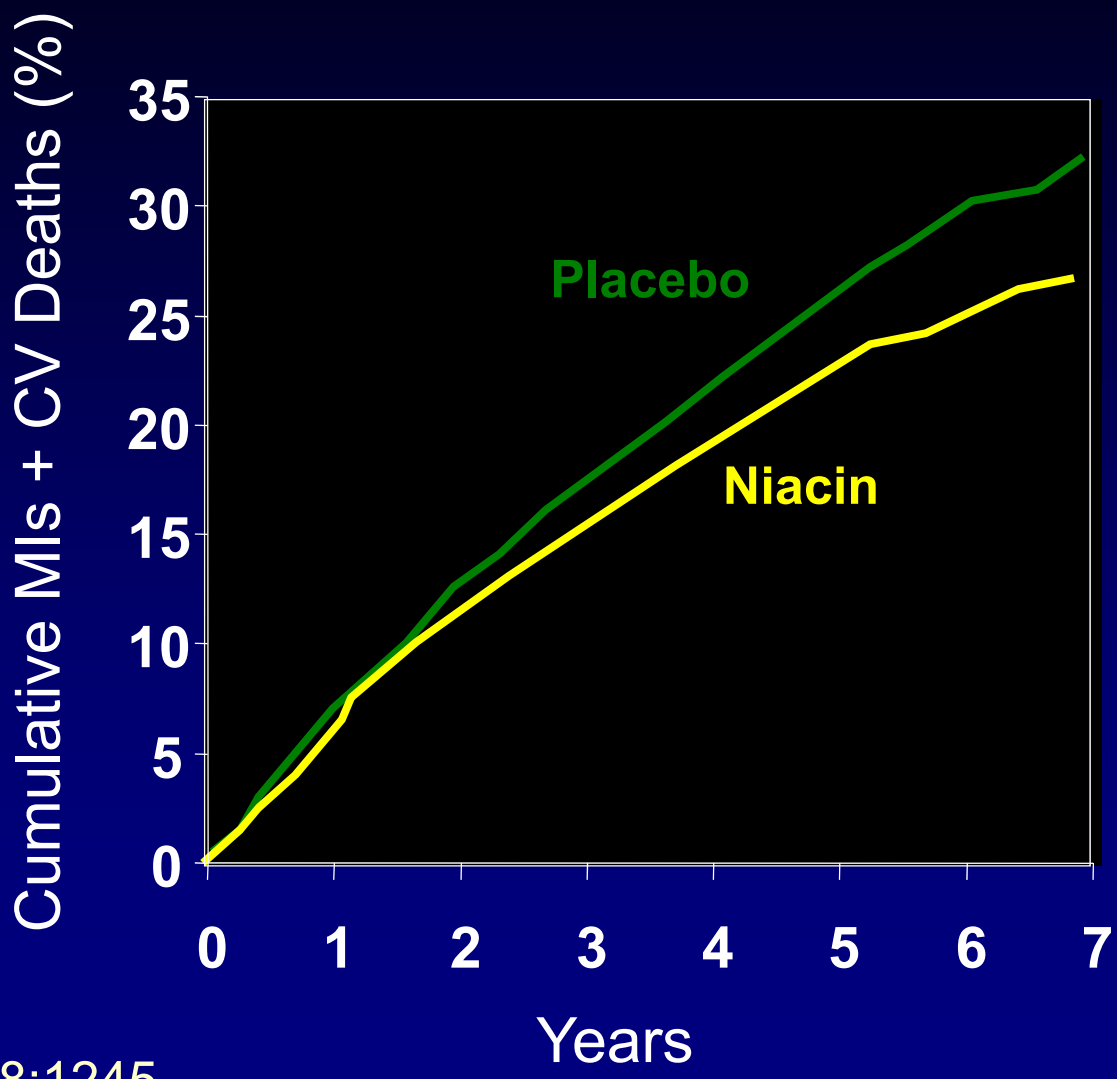


Niacin – the First Paradox

Prior clinical trials suggested CV event reduction with niacin, but AIM-HIGH and HPS2-THRIVE did not.

Coronary Drug Project

- 3,908 men aged <65 yrs with history of MI.
- 27% decrease in nonfatal MI in niacin group.
- Follow-up 9 years after end of trial: 11% lower total mortality in niacin group.



JAMA 1975; 231:360; JACC 1986; 8:1245

Stockholm Ischemic Heart Disease Study

- 5-year secondary prevention study
- Combination treatment with niacin and clofibrate
- Total mortality decreased 26% in drug treatment group.
- Ischemic heart disease mortality decreased 36%.

