

# Simvastatin With or Without Ezetimibe in Familial Hypercholesterolemia

## The ENHANCE trial

ClinicalTrials.gov number: NCT00552097

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Kastelein, et al, N Eng J Med 2008; In Press

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JOURNAL *of* MEDICINE

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in Familial Hypercholesterolemia

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for the ENHANCE Investigators\*

# Presenter Disclosure Information

John J.P. Kastelein, MD, PhD

The following relationships exist related to this presentation:

- Dr. Kastelein consults for Merck & Schering Plough
- Dr. Kastelein is also a consultant for several other pharmaceutical companies with lipid-lowering agents.

**Although the authors allowed the sponsors to review the manuscript and the presentation, all data analyses and interpretation of the results are those of the academic investigators.**

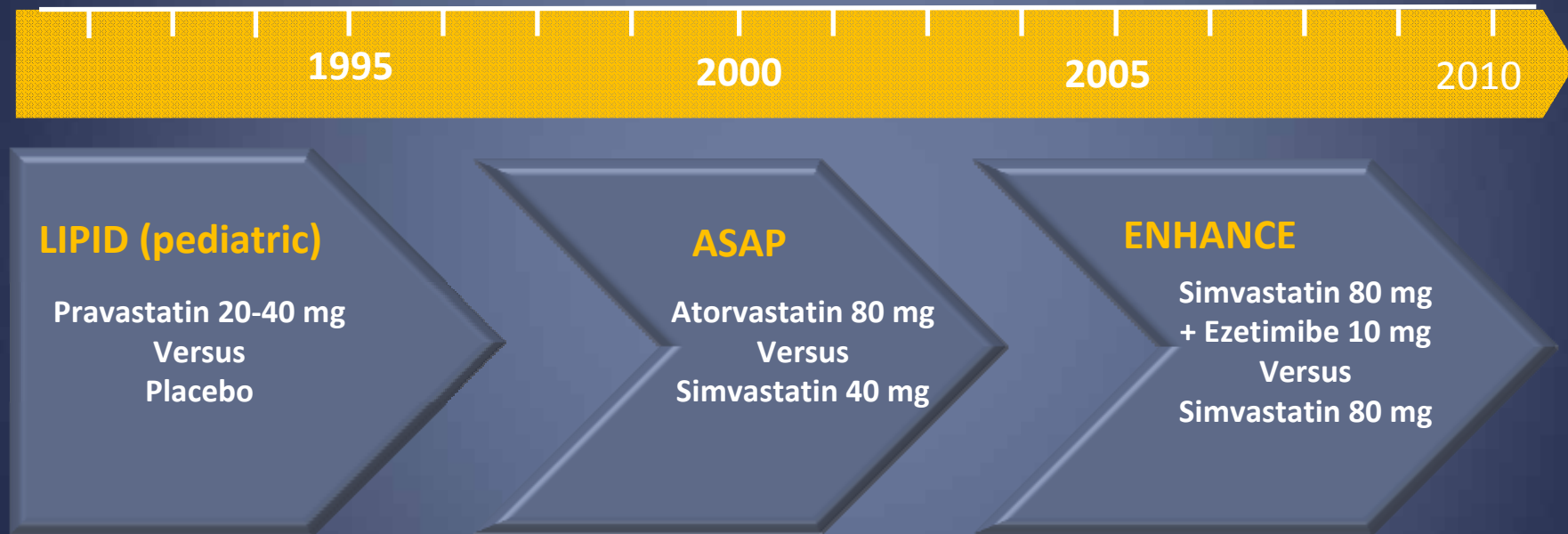
## Background

Ezetimibe, a cholesterol-absorption inhibitor, reduces levels of LDL-c when added to statin treatment.

However, the effect of Ezetimibe on the progression of atherosclerosis is unknown

# ENHANCE logical next step after ASAP

## Timeline



Wiegman et al, Efficacy and Safety of Statin Therapy in Children With FH. JAMA 2004; 292(3):331-7  
Smilde et al, Atorvastatin versus Simvastatin on Atherosclerotic Progression study. Lancet 2001;357:577-81

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# ENHANCE Study Design

Pre-randomization Phase

FH:  
LDL-c  $\geq$  210 mg/dL

Screening and  
Fibrate  
Washout

Placebo Lead-  
In/ Drug  
Washout

R  
A  
N  
D  
O  
M  
I  
Z  
A  
T  
I  
O  
N

Ezetimibe 10 mg-Simvastatin 80 mg

Simvastatin 80 mg

IMT assessment

-10 to -7

-6

0

3

6

9

12

15

18

21

24

Weeks

Months

# ENHANCE Study Population

## Major inclusion criteria

- Age 30-75 years
- HeFH:
  - Genotyping
  - Diagnostic criteria WHO
- Untreated LDL-C levels > 210 mg/dL (5.43 mmol/l)
- Patients on lipid-lowering treatment  
LDL-c after wash –out > 210 mg/dL (5.43 mmol/l)

