

ARBITER 6-HALTS

HDL And LDL Treatment Strategies

Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness

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- **Allen J. Taylor, M.D.**
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Extended-Release Niacin or Ezetimibe and Carotid
Intima–Media Thickness

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Additional information can be found in an on-line supplement at: www.nejm.org

Trial Conduct and Support

- Investigator-initiated study
- Unrestricted grant
 - Abbott (originated by Kos Pharmaceuticals)
- Administered by independent, 3rd party foundation
 - The Henry M. Jackson Foundation for the Advancement of Military Medicine
- All aspects of study design, conduct, analysis, and reporting are solely those of the authors

Background

- Statins reduce LDL-C and clinical events
- However, because of residual cardiovascular risk with statin monotherapy, treatment may be intensified with combination therapy strategies to either:
 - Increase HDL-C
 - Achieved in clinical practice with niacin
 - Further reduce LDL-C
 - Achieved in clinical practice with a variety of interventions
 - Ezetimibe: Commonly used, however no data supporting its clinical efficacy

ARBITER 6-HALTS

- “HALTS”: HDL And LDL Treatment Strategies
- Purpose
 - Compare the effectiveness of combination lipid lowering therapy with either extended-release niacin or ezetimibe added to long-term statin therapy for the endpoint of carotid intima-media thickness over 14 months
- PROBE Design
 - Prospective, randomized, parallel-group, open-label study involving blinded evaluation of endpoints
 - Walter Reed Army Medical Center- Washington, D.C.
 - Washington Adventist Hospital- Takoma Park, MD

Eligibility

- Eligible patients
 - ≥ 30 years old
 - Known cardiovascular disease (n=279)
 - CHD risk equivalent
 - Diabetes mellitus (n=38)
 - FRS $\geq 20\%$ (n=26)
 - Coronary calcium score >200 for women; >400 for men (n=20)
- Treatments/lipids
 - Currently treated with a consistent dose of statin monotherapy
 - Lipid panel w/i 3 months:
 - LDL-C <100 mg/dL
 - HDL-C <50 mg/dL (men); <55 mg/dL (women)

HDL threshold selected to be representative of the US population median values- Not a classically “low HDL” population

Study Flow

Patients approached for consent (n = 630)

Declined participation (n = 267)

Randomized to ezetimibe or ER niacin (n = 363)

Ezetimibe 10 mg/d (n = 176)

- Withdrawal (n = 9)
 - Side effects (n = 3)
 - Withdrew consent (n = 6)
- Died (n = 7)

In study as of 4 June, 2009
(n=160)

In study and completed 14 month
endpoint assessment as of 4
June, 2009 (n = 111)

ER Niacin 2000 mg/d (n = 187)

- Withdrawal (n = 27)
 - Side effects (n = 17)
 - Withdrew consent (n = 10)
- Died (n = 1)

In study as of 4 June, 2009
(n=159)

In study and completed 14 month
endpoint assessment as of 4
June, 2009 (n = 97)

Endpoints

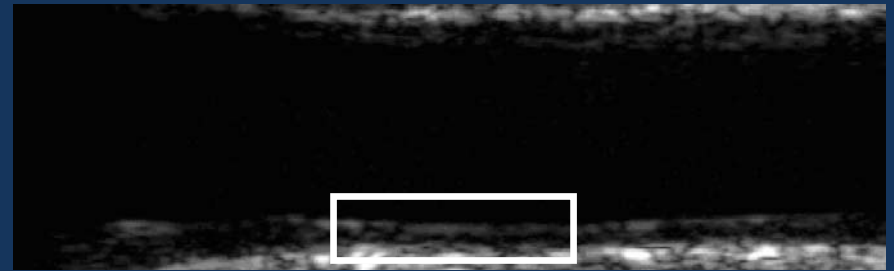
- Primary endpoint
 - Between-group difference in the change from baseline in mean carotid intima-media thickness after 14 months
- Secondary endpoints
 - Change in serum lipids (baseline, 2, 8, 14 months)
 - Composite of major adverse cardiovascular events (MI, myocardial revascularization, hospital admission for ACS, CHD death)
 - Study drug discontinuation due to adverse effects
 - Health-related quality of life (EQ5D)