Acta Med Scand 1988;223:405-418

HDL Atherosclerosis Treatment Study (HATS)

- 160 pts with measurable CAD by angiography
- HDLC <35 and LDLC <145 mg/dl
- Randomized to (a) placebo or (b) niacin 2-4 grams daily dose combined with simvastatin 20 mg daily

Brown BG, NEJM 2001; 345:1583

HDL Atherosclerosis Treatment Study (HATS)

- Niacin-statin → ~85% reduction of angiographic progression after 3 years ($p < 0.01$)
- Niacin-statin → 70% reduction of cardiovascular events (7 vs. 23 events, $p < 0.01$, includes revascularization events)

Brown BG, NEJM 2001; 345:1583

Other Niacin Combination Rx Trials

Study	Treatments (Total N, follow-up)	Clinical Outcomes with Niacin
Familial Atherosclerosis Treatment Study (FATS) (Brown *et al* NEJM 1990)	Niacin + colestipol vs. lovastatin + colestipol vs. placebo (146 pts, 2.5 y)	Clinical events reduced by 73% (P<0.05)
Armed Forces Regression Study (AFREGS) (Whitney *et al* Ann Intern Med 2005)	Niacin, gemfibrozil, and cholestyramine vs. limited use cholestyr-amine (143 pts, 2.5 y)	Clinical events reduced by 50% (P<0.05)

Did Something Change Between Earlier Trials and AIM-HIGH/HPS2-THRIVE?

1. Intensive LDL reduction with statin ± ezetimibe, niacin as add-on therapy.
2. Four out of 5 previous trials were combination therapy versus no drug at all or double placebo.
3. Larger trials, better design, more definitive.
4. Bedtime dosing versus mealtime dosing.

Niacin – the Second Paradox

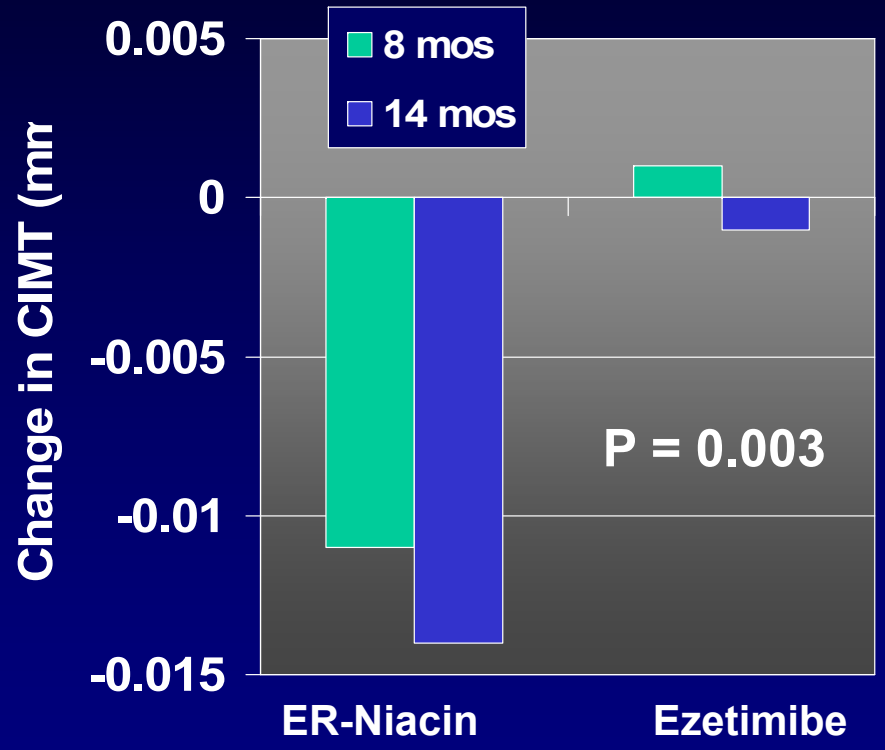
Whether it is administered at mealtime or bedtime, niacin prevents or reverses atherosclerotic lesion progression. However, in AIM-HIGH and HPS2-THRIVE did not reduce atherothrombotic events.

Both IR and ER Niacin Improve Arterial Wall Morphology

- First study to show coronary lesion regression used IR niacin-colestipol combination therapy.
- FATS and HATS both showed net regression of coronary lesions by quantitative angiography.
- 3 trials have shown reduction of carotid intima-media thickness by U/S with ER niacin added to baseline statin therapy.
- 1 trial showed reduction of carotid wall area by MRI with ER niacin added to baseline statin therapy (Lee et al. JACC 2009;54:1787).