## Major exclusion criteria

- High-grade carotid stenosis
- History carotid endarterectomy
- Carotid stenting
- Congestive heart failure III/IV

# ENHANCE cIMT Methodology

## Carotid Intima-Media thickness (cIMT) measurements

- Measurements were made at a predefined angle of insonation
- Only the far-walls of all segments were imaged
- Images were stored in DICOM for offline image analyses



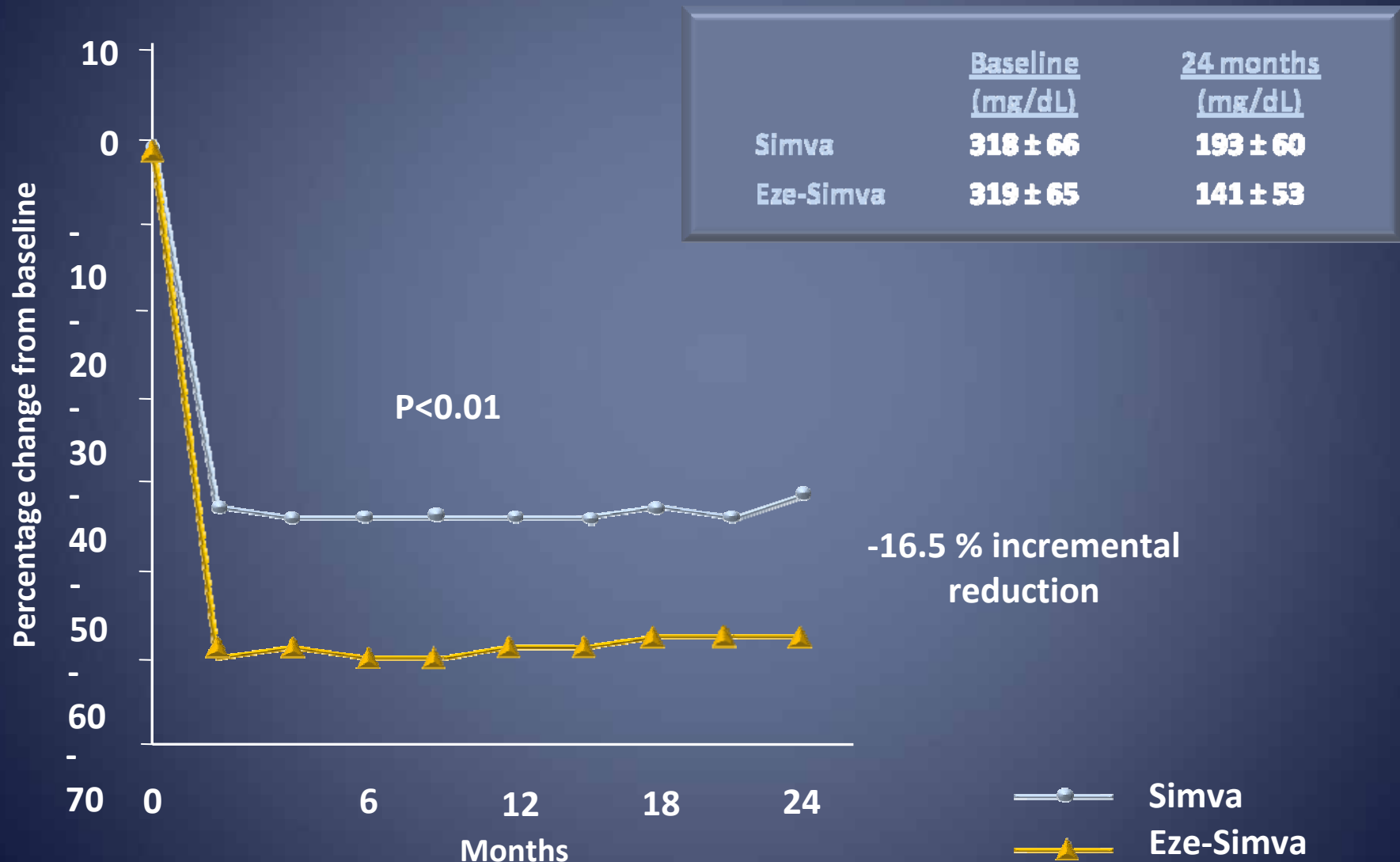
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de Groot E, et al. *Circulation*. (2004) 109[Suppl III]:III-33-III-38.