Carotid Ultrasound

- Broadband linear array probe (13 MHz)
- Ultrasound exams
 - Baseline, 8 months, 14 months
 - Single sonographer
 - Except for first 20 baseline exams at Washington Adventist
- Imaging:
 - Far wall, distal common carotid artery
 - 4 views: right/left, anterior and lateral
 - 2 complete image sets obtained
 - Digitized still-frame images
 - ECG gated to diastole

Carotid Intima-Media Thickness: Measurement

- Off-line work station
 - Single interpreter, blinded to treatment
 - Automated border detection software
 - Sonocalc (Sonosite, Bothell WA)
 - Distal 1cm of the CCA (excl. plaque)
 - Duplicate measurements
- No scans excluded on the basis of image quality.
 - 4968/4992 (99.5%) images available for analysis



	Absolute Value	Correlation	P
Inter-test	0.0011 ± 0.0125 mm	r = 0.997	P < 0.001
Intra-observer	0.0001 ± 0.0055 mm	r = 0.999	P < 0.001
Reader drift	Standard image set (n = 10) repeated every 6 months. Maximum difference at any time point <0.001mm.		

As a result of multiple procedural advances in CIMT, these data are among the highest reproducibility ever reported in a CIMT trial.

Prespecified Interim Analysis

- Trial design: Sample size ($n = 300$) based upon conservative estimate of image reproducibility using older technology and measurement techniques.
- Prespecified interim analysis: Conceived on the basis of multiple refinements in the imaging methodology which were judged to be likely to increase the efficiency of the trial.
 - Single, prespecified, blinded analysis after 60% (180) of the subjects had completed the study
- Independent Data Advisory Committee
 - 4 June 2009, without sponsor involvement

Prespecified Interim Analysis

- The Committee judged blinded data demonstrating
 - High precision in the CIMT assessments
 - Evidence that the primary endpoint was met
 - Consistency of findings at all time points for all CIMT measurements
 - Sensitivity analyses demonstrating certainty of the findings
 - Secondary analyses revealing a potential paradoxical effect of one agent
- It was the unanimous judgment of committee that the trial should be immediately terminated within the findings of the primary endpoint. This represented loss of clinical equipoise, and thus termination was in the best interest of the volunteer research subjects. The institutional review boards concurred.

Following termination, final visits were conducted, resulting in 208 patients with 14 month endpoint data.

Results: Overall Baseline Characteristics

- N = 208
- 80% male
- Age: 65 ± 11 years
- All on statins
 - 42 ± 25 mg/d
 - 6 ± 5 years duration
 - 95% simvastatin or atorvastatin

Baseline measured variables

- TC 147 ± 26 mg/dL
- LDL-C 82.1 ± 23.1 mg/dL
- HDL-C 42.4 ± 8.5 mg/dL
- TG 134 ± 68 mg/dL

- CIMT
 - Mean 0.8977 ± 0.1583 mm
 - Max 1.0179 ± 0.1653 mm

- Baseline characteristics balanced in the 2 treatment groups.
- Baseline statin dose: Little room for additional statin titration.