ARBITER- 6/HALTS: Effect on Carotid Wall Thickness of Adding Extended-Release Niacin vs Ezetimibe to Ongoing Statin Therapy

- 363 pts randomized and 208 completed 14-month assessment of CIMT.
- Extended-release niacin up to 2000 mg h.s. (avg dose 1715 mg) or ezetimibe 10 mg/d added to background statin rx.
- HDLC 42.4 → 49.9 mg/dl in niacin-treated pts.



Taylor AJ, NEJM 2009; 361:2113-22

Assuming it is true that lesions are getting better, but events are just as frequent, how can that happen?

- An “off-target” effect of niacin promotes CV events.
- The net result of CV event promotion and lesion improvement is no change in CV events.

Niacin – the Third Paradox

In AIM-HIGH, bedtime ER niacin erased the influence of LDL-C on atherothrombotic events.

AIM-HIGH Trial

AIM-HIGH compared combined therapy with statin + extended-release niacin (ERN) vs. intensive statin therapy alone in 3,414 patients with established CV disease and low baseline HDL-C.

Primary endpoint was a composite of time to first event for coronary death, MI, ischemic stroke, hospitalized ACS, or symptom-driven revascularization.

Overall result – no effect of ERN.

N Engl J Med 2011; 365:2255-67

Analysis of Lipoprotein Correlations

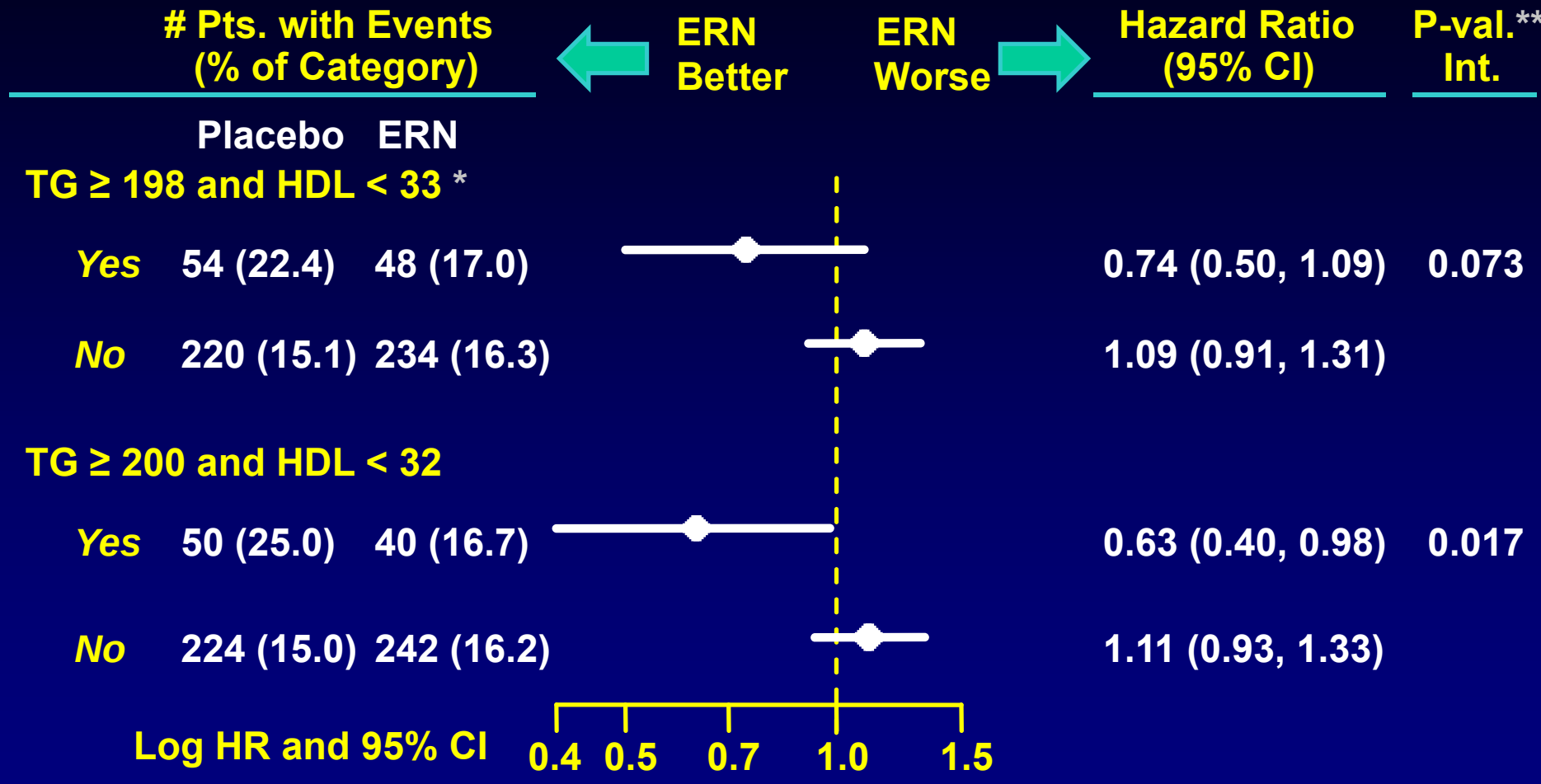
1. Do baseline lipoprotein levels predict differential benefit or harm from niacin administration?

