Niacin Nicotinic Acid (Vitamin B3)

Niacin- Introduction

- What is nicotinic acid (niacin)?
- What are the recognized side effects of niacin?
- What are the key results from clinical and imaging trials of niacin treatment?
- How did results from “historical” trials differ from results of the more “recent” AIM-HIGH and HPS2-THRIVE RCTs, and how did trial designs differ?
- What are current recommendations for niacin therapy?

AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; HPS2-THRIVE=Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; RCT=randomized controlled trial.

Niacin (Vitamin B3) Therapy

- Nicotinic acid (niacin) affects the following lipoproteins in a dose-dependent manner:[1]
  - ↑ HDL-C 10%-35%[2]
  - ApoB-containing particles (VLDL-C, LDL-C and Lp[a])[2]
  - ↓ TG by 20%-30%[2]
  - ↓ LDL-C by 10%-25%[2]
  - ↑ HDL-C and ↓ TG are associated with ↑ LDL subfraction diameter (size), and ↓ LDL particle number; LDL pattern B appears to be converted to LDL pattern A[2]
  - ↓ Lp(a) levels by 20%-30%[3]

Apo=apolipoprotein; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein (a); VLDL-C=very low-density lipoprotein cholesterol; TG=triglycerides.

[1]Niaspan (niacin extended-release) [PI]; 2016.
[2]Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[3]Tsimikas S. *Curr Opin Endocrinol Diabetes Obes*. (2016) 23(2):157–164.

Niacin (Vitamin B3) Therapy

- Currently available in 3 formulations:
  1. Immediate-release (crystalline) niacin (OTC and prescription)[1]
  2. Long-acting niacin, also called slow-, sustained-, or controlled-, time-release (OTC only as a non-USDA-approved supplement)[1]
  3. Extended-release niacin (prescription, USDA-approved for lipid-lowering)[1,2]
- OTC "no-flush" niacin preparations containing nicotinamide (not nicotinic acid) have no lipid-modifying efficacy[1]

OTC=over-the-counter; USDA=United States Department of Agriculture.

[1]Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[2]Niaspan (niacin extended-release) [PI]; 2016.

Starting Dosages and Dose Ranges: Niacin

	Usual recommended starting daily dosage	Usual dose range*	Method of administration (all oral)
Niacin (nicotinic acid)			
Immediate-release[1]	250 mg	250-3,000 mg	QD-TID
Slow-release	250 mg	250-3,000 mg	QD-BID
Extended-release[1,2]	500 mg	500-2,000 mg	QD

- Immediate-release formulations are available as dietary supplements and by prescription.[1]
- Slow-release formulations are considered dietary supplements.[1]
- Extended-release formulations are considered prescription-grade.[1]
- Doses ranging from 1,000 to 6,000 mg/day have been used in clinical trials.
- Side effects and adverse effects increase with increasing doses.[1,2]

BID=twice daily; QD=once daily; TID=three times daily.

[1]Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[2]Niaspan (niacin extended-release) [PI]; 2016.

Metabolic Effects and Key Considerations: Niacin

Metabolic Effects (dose-dependent):[1-3,5]

- ↑HDL-C 10%-35%, possibly by ↓ degradation of Apo A-1
- ↓TG 20%-30% by ↑ FFA oxidation, hepatic DGAT-2 inhibition, and ↓ TG synthesis
- ↓LDL-C ~12% (1.5 gm Slo-niacin) or 14%-18% (2 gm niacin-ER) by ↓ hepatic synthesis of TG, ↑ Apo B degradation, and ↓ VLDL-C and LDL-C formation
- ↓Lipoprotein (a) ~38% (4 gm IR niacin); MOA unknown
- ↑ LDL particle size and ↓ particle number treating high TG/low HDL-associated LDL-discordant dyslipidemia

Considerations:[1,4]

- Niacin intolerance: usually skin flushing (often mitigated by aspirin 81 mg or improves over time) and pruritus; less often abdominal discomfort, nausea, peptic ulcer
- ↑ Serum glucose leading to incident diabetes in patients with prediabetes and requiring adjustment in diabetes medications in patients with diabetes
- ↑ Uric acid levels; may lead to gout
- Hepatoxicity (rare, but may be severe)
- Atrial fibrillation

Apo=apolipoprotein; DGAT-2=diacylglycerol acyltransferase-2; ER=extended-release; FFA=free fatty acid; HDL=high-density lipoprotein; HDL-C=high-density lipoprotein cholesterol; IR=immediate-release; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; MOA=mechanism of action; Slo=slow release; TG=triglyceride; VLDL-C=very low-density lipoprotein cholesterol.

