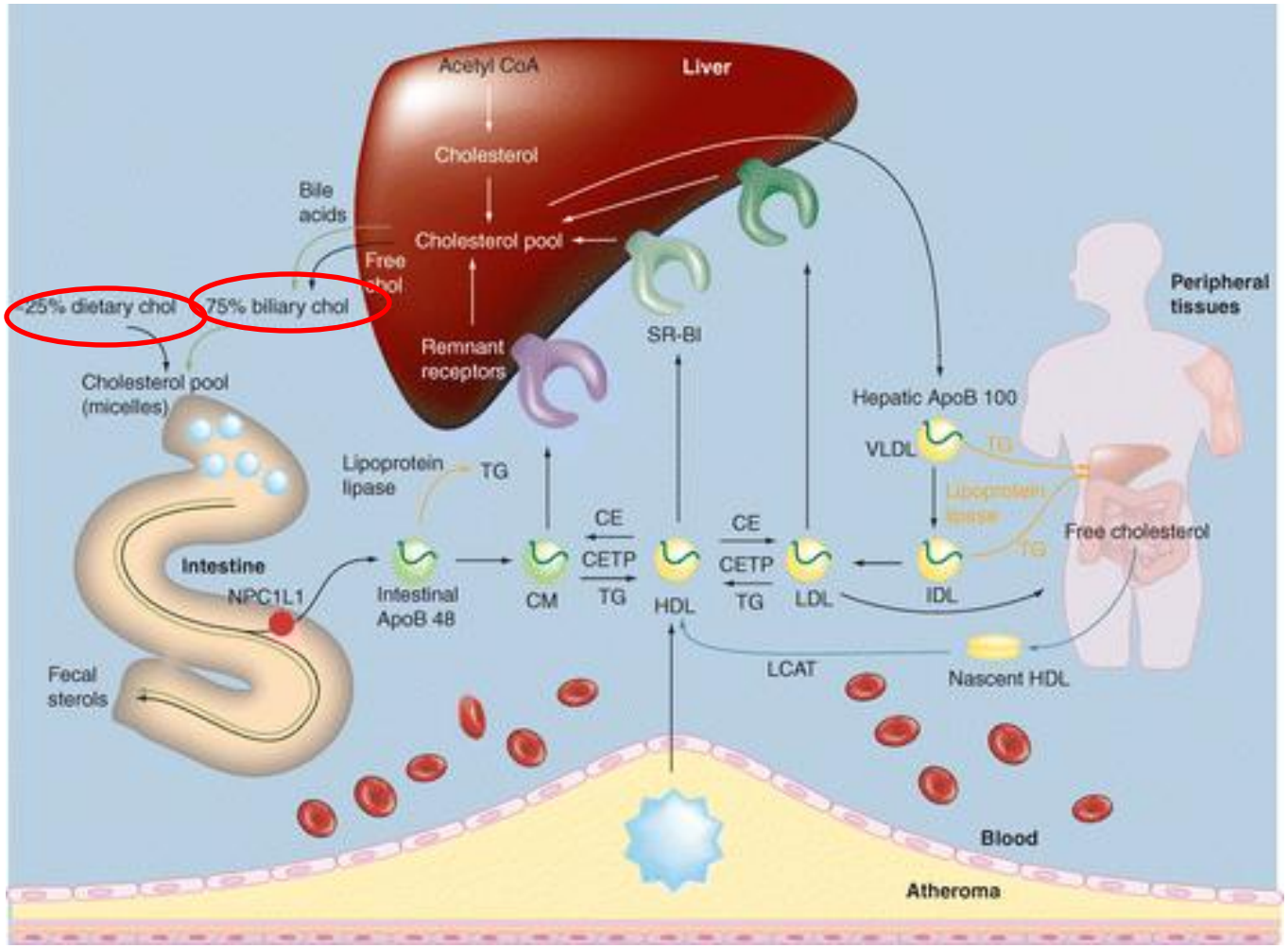
Ezetimibe and Vytorin

Teng-Yao Yang
Cardiovascular Department
Chang Gung Memorial Hospital, Chia-Yi

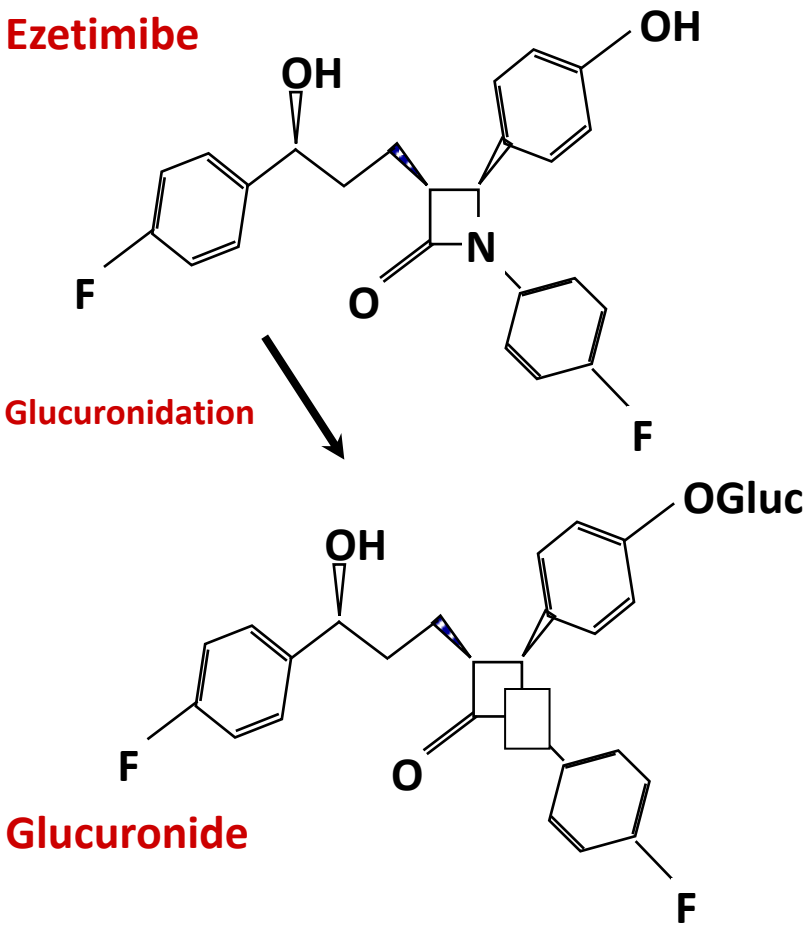
Contents



Niemann–Pick C1-like 1 protein (NPC1L1)

Expert Rev Cardiovasc Ther. 2008;6(4):447-470.

Metabolism of Ezetimibe



- Rapidly metabolized to an active glucuronide metabolite
- Both parent drug and metabolite inhibit cholesterol absorption
- Glucuronide metabolite more potent than parent drug in inhibiting cholesterol absorption
- Repeated enterohepatic circulation results in long duration of action

Adapted from Catapano AL *Eur Heart J Suppl* 2001;3(suppl E):E6-E10; van Heek M et al *Br J Pharmacol* 2000;129:1748-1754; Patrick JE et al *Drug Metab Dispos* 2002;30:430-437; Ezzet F et al *Clin Ther* 2001;23:871-885.