   Analyze by tertiles.

2. Do in-trial lipoprotein levels predict the primary endpoint of CV events in placebo- and in ERN-treated subjects?

   Determine hazard ratios (HR) using Cox proportional hazards models.

Effect of High Risk Groups on Primary Outcome



**Highest tertile of TG and lowest tertile of HDL-C* ***Heterogeneity by treatment*

Guyton et al. J Am Coll Cardiol 2013; online July 20

Effects of ERN in Baseline Subgroups

- Subgroup with baseline HDLC < 32 mg/dl and triglyceride ≥ 200 mg/dl shows possible benefit from ERN treatment. This is similar to ACCORD* and other fibrate trials.
- This subgroup represents only 13% of CVD patients already pre-selected for low HDL-C. However, patients with triglyceride >400 mg/dl were excluded from the AIM-HIGH trial.

Guyton et al. J Am Coll Cardiol 2013; online July 20
Ginsberg et al. New Engl J Med 2010; 362:1563-74

Relation of In-Trial Lipoproteins to Cardiovascular Events

	Placebo + Statin		ERN + Statin	
	HR*	*P*	HR*	*P*
LDL-C	1.39	*<0.001*	1.01	*0.96*
HDLC	0.95	*0.37*	0.99	*0.79*
NonHDLC	1.30	*<0.001*	0.98	*0.78*
TC/HDLC	1.20	*0.003*	1.04	*0.64*

* HR, hazard ratio. HR unit is 1 SD of baseline distribution. Adjusted for covariates as listed in AIM-HIGH main paper.

Test for heterogeneity of joint effects of HDL-C, LDL-C and LogTG across treatments: p=0.025

Guyton et al. J Am Coll Cardiol 2013; online July 20

Bedtime ER niacin erases the relationship between lipoproteins and CV events.