[1]Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[2]Kammana VS, Kashyap ML. *Am J Cardiol*. (2008) 101(8A):20B–26B.
[3]Knopp RH, et al. *J Clin Lipidol*. (2009) 3(3):167–178.
[4]Niaspan (niacin extended-release) [PI]; 2016.
[5]Carlson LA, et al. *J Intern Med*. (1989) 226(4):271–276.

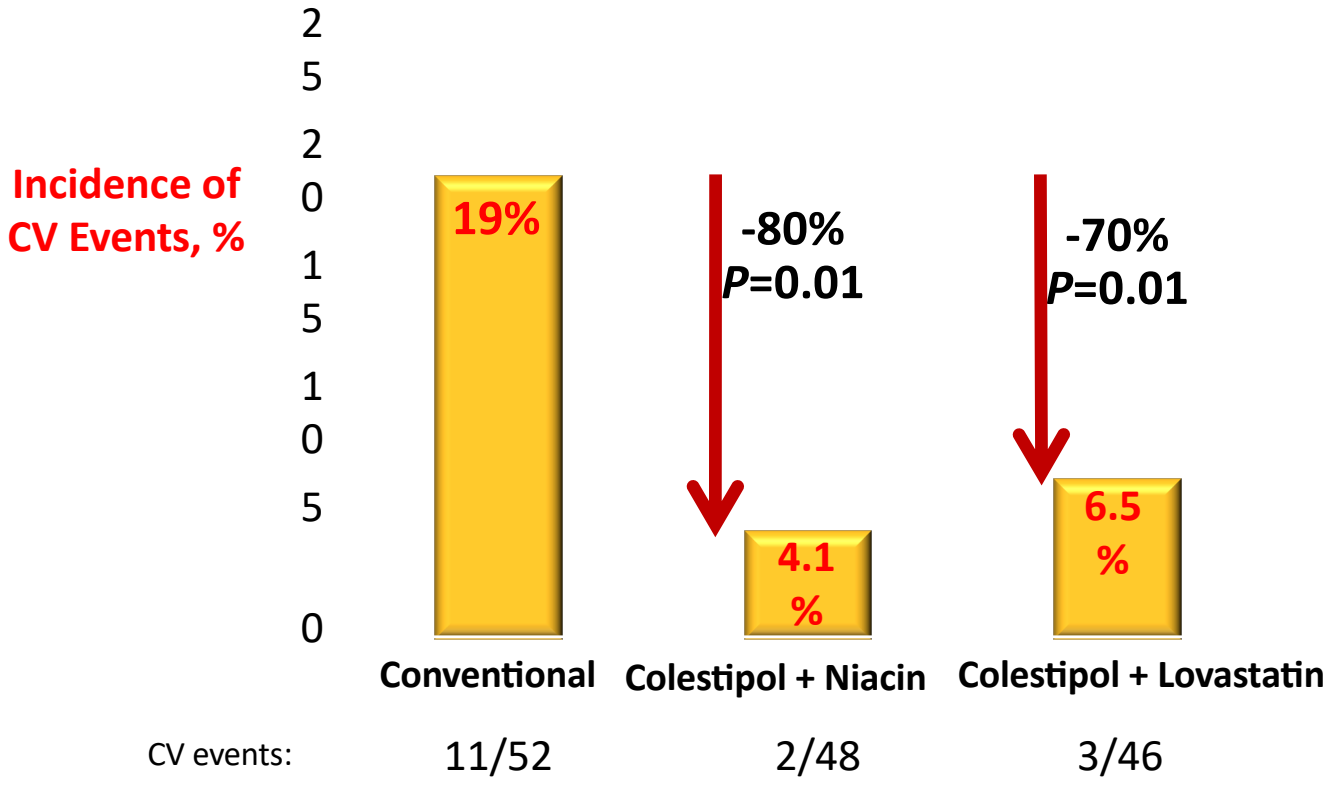
Monitoring Niacin Therapy

- Liver transaminase levels should be measured before and 3 months after niacin because most liver abnormalities occur within 3 months of treatment initiation.[1,2]
- Liver transaminase levels should be measured periodically thereafter (ie, semiannually or annually).[1,2]

[1]Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[2] Niaspan (niacin extended-release) [Prescribing InformationI];2016.