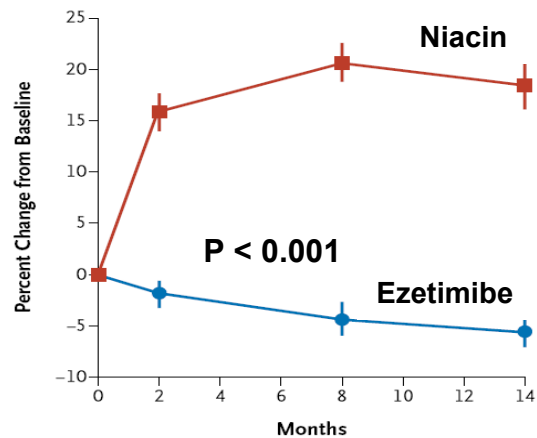
Results: Lipid Concentrations

- Niacin: HDL increased by 18.4% to 50 mg per deciliter

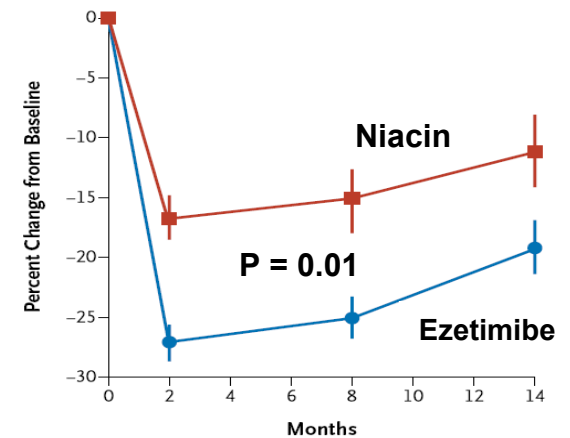
- ↓ LDL and TG

- Ezetimibe: LDL decreased by 19.2%, to 66 mg per deciliter

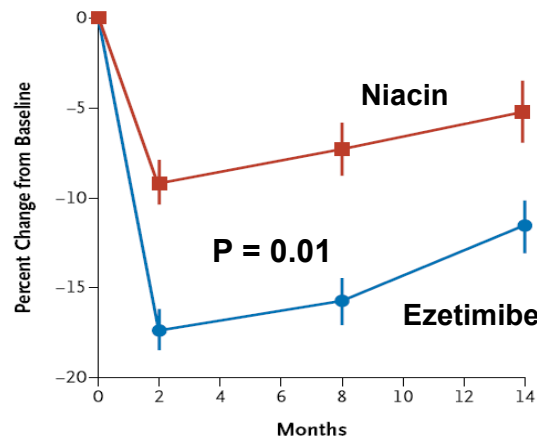
A HDL Cholesterol



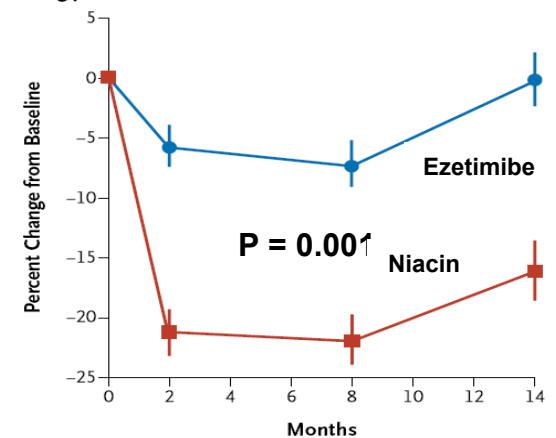
B LDL Cholesterol



C Total Cholesterol



D Triglycerides



Δ LDL-C

Δ HDL-C

Δ TG (median)