Pharmacokinetics of Ezetimibe

Metabolism

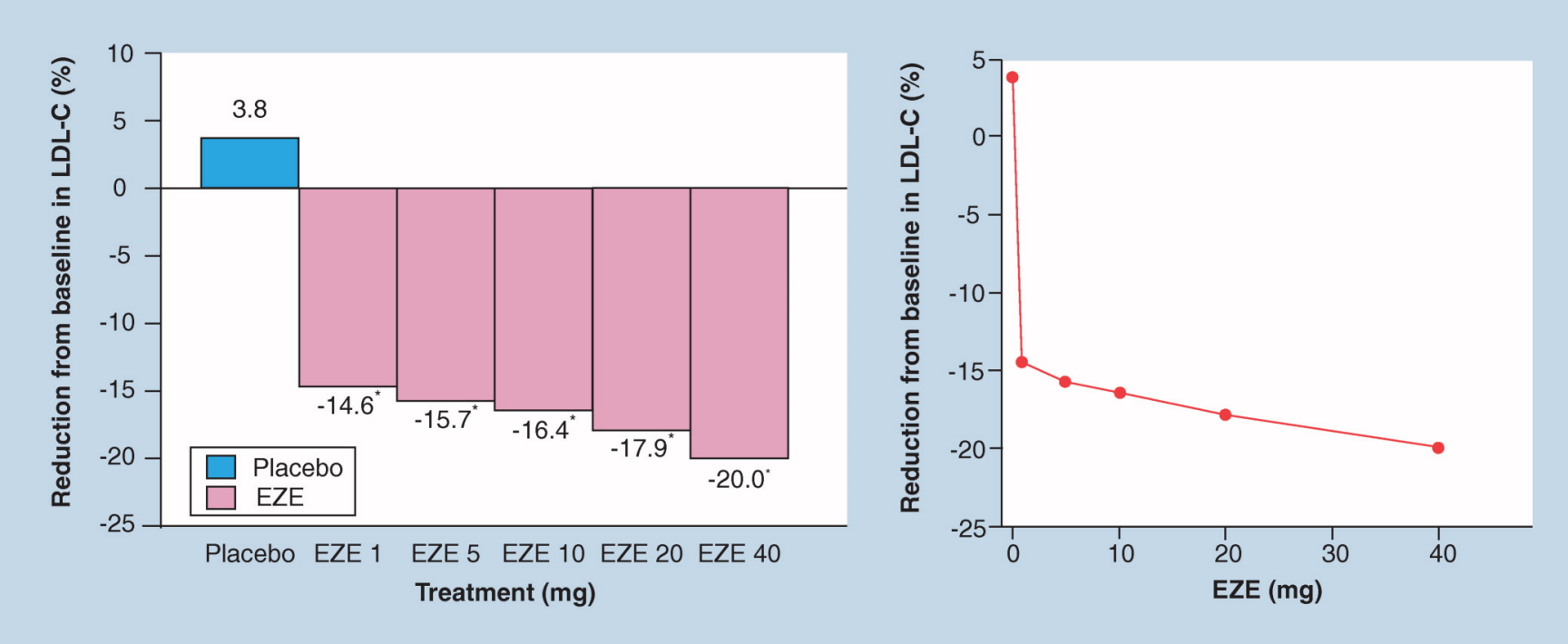
- **Ezetimibe is metabolized primarily in the small intestine and liver via glucuronide conjugation with subsequent biliary excretion**

Elimination

- **half-life of ezetimibe approximately 22 hours**
- **Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling.**

Adapted from Bays HE et al *Clin Ther* 2001;23:1209-1230*;* Kirsten R et al *Clin Pharmacokinet* 1998;34:457-482.