Familial Atherosclerosis Treatment (2.5 ys) Study (FATS)*
Reduction in Coronary Events

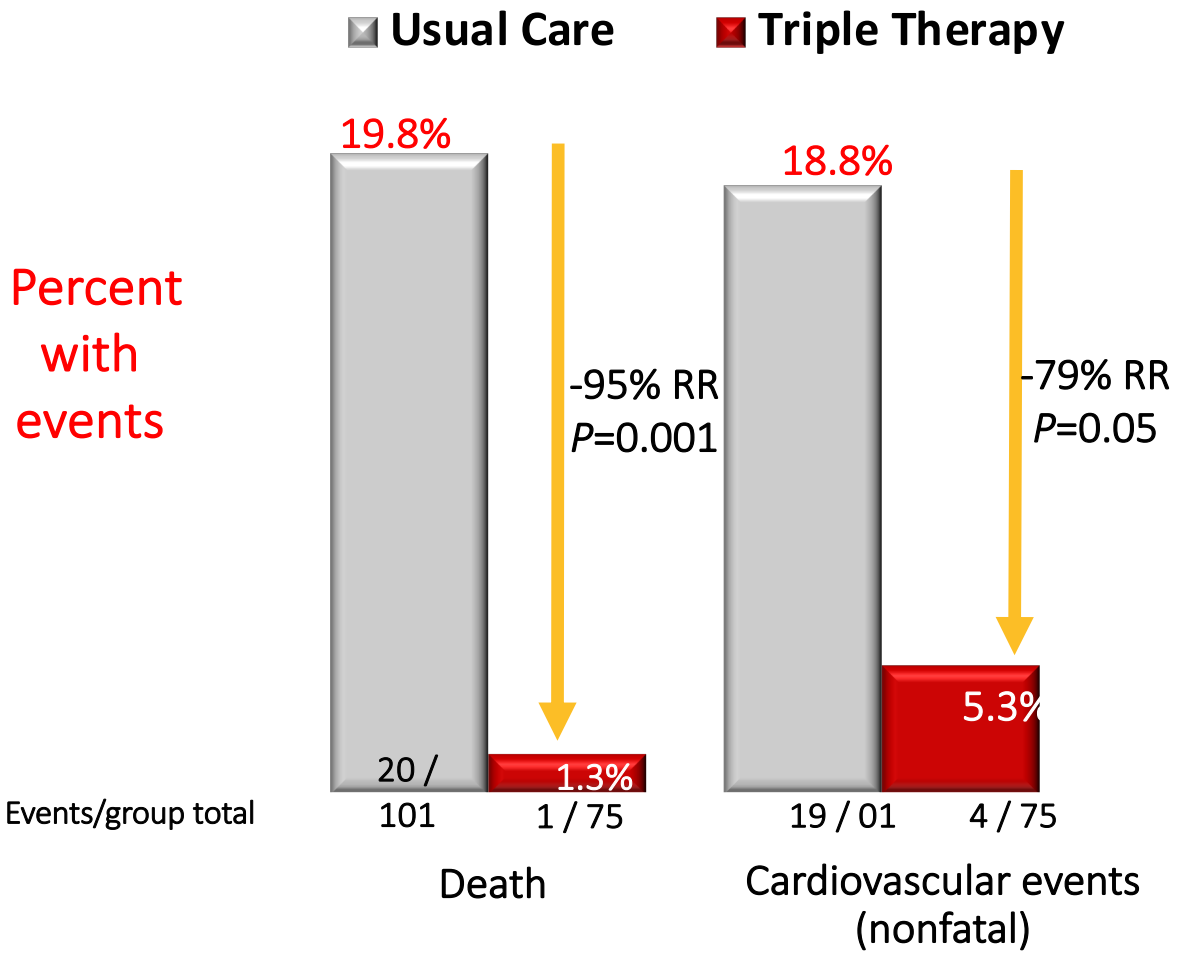
***Males (N=146, <63 y/o), Apo B >125 mg/dL, FH+CAD, angiographic CAD (average severity stenosis 34%; mandatory 1 vessel >50% or 3 vessels >30% stenosis)**



Apo B=apolipoprotein B; CAD=coronary artery disease; CV=cardiovascular; FH=familial hypercholesterolemia; y/o=years old.
Brown G, et al. *N Engl J Med*. (1990) 323:1289–1298.