Ezetimibe

-17.6±20.1 mg/dL

-2.8±5.7 mg/dL

-9 mg/dL

Niacin

-10.0±24.5 mg/dL

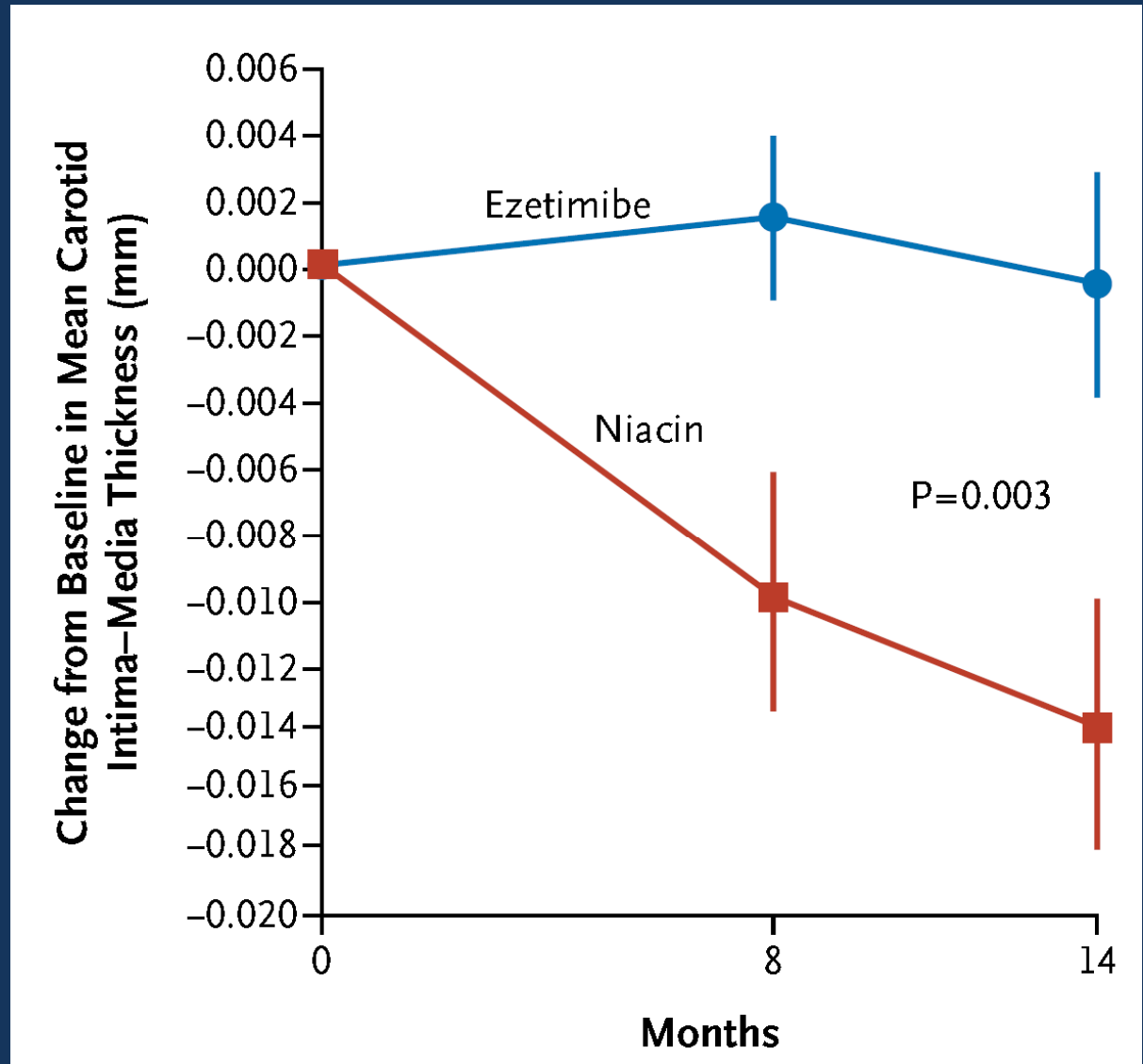
+7.5±9.2 mg/dL

-36 mg/dL

Results: Primary Endpoint

Between-group Change in Carotid Intima-Media Thickness

- Niacin was superior to ezetimibe for the primary endpoint of the between group difference in carotid intima-media thickness.
 - P = 0.003
 - GLM for repeated measures



