

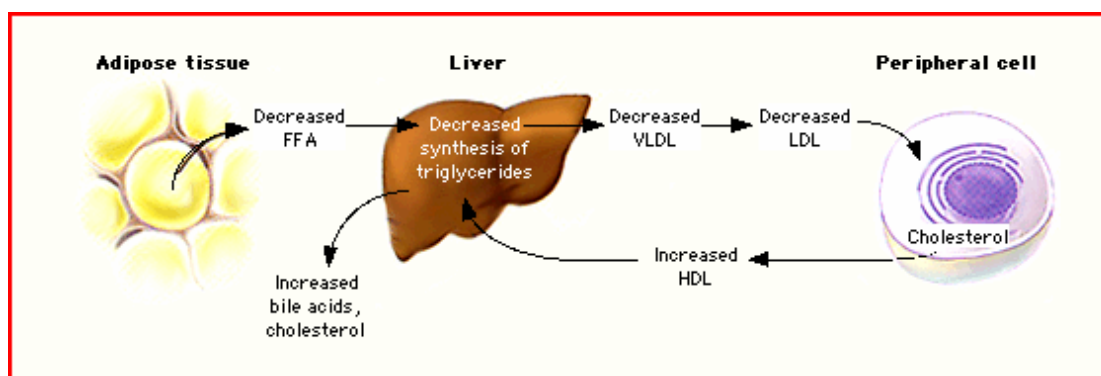
Chapter (11)
Lipid Modification with Nicotinic Acid

Nicotinic Acid is available in several formulations that include immediate-release (crystalline) and sustained release ones such as Niacor® and prolonged release Niaspan®.

Nicotinic acid (niacin) has a variety of effects on lipid metabolism (Figure 11-1):

- Inhibits hepatic production of VLDL and consequently its metabolite LDL.
- Inhibits catabolism and increases the plasma half life of Apo-A1.
- Inhibits lipolysis.
- Raises HDL levels (up to 35 %) by:
 - reducing lipid transfer of cholesterol from HDL to VLDL
 - delaying HDL clearance.
- Reduces LDL oxidation.
- Reduces plasma fibrinogen levels.
- Has Peroxisome Proliferator activator receptor (PPAR) gamma agonist effect.

Figure (11-1)



Mechanism of Action of Nicotinic Acid. Nicotinic acid inhibits the mobilization of free fatty acids (FFA) from peripheral adipose tissue to the liver. As a consequence of this decrease or an additional hepatic effect, the synthesis and secretion of very low density lipoprotein (VLDL) are reduced, and the conversion of VLDL to low density lipoprotein (LDL) is decreased. Nicotinic acid can also increase serum high-density lipoprotein (HDL) cholesterol concentration by up to 30 percent; the mechanism responsible for this effect is a reduction in lipid transfer of cholesterol from HDL to VLDL and delayed HDL clearance. *Source: Knopp, RH, Ginsberg, J, Albers, JJ, et al. Metabolism 1985; 34: 642.*

PREPARATIONS

- Over-the-counter (OTC) preparations of niacin are available, but OTC preparations marketed as causing "no flush" may have no free nicotinic acid and are ineffective in treating dyslipidemia. They are merely vitamin supplement.
- Some formulations of sustained-release OTC niacin have been associated with an increased risk of hepatotoxicity.

- The prolonged*-release prescription brand Niaspan appears to be safe and effective although more expensive.
- OTC immediate-release niacin preparations are inexpensive, contain a full amount of free nicotinic acid, and are safer than most sustained-release preparations. Side-effects, however, limit their use.

Table (11-1): Net Change in HDL-C Concentration in Patients Treated with Nicotinic Acid Derivatives vs. controls

	No of Trials	No. of Patients	Net Change (mg/dl)	95% CI (random)	Percent Change
Acipimox	9	492	+3.0	-5.8 to 6.57	+7.0%
ER-niacin	6	648	+9.2	6.96 to 11.42	+21.9%
IR-niacin	10	814	+9.2	8.56 to 9.91	+22.5%
SR-niacin	6	536	+6.0	5.15 to 6.74	+12.7%
Pooled	29	2,490	+6.7	5.10 to 8.44	+15.7%

ER: Extended release (Niaspan) IR: Immediate release SR: sustained release

USES & DOSAGE

- Nicotinic acid is effective in patients with hypercholesterolemia and in combined hyperlipidemia associated with normal and low levels of HDL cholesterol (hypoalphalipoproteinemia).
- The HDL raising properties of nicotinic acid occur with dosages as low as 1 to 1.5 g/day. In contrast, the VLDL and LDL lowering effects are typically seen with higher doses (3 g/day).
- Additional LDL lowering can be attained by the addition of a bile acid sequestrant and/or HMG CoA reductase inhibitor. A combination tablet with extended release niacin and Lovastatin is now available and may help with compliance in patients who are already on a stable dose of both drugs.
- Therapy with crystalline nicotinic acid is initiated at 100 mg TID and gradually increased to the targeted dosage as tolerated.
- Pretreatment with aspirin 30 minutes prior to dosing can minimize flushing and other prostaglandin-mediated side effects noted below. This adverse reaction often diminishes in 7-10 days.