FATS 10-year Follow-up:

Clinical Benefit with Aggressive Triple-therapy Lipid Lowering[1,2]



10-year follow-up, 75 patients on daily triple therapy:

40 mg lovastatin
2.5 g niacin
20 gm colestipol

TG 210 → 134 mg/dL
HDL 43 → 53 mg/dL
LDL 202 → 106 mg/dL

v

101 pts with "Usual Care"

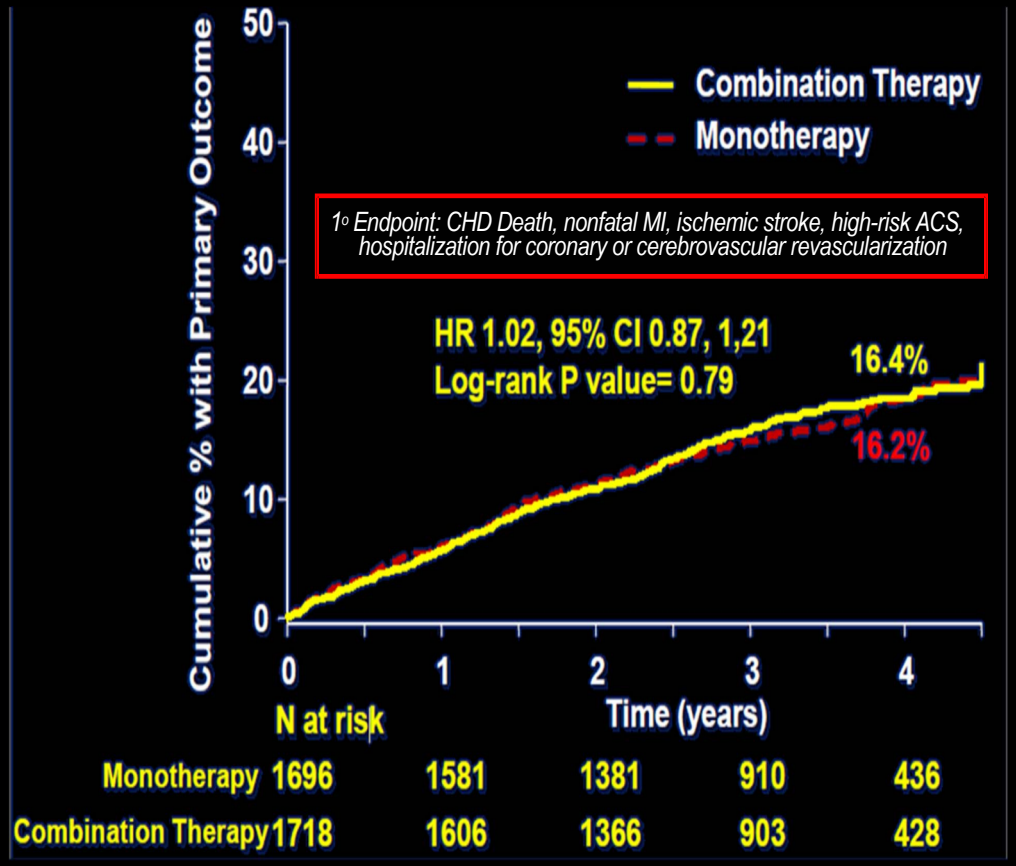
TG 208 → 220 mg/dL
HDL 38 → 40 **mg/dL**
LDL 188 → 166 **mg/dL**

FATS=Familial Atherosclerosis Treatment (2.5 ys) Study; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TG=triglyceride.

[1]Brown BG. *European Heart Journal Supplements.* (2005) 7(Supplement F):F34–F40.
[2]Brown BG. *European Heart Journal Supplements.* (2006) 8(Supplement F):F60–F67.

AIM-HIGH Study Results

Primary Outcome



ACS=acute coronary syndrome; AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; CHD=coronary heart disease; CI=confidence interval; HR=hazard ratio.

The AIM-HIGH Investigators. *N Engl J Med.* (2011) 365(24):2255–2267.

HPS2-THRIVE and AIM-HIGH: Summary of Adverse Events and Serious Adverse Events

An excess in certain serious adverse events was observed in HPS2-THRIVE, including unanticipated increases in infections and bleeding. In this study, laropiprant, a prostaglandin D2 receptor-1 antagonist, was used in addition to niacin-ER to retard cutaneous flushing.

Serious Adverse Event (%)			
	AIM-HIGH[1]		
	Placebo + statin	**Niacin-ER + statin**	***P*-value**
Any	32.5	34.2	0.30
GI	5.5	7.4	0.02
Infection	5.8	8.1	0.008
Bleeding	2.9	3.4	0.36
	HPS2-THRIVE[2]		
	Placebo + statin	**Niacin-ER + statin + laropiprant**	***P*-value**
Any	52.7	55.6	<0.001
GI	3.8	4.8	<0.001
Infection	6.6	8.0	<0.001
Bleeding	1.9	2.5	<0.001

AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; ER=extended release; GI=gastrointestinal; HPS2-THRIVE=Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events.