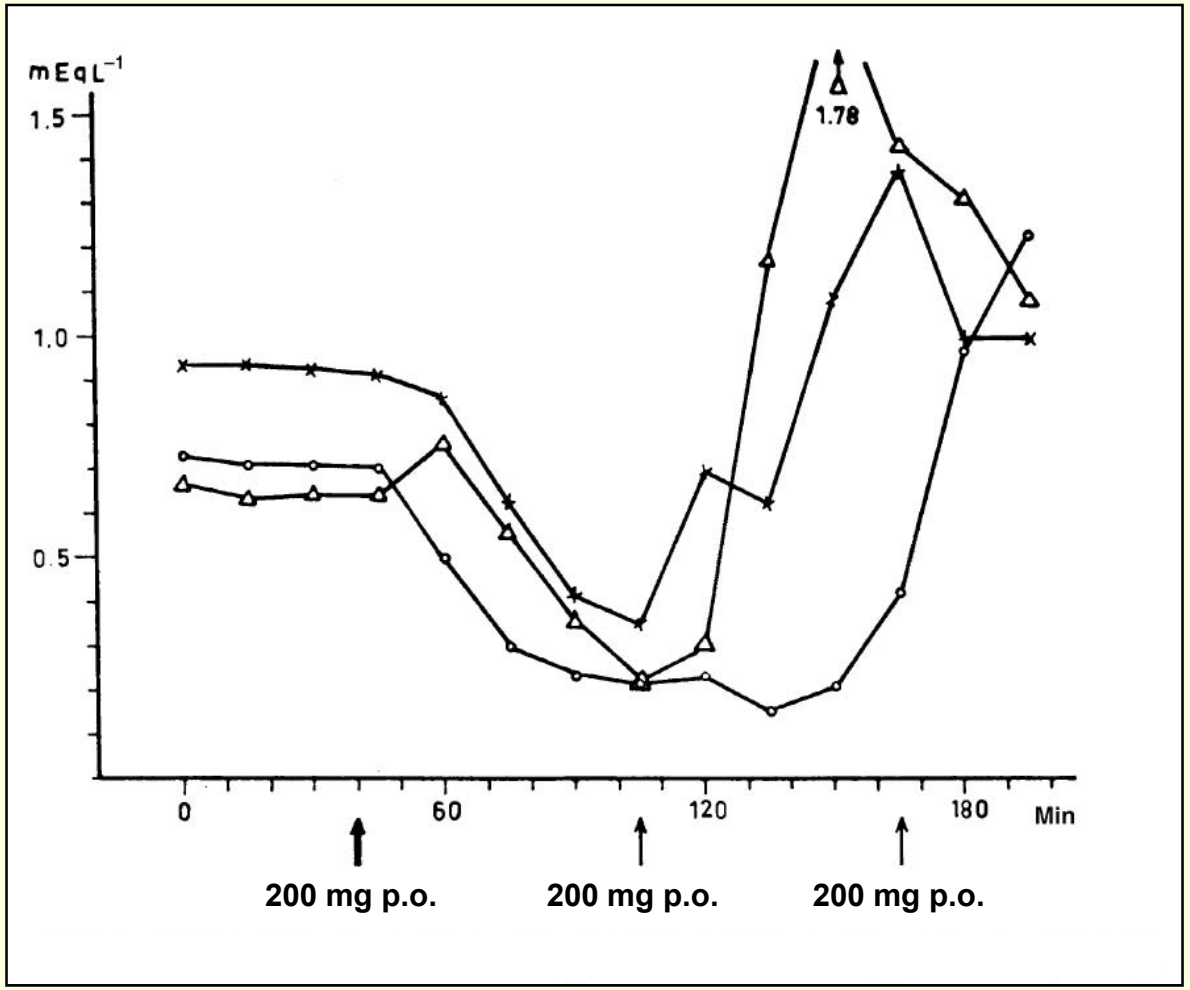
1. Niacin must alter lipoproteins enough to remove their impact on atherosclerosis, or niacin must influence events through nonlipoprotein mechanisms, or both.
2. It's very unlikely that niacin will alter LDL enough to make it nonatherogenic.
3. Therefore, it is likely that niacin is affecting CV events in a nonlipoprotein manner.

Niacin's Triple Paradox:

Could Bedtime Dosing Be the Problem?

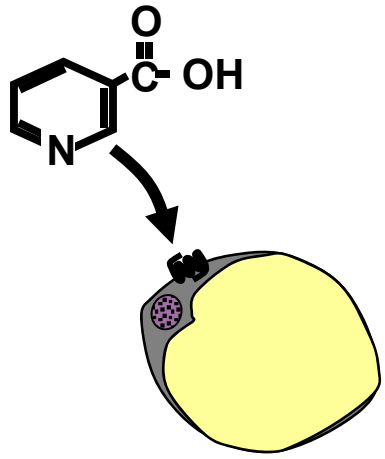
1. Something about bedtime dosing of niacin may be problematic with regard to atherothrombotic events.
2. With bedtime dosing, niacin may increase CV events even while lesions are improving.
3. From AIM-HIGH, ER niacin at bedtime appears to influence CV events in a nonlipoprotein manner.