*Other terminology used often include extended, timed, and controlled release.

- Nicotinic acid is better tolerated when ingested with food, which minimizes gastrointestinal side effects.
- Niaspan® is a prolonged release formulation of nicotinic acid that is administered once daily. Niaspan® is initiated at a dose of 500 mg nightly for one month and the dosage is titrated to 1000 mg. The standard dosage of Niaspan® is 1 to 2 grams nightly. It is advised that the medication be given with a night-time meal.
- The lipid modulating potency of Niaspan is comparable to that of crystalline nicotinic acid (Table 11-2):

Table (11-2): Percent change of lipid components with different doses of Niaspan

Dose of Niaspan (mg/D)	HDL	LDL	Lp(a)	TG
1000	16	-8	-12	-14
2000	24	-16	-25	-32
3000	29	-21	-26	-44

ADVERSE EFFECTS

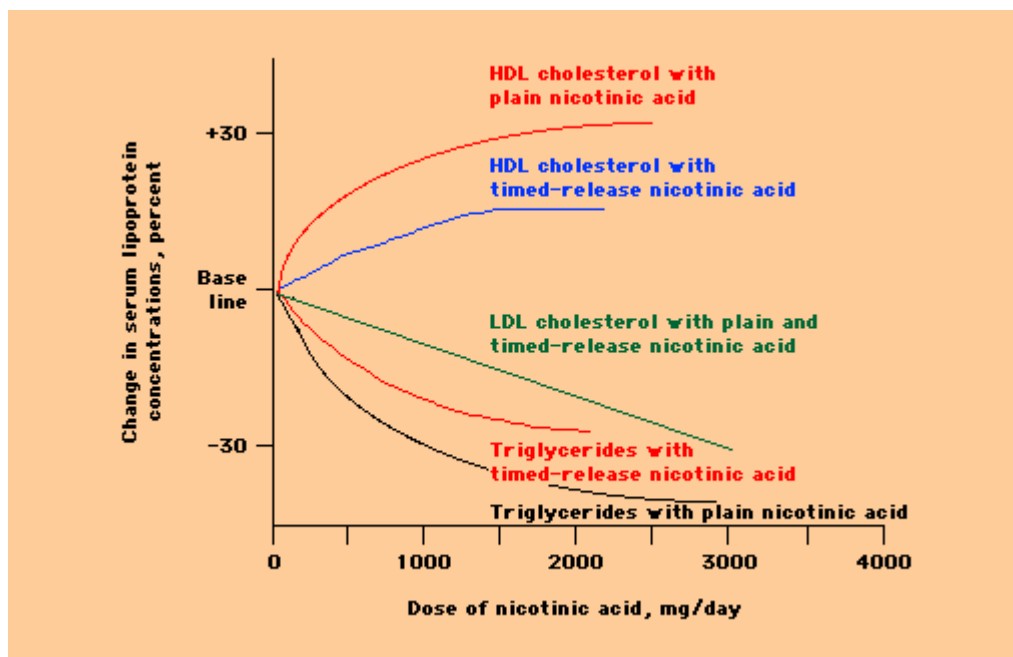
- The use of nicotinic acid is often limited by poor tolerability. At standard doses (1.5- 4.5 g/day), flushing occurs in 80% of patients taking the crystalline preparation, and pruritus, paresthesias, and nausea each occurs in about 20%.
- Flushing appears to be less common with prolonged release Niaspan®. In one study of patients receiving a median dose of 2000 mg/day for 48 weeks, only 4.8% discontinued the drug because of flushing.
- Elevations in hepatocellular enzymes are also common and may mount to severe hepatotoxicity, jaundice, and fulminant hepatitis. The onset of hepatocellular injury is not predictable; therefore regular monitoring of liver function is mandatory. Crystalline niacin is preferred to most sustained-release preparations, since the former is associated with a greater hypolipidemic effect and seemingly less hepatotoxicity.
- Prolonged release Niaspan® has been found to minimally raise transaminases in clinical trials, besides not causing significant hepatotoxicity.

Other important problems with nicotinic acid include

- **Insulin resistance:** As a result, hyperglycemia may develop in susceptible patients and the glycemic state may be worsened in those already being treated for overt diabetes mellitus.
- This effect appears to be greatest with some extended release preparations, and minimized with crystalline niacin and perhaps Niaspan®.