[1]Anderson TJ, et al. *N Engl J Med.* (2014) 371(3):288–290.
[2]The HPS2-THRIVE Collaborative Group. *N Engl J Med*. (2014) 371(3):203–212.

Recent Niacin Outcome Studies with Statin Use

Study	CV risk profile	N	Daily intervention	Statin use	Baseline TG level	Effect on TG level	Primary outcome	Primary outcome results
AIM-HIGH (72)	Age ≥45 years with CVD, low HDL-C levels, and high TG levels (150-400 mg/dL)	3,414	Niacin ER 1,500-2,000 mg/day	Simvastatin ± ezetimibe to maintain LDL-C range of 40-80 mg/dL	162 mg/dL (median)	–28% at 1 year	Nonfatal MI or ischemic stroke, CHD death, hospitalization for ACS, symptom-driven revascularization; mean f/u: 3 years	HR, 1.02 (95% CI, 0.87-1.21); *P* = .79; ARR, NC (16.4% with niacin vs. 16.2% with placebo)
HPS2-THRIVE (73)	Age 50-80 years with CVD	25,673	Niacin ER 2,000 mg/day + laropiprant 40 mg/day	Simvastatin ± ezetimibe to reduce LDL-C levels <135 mg/dL	108 mg/dL (median)	–33 mg/dL	Nonfatal MI, coronary death, stroke, or revascularization; median f/u: 3.9 years	RR, 0.96 (95% CI, 0.90-1.03); *P* = .29; ARR, NC[a] (13.2% with niacin vs. 13.7% with placebo)

While historical data were promising, AIM-HIGH and HPS2-THRIVE clinical studies did not support the use of niacin in combination with statins.

ACS=acute coronary syndrome; AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; ARR=absolute risk reduction; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; ER=extended release; f/u=follow-up; HDL-C=high-density lipoprotein cholesterol; HPS2-THRIVE=Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; HR=hazard ratio; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; NC=not calculated; RR=relative risk; TG=triglyceride; VLDL-C=very low-density lipoprotein cholesterol.

Handelsman Y, Shapiro MD. *Endocr Pract*. (2017) 23(1):100–12.

FDA Withdraws Approval of Niaspan ER and in Combination with Statins

On April 18th 2016, the FDA announced retraction of prior approvals related to combinations of statins with niacin extended release (ER) and statins with fenofibric acid delayed release (DR).[1] The decision to remove these indications was prompted by evidence from three large published trials, which failed to show reductions in important cardiovascular events when either niacin ER or fenofibric acid DR was added to statin therapy in the populations studied.[2-4] The FDA has concluded that existing evidence does not support that reducing triglycerides or raising of high-density lipoprotein cholesterol (HDL) with any drug, including fenofibric acid or niacin, improves cardiovascular risk in patients on statins and therefore, the benefit of either combination with statins no longer exceeds the potential risk. The VA Pharmacy Benefits

ER=extended release; FDA=food and drug administration.

[1]FDA Federal Register. (2016): https://www.gpo.gov/fdsys/pkg/FR-2016-04-18/pdf/2016-08887.pdf. Accessed 11/25/18.
[2]The ACCORD Study Group. *N Engl J Med.* (2010) 362(17):1563–1574.
[3]The AIM-HIGH Investigators. *N Engl J Med.* (2011) 365(24):2255–2267.
[4]The HPS2-THRIVE Collaborative Group. *N Engl J Med*. (2014) 371(3):203–212.

Unqualified and Misunderstood Conclusions from AIM-HIGH and HPS2-THRIVE RCTs: Selected, But Important, Facts (1 of 2)

- Niacin formulations raise HDL-C and lower LDL-C, non-HDL-C, Apo B, TG, small dense LDL, LDL-P, and Lp(a) in dose-dependent manner.[1]
- Clinical trial data support the efficacy of niacin in slowing plaque progression, plaque regression, and reducing CVD risk when used alone and in combination with statins or other LDL-lowering agents.[1]
- The AIM-HIGH and HPS2-THRIVE RCTs were designed to test the "HDL-raising hypothesis" in patients with relatively low HDL-C and well-controlled LDL-C. Niacin-ER was prescribed at 2,000 mg/day against a background of simvastatin 40 mg/day.[2,3] To reduce flushing, the HPS2-THRIVE also used 40 mg laropiprant (a prostaglandin D2 receptor DP1 antagonist); significantly increased serious adverse effects were noted.[3]
- Attempting to maintain between-group LDL-C equipoise in AIM-HIGH, the "principal goals of the first year…included 5 visits…to…adjust the simvastatin dosage, with the possible addition of ezetimibe 10 mg, to achieve a target LDL-C in the range [of] 40-80 mg/dL."[2]
- AIM-HIGH and HPS2-THRIVE aimed for LDL-C equipoise by design. In AIM-HIGH, to offset the LDL-C-lowering of niacin-ER, the placebo group received either ezetimibe 10 mg or higher-dose simvastatin, adjusted to a target LDL-C 40-80 mg/dL. The between-group LDL-C difference was nominal, as were between-group changes in other lipid levels.[2,3]

AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; Apo=apolipoprotein; C=cholesterol; CIMT=carotid intima-media thickness test; CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; ER=extended release; HDL=high-density lipoprotein; HPS2-THRIVE=Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; LDL=low-density lipoprotein; LP(a)=lipoprotein (a); P=particle; RCT=randomized controlled trial; TG=triglyceride.

[1]Bruckert E, et al. *Atherosclerosis*. (2010) 210:353–361.
[2]The AIM-HIGH Investigators. *Am Heart J*. (2011) 161(3):471–477.
[3]The HPS2-THRIVE Collaborative Group. *N Engl J Med*. (2014) 371(3):203–212.

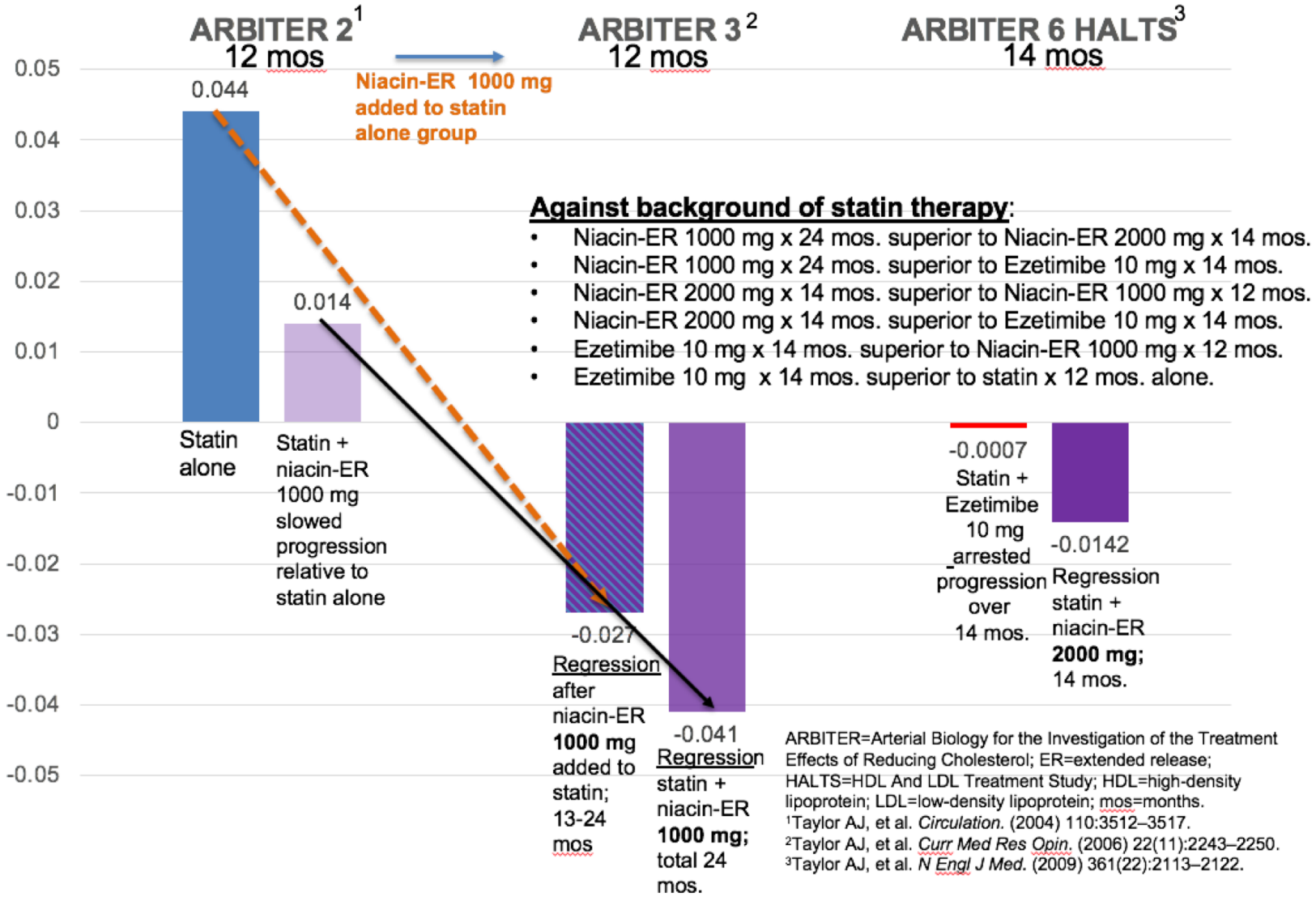
Unqualified and Misunderstood Conclusions from AIM-HIGH and HPS2-THRIVE RCTs: Selected, But Important, Facts (2 of 2)