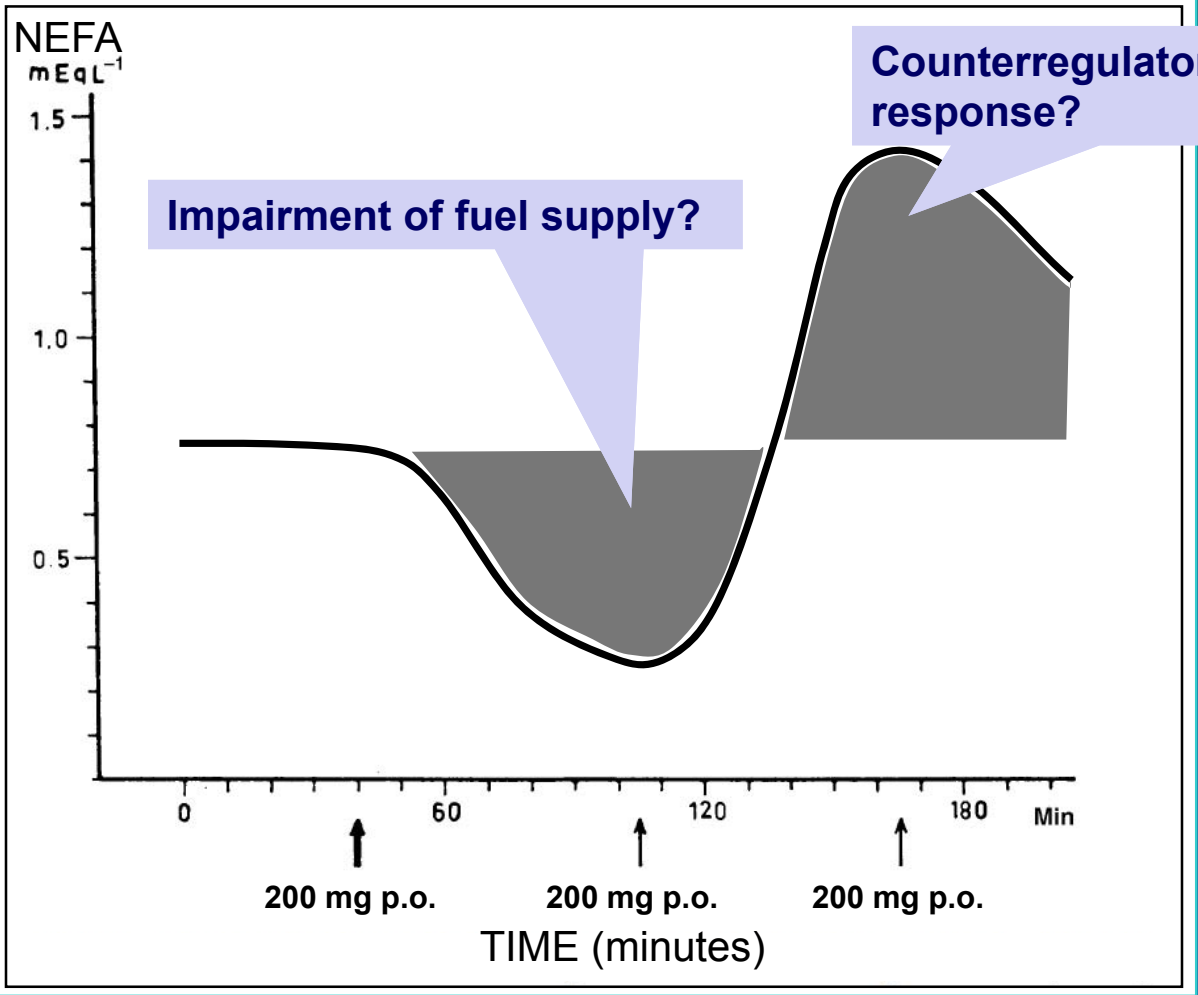
Effect of Niacin on Plasma Nonesterified Fatty Acids



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

Receptor-mediated Effect of Niacin on Adipocyte Lipolysis and Plasma Nonesterified Fatty Acids (NEFA)