Results: Carotid Intima-Media Thickness

	Ezetimibe (N = 111)	Niacin (N = 97)	P Value
Baseline ←			
Mean thickness (mm)	0.8957±0.1484	0.9001±0.1558	0.83
Maximal thickness (mm)	1.0065±0.1548	1.0092±0.1650	0.90
Change from baseline to 8 mo ←			
Mean thickness (mm)	0.0014±0.0020	-0.0102±0.0030	0.001
P value for change from baseline	0.48	0.001	
Maximal thickness (mm)	-0.0028±0.0031	-0.0128±0.0043	0.057
P value for change from baseline	0.38	0.004	
Change from baseline to 14 mo ←			
Mean thickness (mm)	-0.0007±0.0035	-0.0142±0.0041	0.01
P value for change from baseline	0.84	0.001	
Maximal thickness (mm)	-0.0009±0.0039	-0.0181±0.0050	0.006
P value for change from baseline	0.81	<0.001	

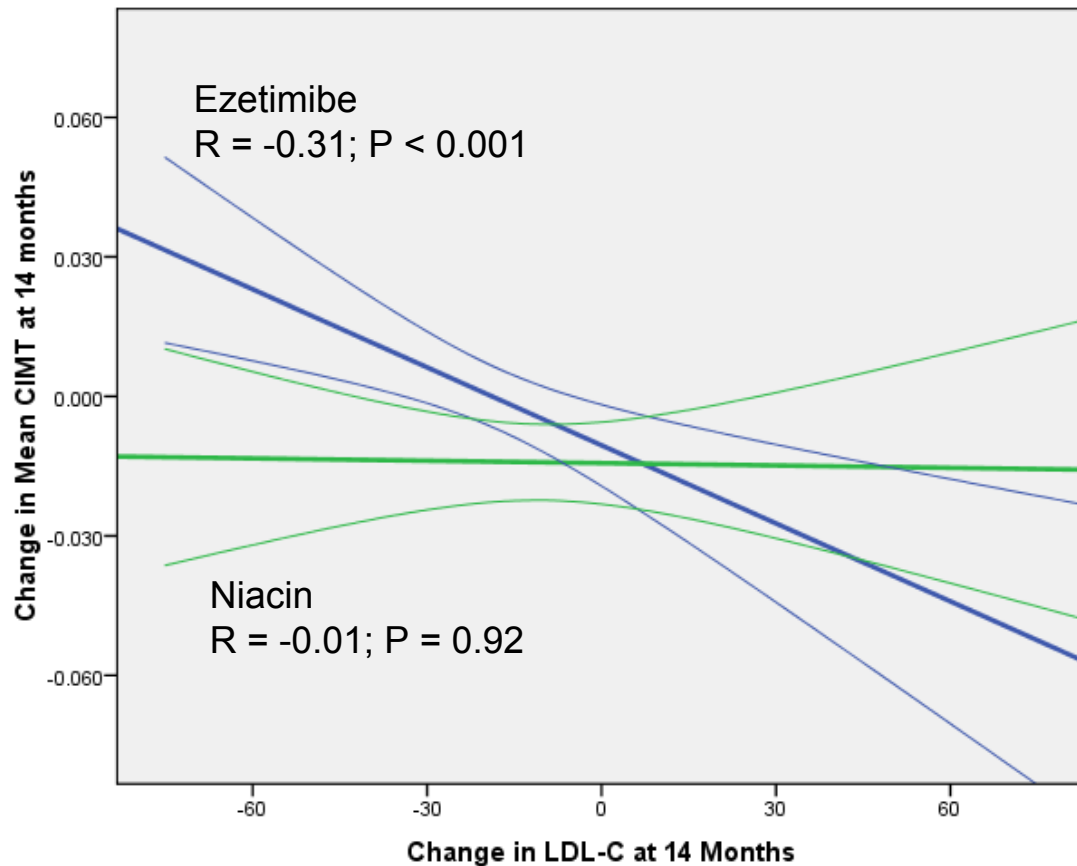
Niacin

- Superior to ezetimibe for the change in mean and maximal CIMT at both 8 and 14 months.
- Significant regression in mean and maximal CIMT at both 8 and 14 months.
- Progressive regression from 8 to 14 months (P = 0.02).