- The AIM-HIGH and HPS2-THRIVE RCTs were not designed to evaluate the benefits of niacin-ER to reduce CVD events in patients with elevated TG, LDL-C, non-HDL-C, Apo B, small dense LDL, LDL-P, or Lp(a).1,2
- Reported adherence to niacin–laropiprant fell to 89% during the first year and to 70% by the scheduled study end.2
- In neither AIM-HIGH nor HPS2-THRIVE were the cohorts at risk from high TG (defined as >180 mg/dL); baseline TG were 162 mg/dL and 120 mg/dL, respectively.1,2
- FDA conclusions were based solely on face-value observations of the 2 RCTs, without qualification of results with trial design and nominal between-group lipid parameter differences.
- According to AACE, since previous niacin trials showed CVD benefits utilizing higher doses of niacin and were associated with much greater between-group differences in LDL-C, expected niacin benefits may result from its LDL-C–lowering properties.3
- However, the exact mechanisms by which niacin used with background LDL-C-lowering therapy exerts CV risk reduction has yet to be tested in a well-designed large randomized trial.

AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; Apo=apolipoprotein; CIMT=carotid intima-media thickness; CV=cardiovascular; CVD=cardiovascular disease; CVOT=cardiovascular outcome trial; ER=extended release; FDA=U.S. Food and Drug Administration; HDL=high-density lipoprotein; HPS2-THRIVE=Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; LDL=low-density lipoprotein; LP(a)=lipoprotein (a); P=particle; RCT=randomized controlled trial; TG=triglyceride.

[1]The AIM-HIGH Investigators. Am Heart J. (2011) 161(3):471–477.
[2]The HPS2-THRIVE Collaborative Group. N Engl J Med. (2014) 371(3):203–212.
[3]Garber AJ, et al. Endocrine Practice. (2016) 22(1):84-102.

Change in Carotid Intima Media Thickness: ARBITER 2, 3 and 6



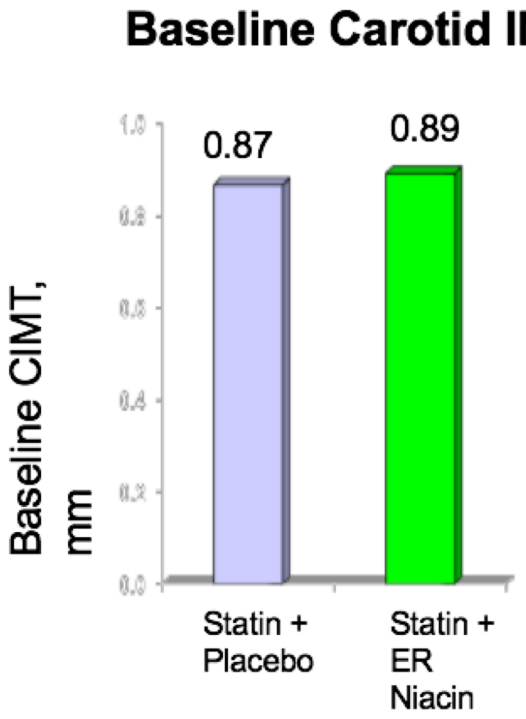
ARBITER=Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; ER=extended release; HALTS=HDL And LDL Treatment Study; HDL=high-density lipoprotein; LDL=low-density lipoprotein; mos=months.