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

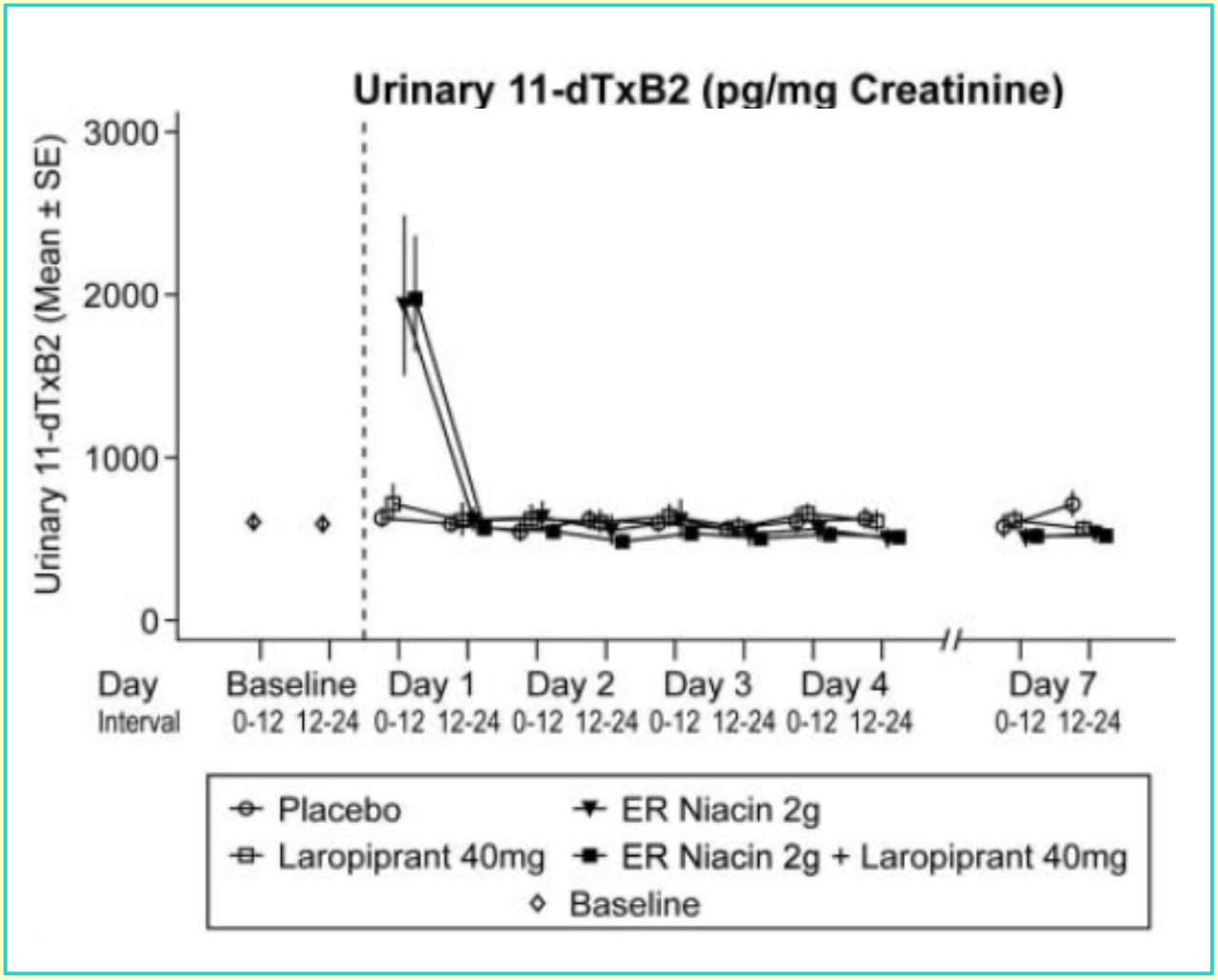
Catecholamine Response to Niacin

- 3 groups of 11 subjects each: controls, psychological stress, psychological stress plus niacin
- 3 urine collections over 2 hours each: A. Prior to stress, B. stressful period, C. post-stress.
- Niacin 500 mg p.o. every half hour from 0.5 to 3 hours.

	Epinephrine, ng/min, mean ± s.e.m.		
Period	Controls	Stress	Stress + NA
A	7.62 ± 1.10	9.53 ± 2.37	13.39 ± 1.39
B	5.59 ± 0.96	13.31 ± 3.94	19.52 ± 2.70
C	6.57 ± 0.90	8.85 ± 1.72	14.96 ± 1.73