# Baseline characteristics

	Simvastatin Monotherapy	Simvastatin plus Ezetimibe	P-value
All randomized patients	n=363	n=357	
Age (yr)	45.7±10.0	46.1±9.0	0.69
Male sex no. (%)	179(49%)	191 (54%)	0.26
Body-mass index	26.7±4.4	27.4±4.6	0.047
History of diabetes	5(1%)	8 (2%)	0.38
Hypertension	51 (14%)	67 (19%)	0.09
Current smoking	104 (29%)	102 (29%)	0.98
History of MI	26 (7%)	14 (4%)	0.06
Prior use of statins	297 (82%)	286 (80%)	0.56
Systolic mm Hg	124±15	125±15	0.31
Diastolic mm Hg	78±10	78±9	0.41

# LDL-cholesterol

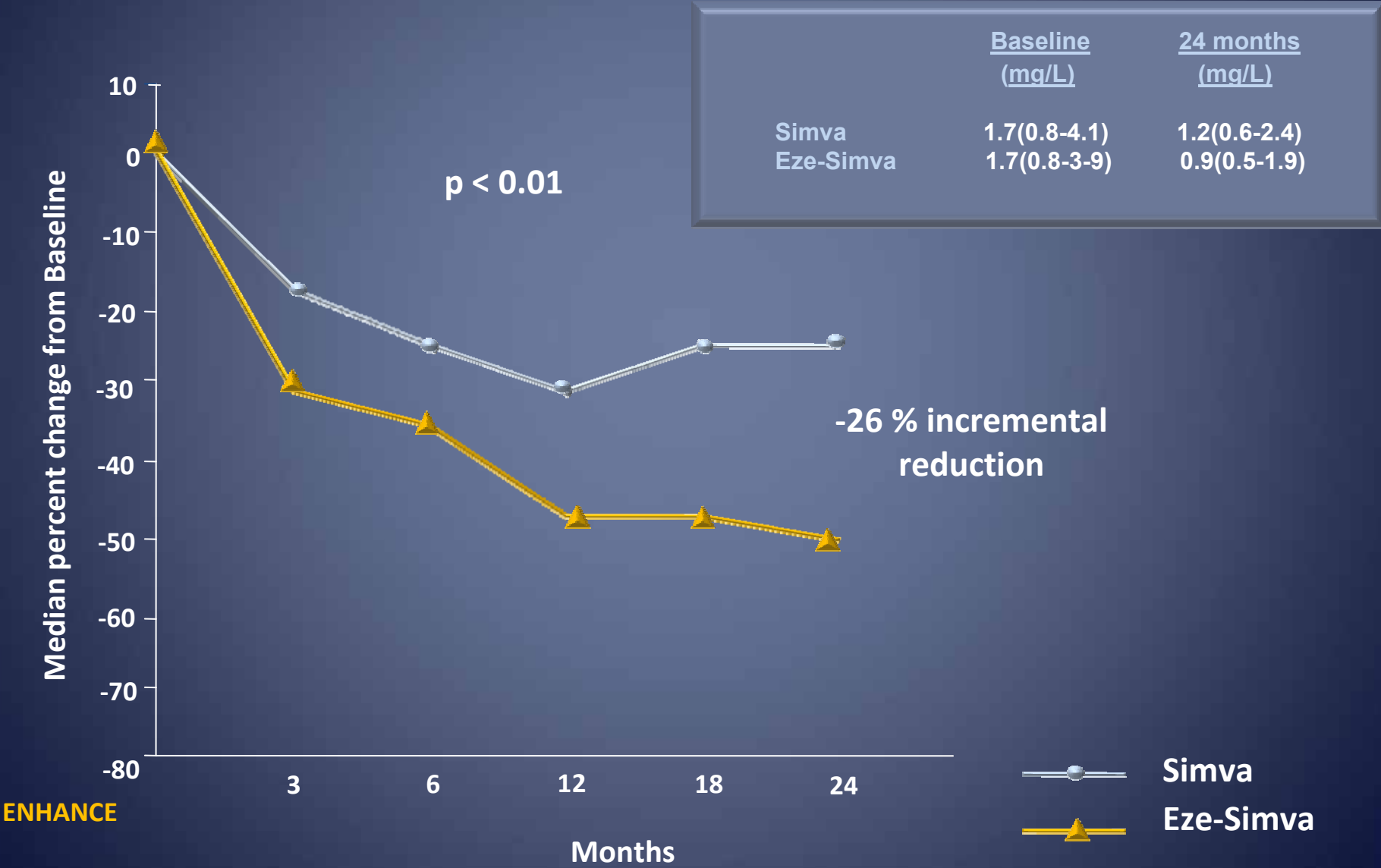


# Other Lipids and Apolipoproteins

## Percent Change From Baseline

	<u>Simvastatin 80</u>	<u>EZE/simva 10/80</u>	<u>P value</u>
Total Cholesterol	-31.9±0.8	-45.3±0.8	<0.01
LDL-cholesterol	-39.1±0.9	-55.6±0.9	<0.01
Triglycerides (median)	-23.2	-29.8	<0.01
HDL-cholesterol	7.8±0.9	10.2±1.0	0.05
Apo B	-33.1±0.9	-46.7±0.9	<0.01
Apo A1	6.9±0.8	6.3±0.8	0.56