Dose–Response Effect of Ezetimibe Monotherapy

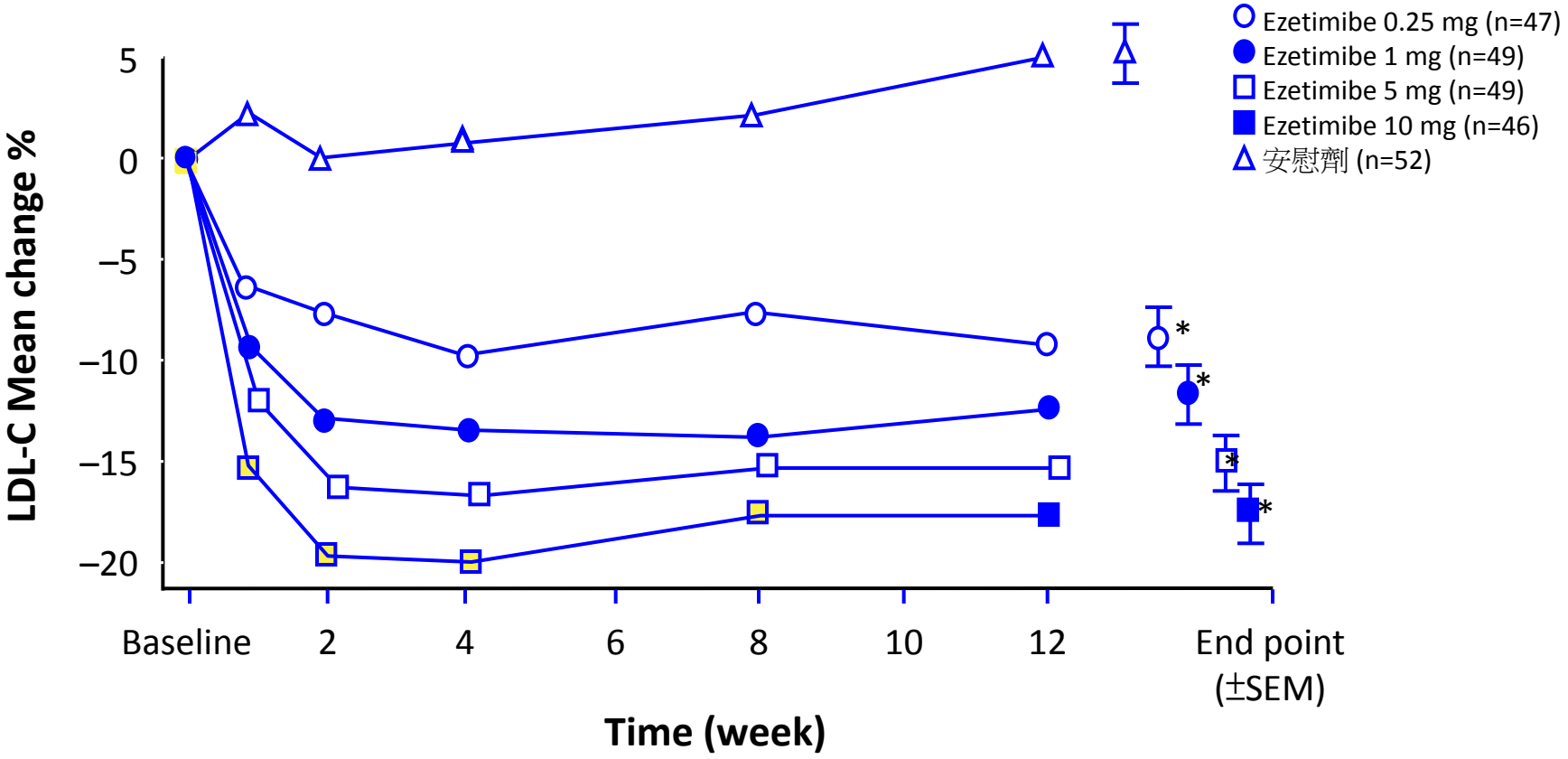


In clinical studies, ezetimibe (10 mg) monotherapy significantly reduces LDL-C levels in hypercholesterolemic patients by **-17.2 to -22.3%** ($p < 0.01$ to < 0.001) compared with placebo