Ezetimibe: No significant net changes in CIMT.

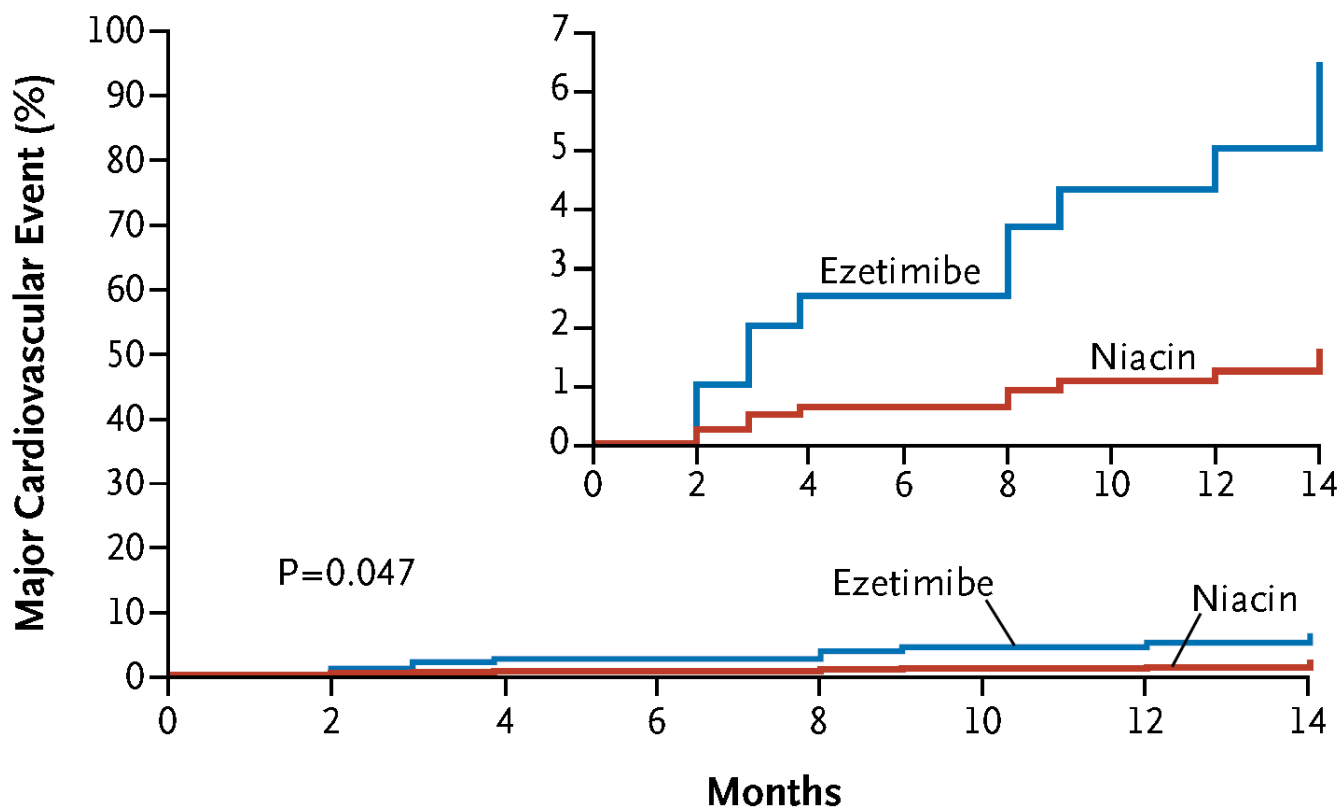
Results: LDL Change vs. CIMT Change

- In a post hoc analysis, we explored the bivariate relationships between changes in LDL cholesterol levels and mean carotid intima-media thickness.