# hsCRP



# Primary Efficacy Outcome

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# No significant changes in 1° or 2° endpoints

Variable	Simvastatin Monotherapy		Simvastatin plus Ezetimibe		P value (mean)
	<u>Mean</u>	<u>Median</u>	<u>Mean</u>	<u>Median</u>	
	<i>Millimeters</i>				
<b>Baseline</b>	<b>n=342</b>		<b>n=338</b>		
Mean cIMT	0.70±0.13	0.69	0.69±0.13	0.68	0.64
Mean maximum cIMT	0.80±0.16	0.78	0.80±0.17	0.76	0.94
<b>24 months follow-up</b>	<b>n=320</b>		<b>n=322</b>		
Mean cIMT	0.70±0.14	0.69	0.71±0.15	0.68	0.29
Mean maximum cIMT	0.81±0.17	0.79	0.82±0.18	0.78	0.27
<b>Difference from baseline</b>					
Mean cIMT	0.0058±0.0037	0.0095	0.0111±0.0038	0.0058	0.29
Mean maximum cIMT	0.0103±0.0049	0.0103	0.0175±0.0049	0.0160	0.27

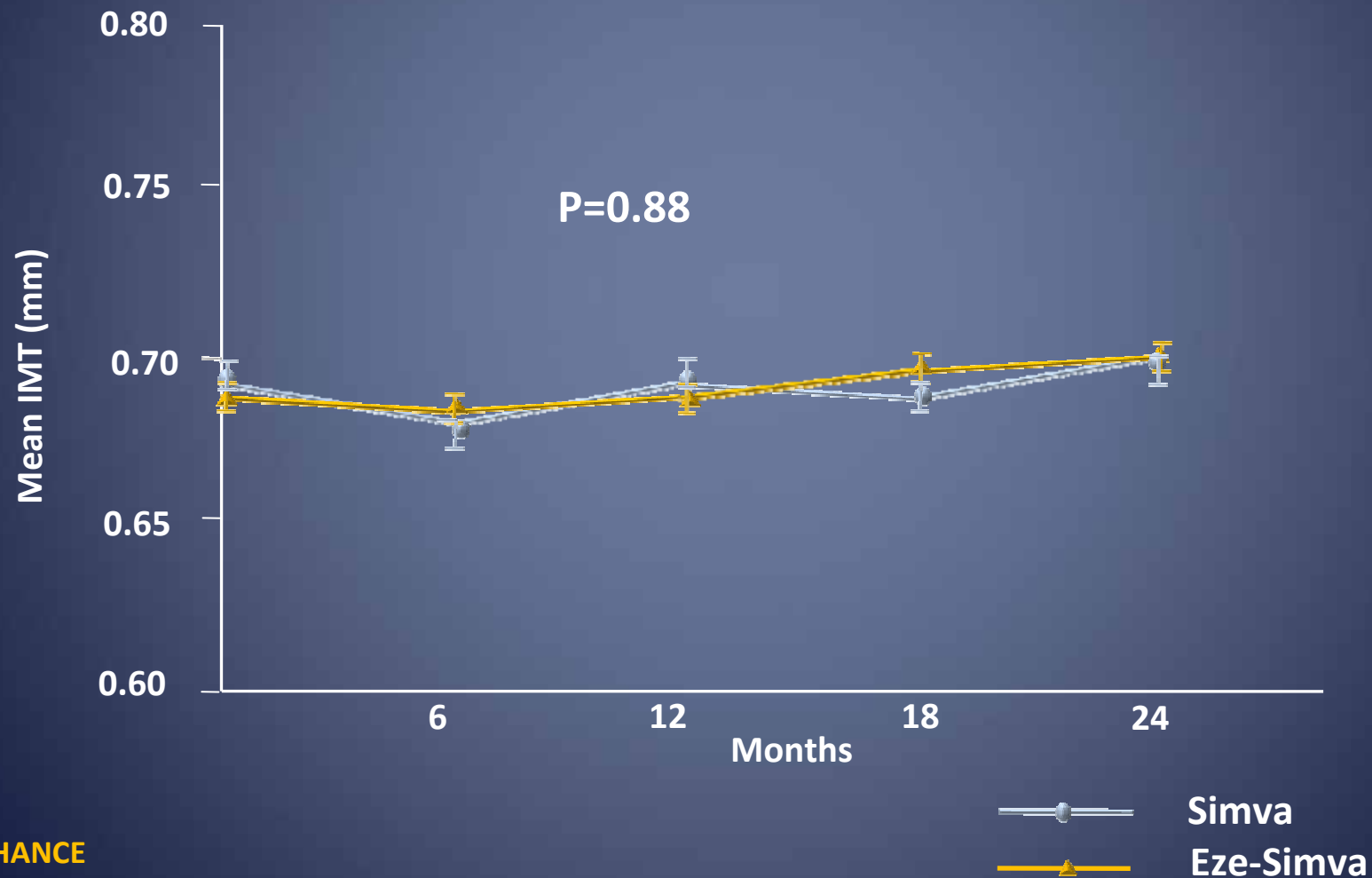
consistent inferential results observed for non-parametric (median) and parametric (mean) analyses