Doses of 20 and 40 mg ezetimibe were well tolerated in early trials; however, these doses provided minimal additional lipid-altering benefit .

Expert Rev Cardiovasc Ther. 2008;6(4):447-470.

Ezetimibe vs Plasma LDL-C：Dosage reaction



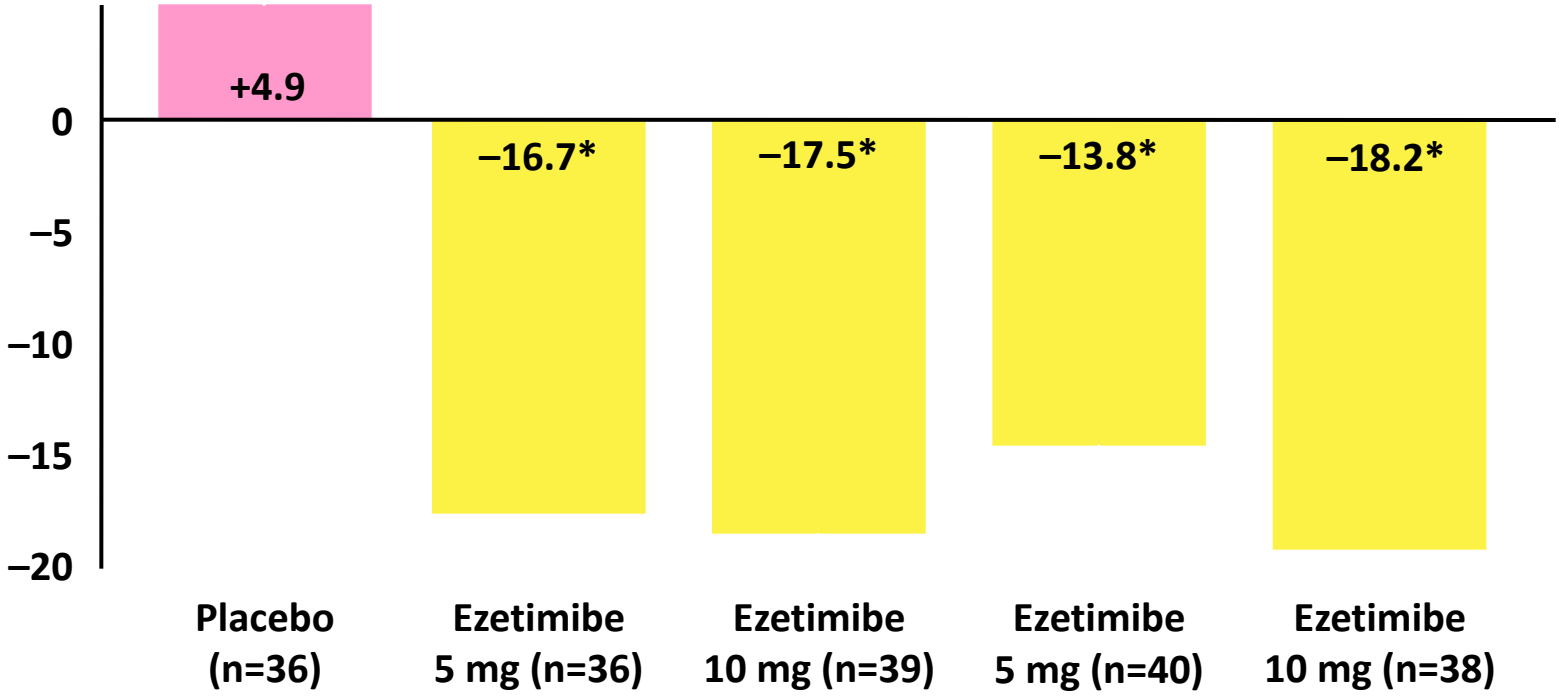
SEM= 標準誤差平均 (standard error of the mean)