- Besides, the American Diabetes Association (ADA) has discarded diabetes mellitus as a contraindication to the use of nicotinic acid in diabetic patients when indicated. This is largely influenced by data from both ADMIT and ADVENT studies which showed no worsening of glycemic control by using this brand in diabetic patients, as well as excellent lipid control.
- **Hyperuricemia and acute gouty arthritis;** Niacin should be avoided in any patient with a history of gout.
- **Hypotension** in subjects treated with vasodilators; and thus may exacerbate unstable angina pectoris.
- **Elevation in plasma homocystein levels** that may negate its favorable effects on the lipid profile, in certain subsets of patients. Thus, after nicotinic acid is titrated to a stable maintenance dose, Homocystein levels should be measured. While many investigators would recommend therapy when homocystein levels exceed 15mol/L, the efficacy of this approach remains uncertain and clinical trials are now ongoing to address this issue.

Figure (11-2)



Plain Nicotinic Acid Has A Greater Effect On Lipoprotein Concentrations Than Timed-Release Nicotinic Acid. Low doses of plain (crystalline) nicotinic acid have more favorable effects than most timed-release forms on serum triglyceride and high-density lipoprotein (HDL) cholesterol concentrations. The plain and timed-release forms have similar effects at any given dose on serum low-density lipoprotein (LDL) cholesterol concentrations. The majority of the effects on serum triglyceride and HDL cholesterol concentrations occur with lower doses of nicotinic acid. *Source: Knopp, RH, N Engl J Med; 341:498.*

EVIDENCE FOR OUTCOME BENEFIT

The benefit of niacin in lipid lowering as compared other classes of lipid lowering agents is shown (figure 11-3). Up to 30% lowering of triglyceride and 35% rise of HDL-C may be expected. However, evidence of benefit in terms of event reduction is rather limited.

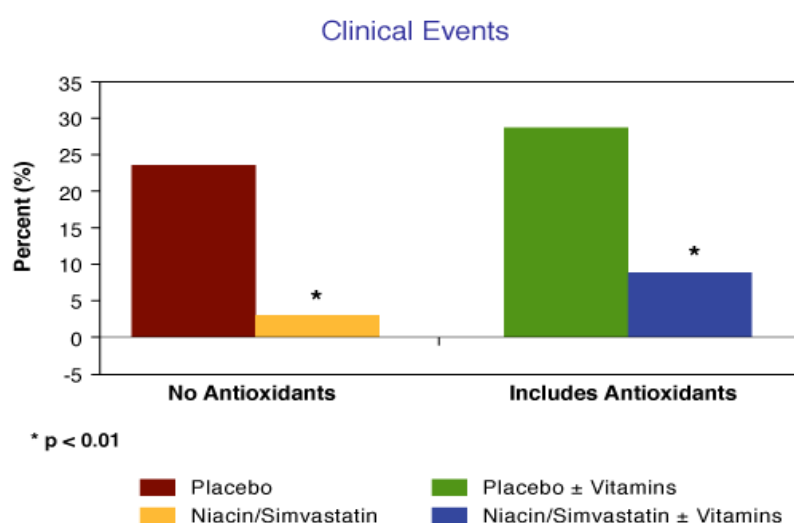
Table 11-3: Effects of Different Classes of Lipid Lowering Drugs on Serum Lipids

Drug Class	Serum LDL-C	Serum HDL-C	Serum Triglycerides
Bile acid sequestrants	-15 to 30%	0 to slight increase	No change*
Nicotinic acid	- 10 to 25%	+15 to 35%	-25 to 30%
HMG CoA reductase inhibitors	- 20 to 60%	+ 5 to 10 %	- 10 to 33%
Gemfibrozil	- 10 to 15 %	+ 15 to 25%	- 33 to 50%
Fenofibrate (micronized form)	- 6 to -20%	18 to 33%	- 41 to 53%
Cholesterol absorption inhibitors	- 17%	No change	No change
Neomycin	- 20 to 25%	No change	No change

* Serum triglyceride levels may increase in patients with preexisting hypertriglyceridemia.

- The Coronary Drug Project prospectively evaluated the effect of niacin in men with previous myocardial infarction. After 9 years of follow-up, niacin reduced total mortality by 11% compared to placebo. Non-fatal MI was reduced by 27% and stroke by 24%.
- The combination of Simvastatin and Niacin (used in HATS study) reduced coronary lesion progression in patients with established coronary artery disease, as well as the first incidence of the combined end-point of death, MI, stroke or revascularization. None of these benefits were observed in patients given anti-oxidant vitamins. In the HAT study, however, there was no arm with Niacin monotherapy, so the benefit observed may be due to Simvastatin (Figure 11-3).

Figure 11-3: HDL Atherosclerosis Intervention Trial (HATS)



- In a surrogate end-point study (ARBITER 2) The addition of Niaspan 1000 mg QD, compared to placebo, in 167 patients with known coronary artery disease was associated with less common carotid intima-media thickness (CCIMT), though the difference between the two groups did not reach significance (P=0.08).