Variable	Simvastatin Monotherapy		Simvastatin plus Ezetimibe		P value (mean)
	<u>Mean</u>	<u>Median</u>	<u>Mean</u>	<u>Median</u>	
	<i>Millimeters</i>				
<b>Baseline</b>	<b>n=342</b>		<b>n=338</b>		
CCA	0.68±0.16	0.66	0.67±0.16	0.64	0.45
CBA	0.80±0.20	0.78	0.79±0.22	0.76	0.51
ICA	0.61±0.17	0.58	0.62±0.17	0.60	0.42
<b>24 months follow-up</b>	<b>n=320</b>		<b>n=322</b>		
CCA	0.68±0.15	0.66	0.68±0.16	0.64	0.93
CBA	0.81±0.22	0.79	0.81±0.23	0.77	0.37
ICA	0.62±0.17	0.59	0.64±0.17	0.60	0.21
<b>Difference from baseline</b>					
CCA	0.0024±0.0043	0.0043	0.0019±0.0044	0.0010	0.93
CBA	0.0062±0.0069	0.0099	0.0144±0.0070	0.0107	0.37
ICA	-0.0007±0.0064	0.0057	0.0099±0.0065	0.0066	0.21

consistent inferential results observed for non-parametric (median) and parametric (mean) analyses