*相較於安慰劑，p<0.01

取材自 Bays HE et al *Clin Ther* 2001;23:1209-1230.

Ezetimibe vs Plasma LDL-C :

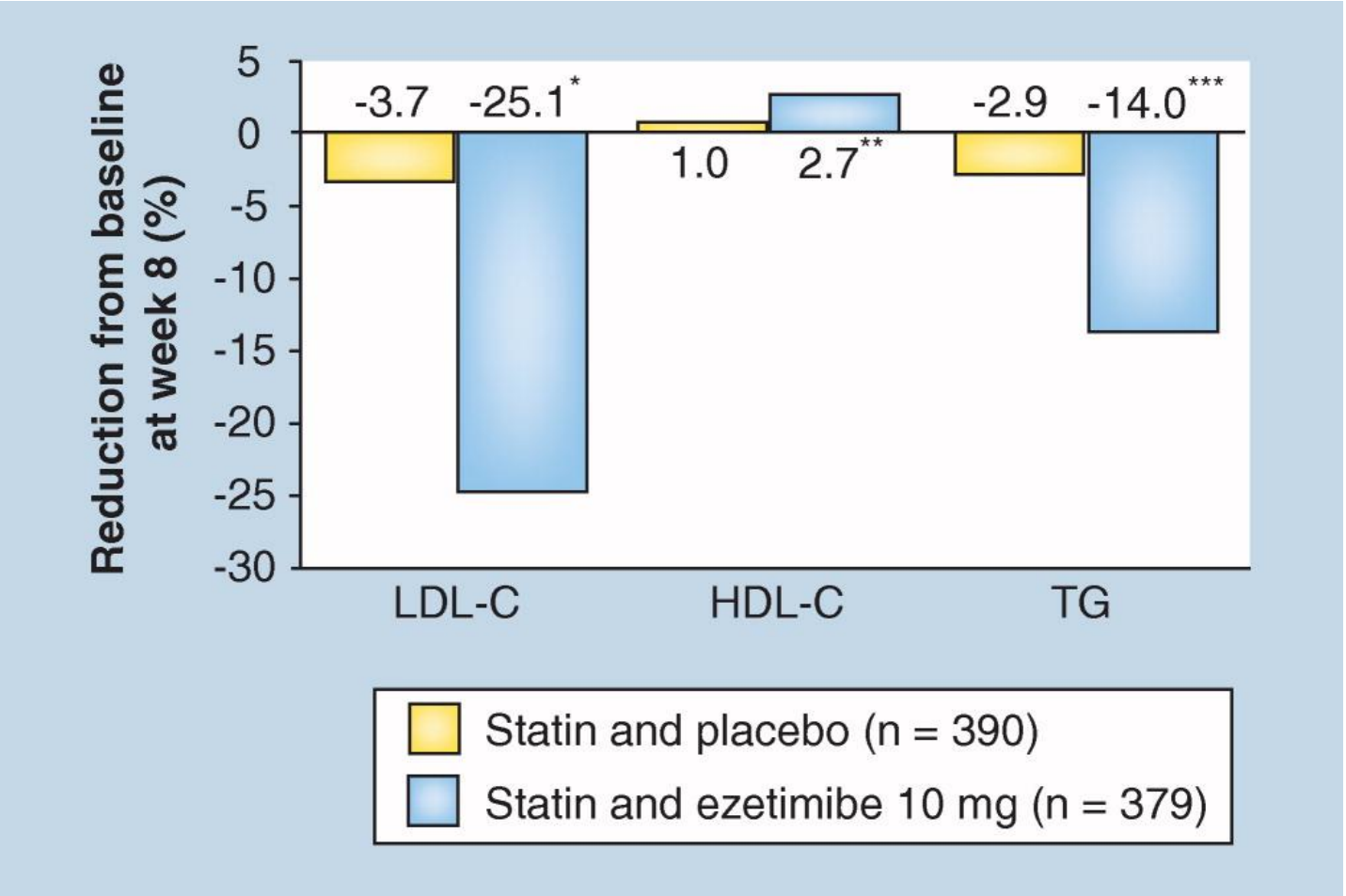
Comparison between morning and evening administration