- Significant inverse relationship between change in LDL-C and change in CIMT in the ezetimibe group.**
- Paradoxical increase in CIMT in patients treated with ezetimibe with greater reductions in LDL cholesterol.**
- This effect was not observed with niacin.**
- Hypothesis generating regarding the net effects of ezetimibe's complex mechanism of action.**

Results: Major Cardiovascular Events



No. at Risk

Ezetimibe	176	174	171	167	160	154	146	143	139	132	126	121	118	113	111
Niacin	187	185	171	163	160	152	138	132	130	116	106	104	101	97	97

Major adverse cardiovascular events occurred at a significantly lower incidence in the niacin (2/160 patients [1.2%]) vs. the ezetimibe group (9/165 patients [5.5%])

•Chi-square $p=0.04$; Log-rank $p = 0.047$

Results: Secondary Analyses/Endpoints

- The effects of niacin on the mean carotid intima–media thickness were consistent across prespecified subgroups stratified according to:
 - sex
 - diabetes
 - quartile of baseline HDL cholesterol level
 - median cutoff points for baseline carotid intima–media thickness and C-reactive protein level
- There was a trend for a greater number of niacin patients to withdraw from the study, most commonly due to adverse drug effects but the differences were not statistically significant.
 - Cutaneous flushing was reported in 36% of patients in the niacin group.
- There was no significant difference between the two groups in the quality of life at baseline or at 14 months.
- Adherence to study medication, as measured by tablet counts, was 95±8% with ezetimibe versus 88±15% with niacin ($P<0.001$).

Limitations

- This comparative-effectiveness study shows the superiority of niacin over ezetimibe using carotid intima–media thickness as a surrogate for clinical effectiveness.
 - The incidence of clinical outcomes was also lower in the niacin group among an overall small number events with borderline statistical significance.
- The trial was conducted using a PROBE design because of the use of commercial source drugs and their disparate side-effect profiles; therefore, the trial utilized blinded evaluation of endpoints and automated border-detection methods for quantitation of the carotid intima–media thickness.
- The trial was stopped at the prespecified interim analysis prior to the full sample of 300 subjects completing the trial.
 - Precision of imaging led to greater trial efficiency, as designed.
 - This decision was based upon definitive findings within the primary endpoint leading to a loss of equipoise, and was made in favor of benefit for the volunteer research patients.

ARBITER 6-HALTS

- Regarding comparative effectiveness, when added to a statin medication, combination therapy using niacin is superior to ezetimibe.
- Niacin leads to significant changes in HDL, LDL, and TG and induces regression of carotid intima-media thickness
- Ezetimibe's clinical efficacy remains unproven. HALTS further questions the proper role of ezetimibe, a less effective therapy, in clinical practice, and ezetimibe's mechanism of action.
- The findings regarding ezetimibe are specific to this drug alone, and should not be translated to the overall effects of treating LDL cholesterol with first-line drugs known to be efficacious (statins, bile acid resins).

Implications: HDL-C

- A “low” HDL cholesterol level has been characterized as a value less than 40 mg/dL for men and 50 mg/dL for women.
- HALTS enrolled men and women with an HDL cholesterol level of < 50 or 55 mg/dL (men and women).
 - The HDL cholesterol values of patients in HALTS are representative of 50% of the adult US population.
 - Therefore, generalization of these results is not limited to patients with traditionally “low” HDL levels.
- Suggests that upwards expansion of the treatable range of HDL cholesterol levels may be warranted.

A Final Thought

- Only through alignment of the care of patients with optimal therapies determined through comparative effectiveness studies can we hope to provide the maximal attainable benefit for our health care investment.
- In 2008, approximately 9 million U.S. patients received treatment with ezetimibe; approximately 2.5 million patients received niacin.
- **ARBITER 6-HALTS**
 - Demonstrates the superior clinical effectiveness of niacin over ezetimibe.
 - Urges more stringent attention to the application of evidenced-based treatments and broader treatment of HDL cholesterol.