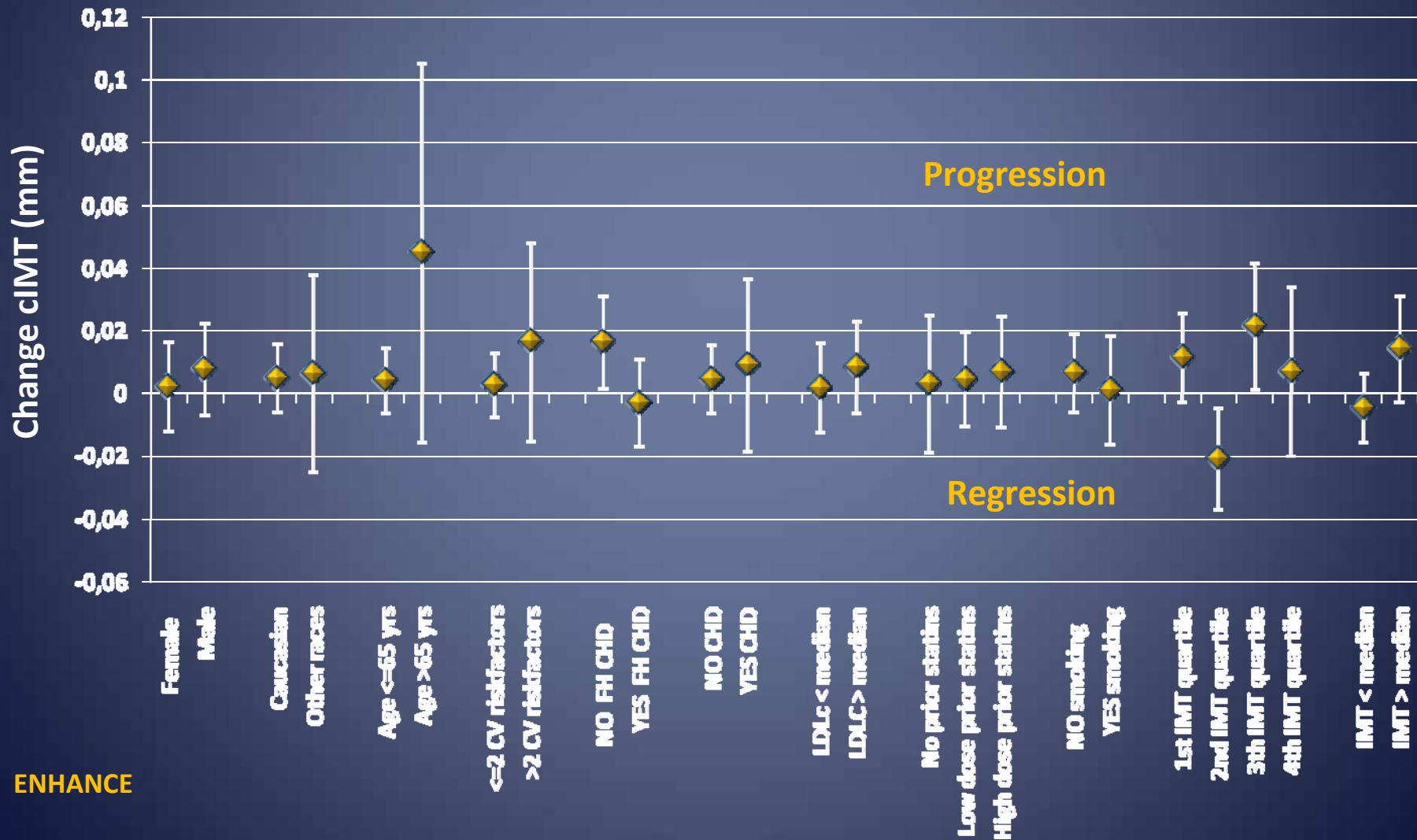
# Mean cIMT during 24 months of therapy

Longitudinal, repeated measures analysis



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# No significant changes across any subgroup



# Discussion

# Possible explanations for the absence of an incremental reduction in cIMT

## Measurement Technique

Technique not accurate enough to reflect changes in atherosclerotic burden?

## The Compound

Ezetimibe lacks vascular benefit despite the observed LDL-c and hsCRP reduction

## The Population

At too low a risk to detect changes, which would limit the ability to detect a differential response

# Quality of cIMT measurement

## Completeness

	Percentage	Number of images
Mean cIMT	88 %	20986/23856
Mean CCA	97 %	7681/7952
Mean CIA	83 %	6603/7952
Mean CBA	84 %	6702/7952

Intraclass correlation coefficient at  
baseline: 0.93

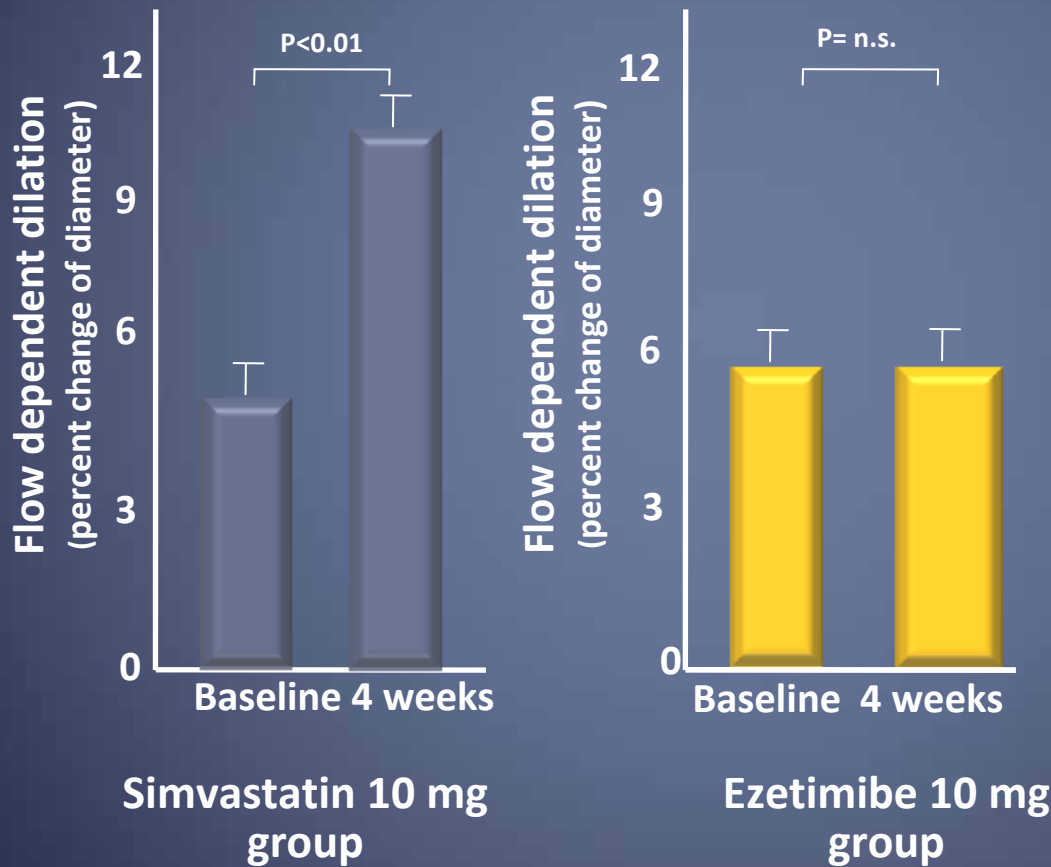
Intraclass correlation coefficient at  
study endpoint: 0.95