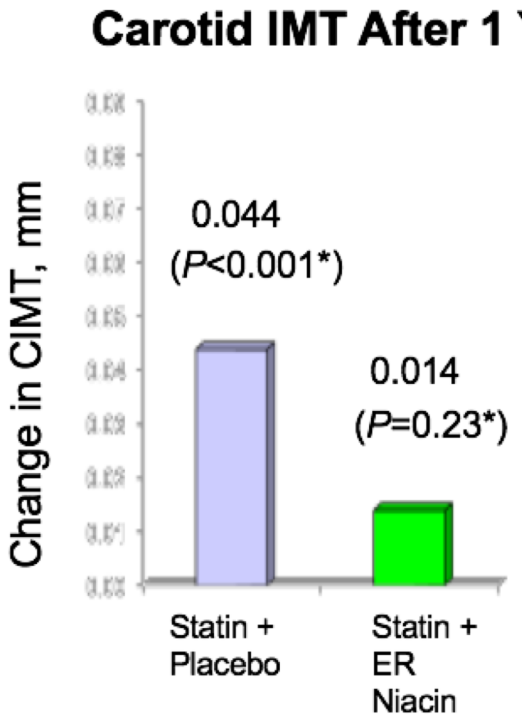
[1]Taylor AJ, et al. *Circulation.* (2004) 110:3512–3517.
[2]Taylor AJ, et al. *Curr Med Res Opin.* (2006) 22(11):2243–2250.
[3]Taylor AJ, et al. *N Engl J Med.* (2009) 361(22):2113–2122.

ARBITER 2

Niacin-ER, 1000 mg (N=167)

↑HDL-C [A AFS] 21% (*P*=0.002); TG ↓10% (*P*=0.03); no change in LDL-C





In ARBITER 2, 1000 mg niacin-ER + statin therapy "slowed progression" relative to placebo + statin therapy after 12 months.

*Within-group comparisons.

ARBITER=Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CIMT=carotid intima-media thickness; ER=extended release; HDL-C=high-density lipoprotein cholesterol; IMT=intima-media thickness; LDL-C=low-density lipoprotein cholesterol; TG=triglyceride.

Taylor AJ, et al. *Circulation.* (2004) 110:3512–3517.

Niacin Therapy- Recommendations

- The AACE Lipid Guidelines recommend niacin therapy principally as an adjunct to reduce TG levels.[1]
- Niacin in combination with statins is an appropriate option for individuals with mixed dyslipidemia (↑TG, ↓HDL-C, ↑LDL-C)[1]
  - Combination (statin + niacin) therapy produces significantly greater HDL-C raising, TG-lowering, and LDL-C-lowering vs statin monotherapy.[1]
- Current dogma is based on two large RCTs testing the "HDL-Raising Hypothesis:"[3,4]
  - Niacin should not be used in individuals receiving aggressive statin treatment due to an absence of additional ASCVD benefits with well-controlled LDL-C (40-80 mg/dL) and TG.[1-4]
- Unlike AIM-HIGH or HPS2-THRIVE,[1,2] many clinical trials did not maintain between-group LDL-C equipoise, and did demonstrate CV benefits with niacin.[5]

AACE=American Association of Clinical Endocrinologists; ASCVD=atherosclerotic cardiovascular disease; HDL=high-density lipoprotein; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; RCT=randomized controlled trial; TG=triglyceride.

[1]Jellinger PS, et al. *Endocr Pract.* (2017) 23(2):1–87.
[2]Niaspan (niacin extended-release) [PI]; 2016.
[3]The AIM-HIGH Investigators. *Am Heart J*. (2011) 161(3):471–477.
[4]The HPS2-THRIVE Collaborative Group. *N Engl J Med*. (2014) 371(3):203–212.

Conclusions

- Nicotinic acid (niacin) has been demonstrated to substantially ↑ HDL-C and LDL subfraction diameter and ↓ LDL-C, TG, and Lp(a) levels.
- Current dogma states that, despite improvements in HDL-C, two large RCTs (AIM-HIGH and HPS2-THRIVE) did not show improved CV outcomes when niacin was added to statins in patients with well-controlled LDL-C.
- Niacin is the least well-tolerated of lipid modifying drugs; intolerance may be mitigated by co-administration with 81 mg aspirin.
- Niacin is recommended as a treatment for high TG, especially in combination with other TG-lowering agents.
- Niacin + statin may be appropriate therapy for individuals with "mixed dyslipidemia," defined as high LDL-C, high TG, and low HDL-C.
- May be appropriate in combination with other LDL-C-lowering agents in the setting of statin-intolerance.

AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides; CV=cardiovascular; HDL-C=high-density lipoprotein cholesterol; HPS2-THRIVE=Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; LDL=lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Lp(a)=lipoprotein (a); RCT=randomized controlled trial; TG=triglyceride.