Carlson LA et al. J.Clin.Invest. 1968;47:1795

Platelet Activation with Niacin

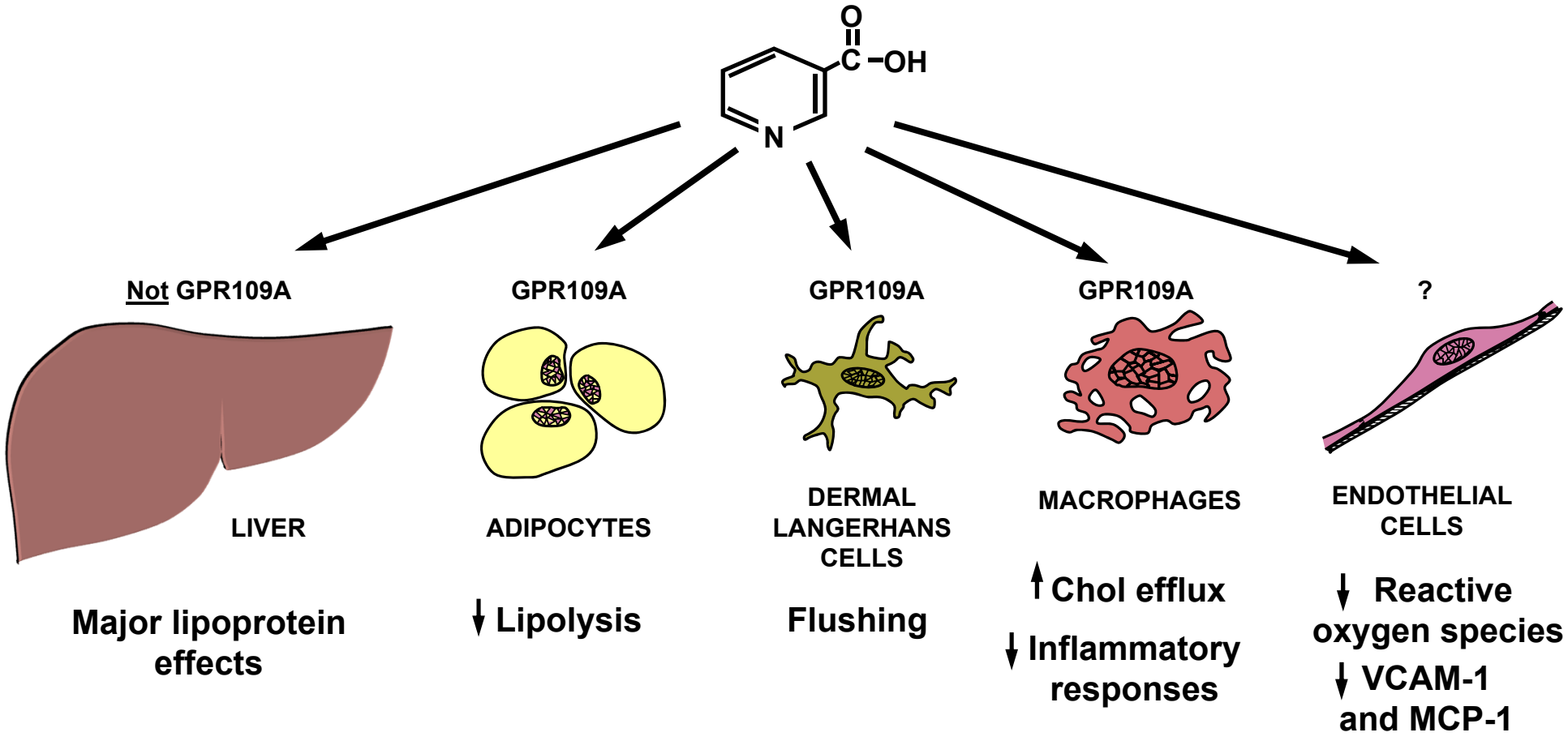


Lauring et al. J Clin Pharmacol 2009; 49:1426.

Fuel Supply Hypothesis Applied to Discordant Results in Niacin Trials

- Favorable effects of niacin were counterbalanced in AIM-HIGH by additional CV events due to fuel imbalance and catecholamine release following bedtime administration of ER niacin.
- Prior niacin trials employed mealtime administration of niacin, avoiding the fuel supply problem and catecholamine release.

MULTIPLE EFFECTS OF NIACIN



Macrophage/monocytoid cell responses to niacin

1. PPARg translocation, transcription of PPARg, CD36 and ABCA1, and ↑cholesterol efflux in monocytoid cells. Rubic et al. Biochem Pharmacol 2004;67:411.

2. GPR109A-dependent ↑ ABCG1 and ↑cholesterol efflux in macrophages. ↓ atherosclerosis progression in mice via GPR109A expressed by bone marrow-derived cells. Lukasova et al, J Clin Invest 2011; 121:1163

3. GPR109A-dependent anti-inflammatory in human monocyte-macrophages. Digby et al., ATVB 2012: 32:669.

Summary, considering the triple paradox of niacin therapy

1. AIM-HIGH and HPS2-THRIVE weaken the HDL hypothesis, but do not disprove it.
2. Nonlipoprotein effects of niacin and other lipid drugs need further exploration.
3. If niacin is used, mealtime dosing is preferred until further evidence becomes available.

What about HDL?

1. From the AIM-HIGH lipid correlations analysis, baseline HDL-C was inversely related to CV events, but only in the placebo group. In-trial HDL-C was not related to CV events in either group.
2. Therefore, the value of HDL-C as a treatment target is diminished by these results.
3. Other measures of HDL quantity and function, such as apoA-I, HDL-P, and cholesterol efflux capacity remain valid targets for research.

A new focus on nonlipoprotein actions of niacin?

1. Nonlipoprotein actions of niacin were strong enough to obscure lipoprotein effects on events in AIM-HIGH.
2. At mealtime, nonlipoprotein actions of niacin (affecting macrophages) could be mostly beneficial.
3. The niacin dose required for nonlipoprotein actions could be as low as 100-200 mg.
4. Similar nonlipoprotein actions may be shared by some of the many organic anions known to activate the niacin receptor.