Standard deviation between the  
paired measure at baseline:  
0.053 mm

Standard deviation between the  
paired measure at 24 months:  
0.056 mm

# The Compound

## Ezetimibe no pleiotropic effects?

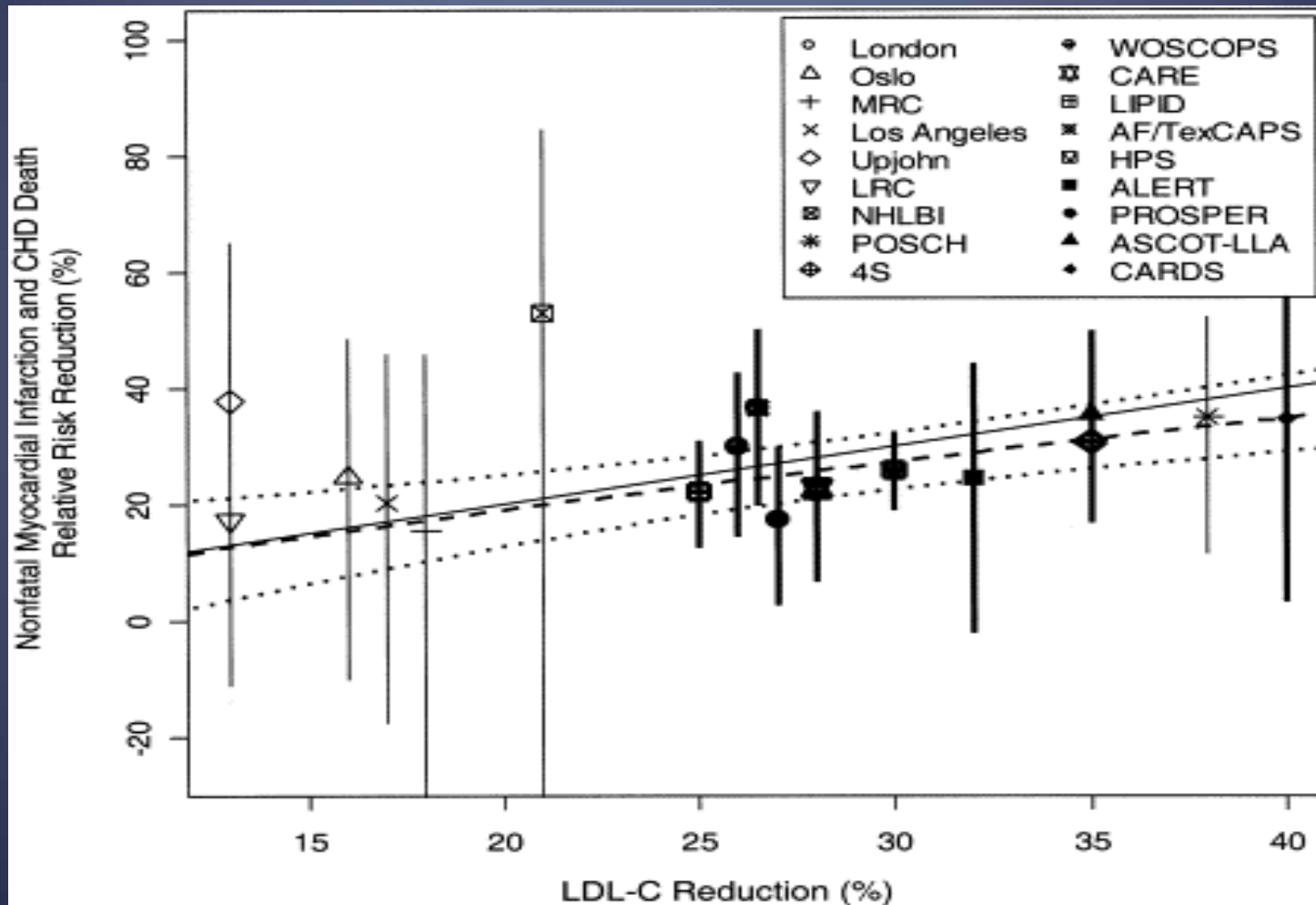


Chronic heart failure patients (NYHA III), n=10 per group

LDL-c reduction similar in both groups.

Simvastatin: 15.6 %  
Ezetimibe: 15.4%

# Pleiotropic Effects of Statins: Benefit Beyond Cholesterol Reduction?



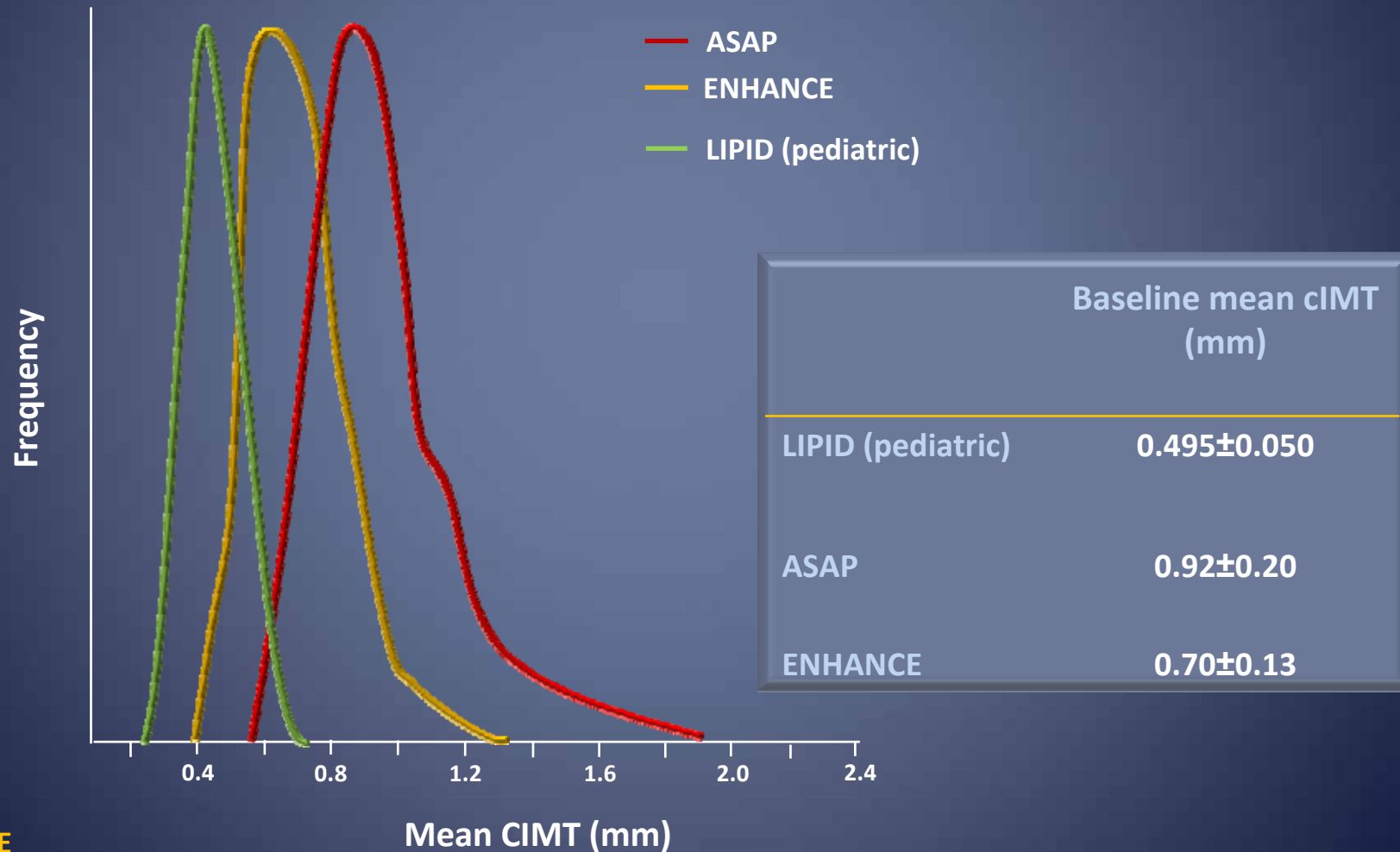
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Robinson et al, J Am Coll Cardiol 2005;46:1855-62

# The Population

The treatment of patients with FH has witnessed profound changes

# Baseline cIMT in LIPID (pediatric), ASAP and ENHANCE



# Safety observations

- Both regimens well tolerated, with overall safety profiles generally similar and consistent with product labels
- One case of viral hepatitis A in the simvastatin-only arm
- One case of myopathy (defined as CPK > 10 ULN, with associated muscle symptoms) in the simvastatin-only arm and 2 cases in the Ezetimibe-Simvastatin arm

Consecutive	Simvastatin n=360	Ezetimibe-Simvastatin n=356	p
ALT and/or AST $\geq 3$ X ULN	8	10	0.62
CPK $\geq 10$ X ULN	8	4	0.25

Subjects with 2 consecutive measurements for ALT and/or AST; a single last measurement  $\geq 3$  ULN; a measurement  $\geq 3$  X ULN followed by  $< 2$  ULN that was taken more than 2 days after the last dose of study medication

## Conclusion

The addition of Ezetimibe to Simvastatin did lead to expected changes in LDL-c and hsCRP, but did not reduce any cIMT parameter

The reason(s) for this discrepancy currently remains unknown

# Acknowledgements

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