*compared with placebo，p<0.01

Adapted from: Bays HE et al *Clin Ther* 2001;23:1209-1230; Data on file, MSD.

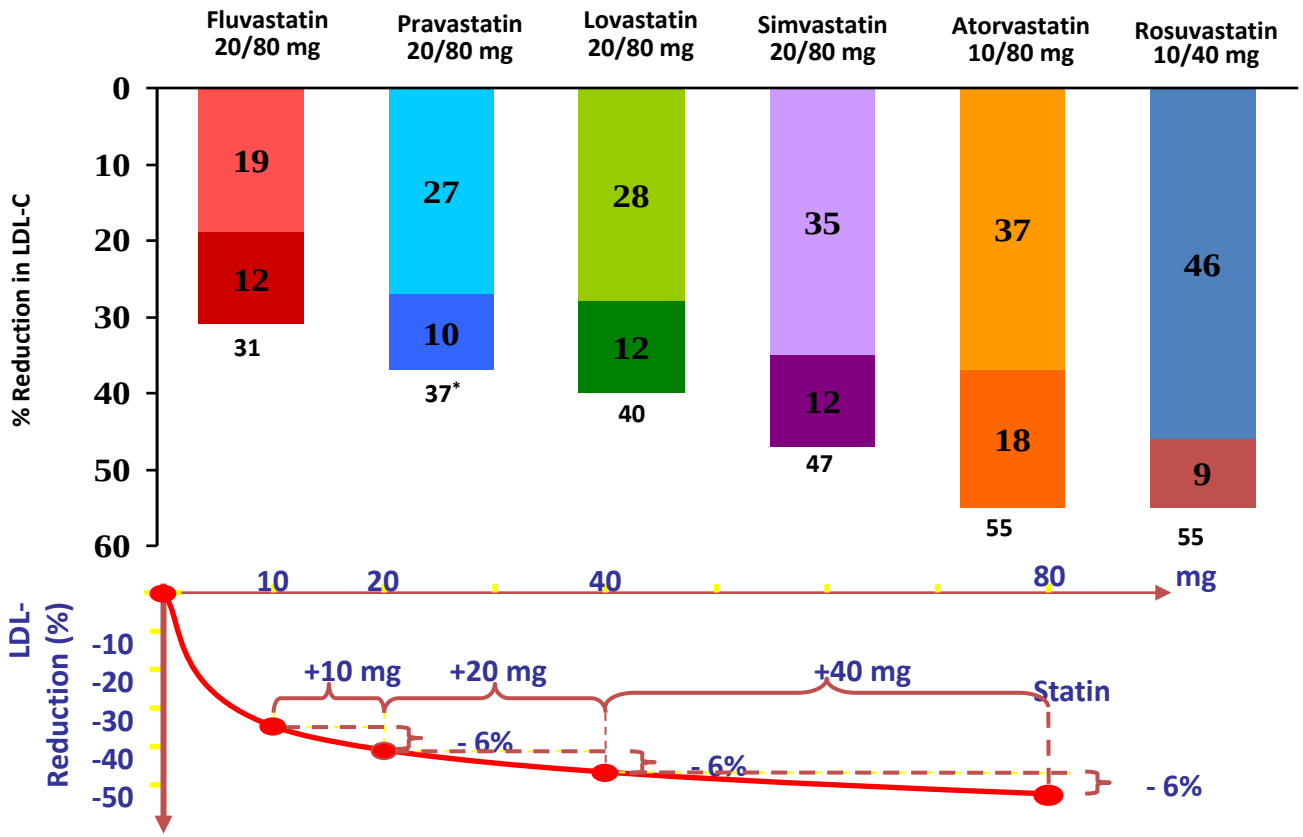
Ezetimibe Add-on to Statin Therapy



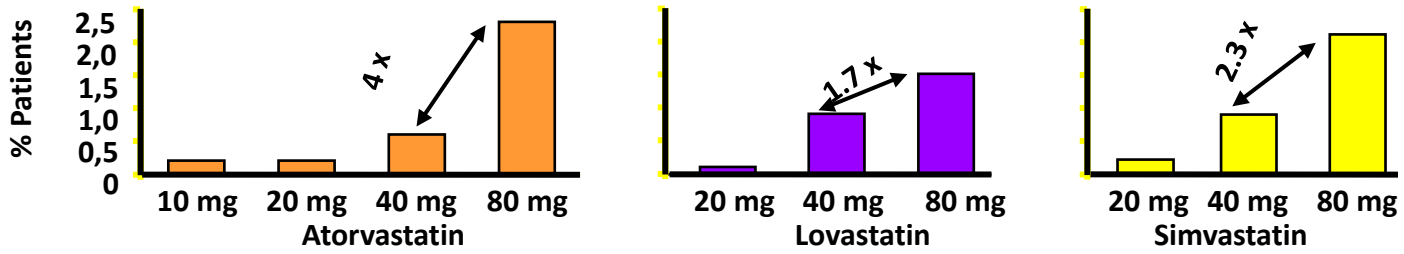
When added to statins, ezetimibe reduces LDL-C levels significantly beyond those with statins alone **(-5.9 to -21.0%;** $p < 0.05$ to < 0.001)

Expert Rev Cardiovasc Ther. 2008;6(4):447-470.

Rule of 6

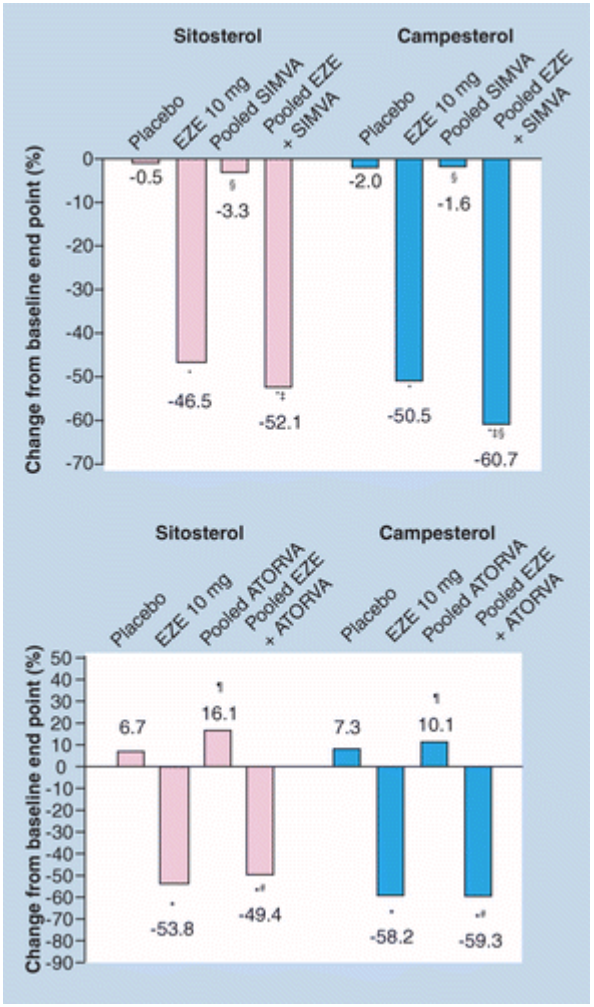


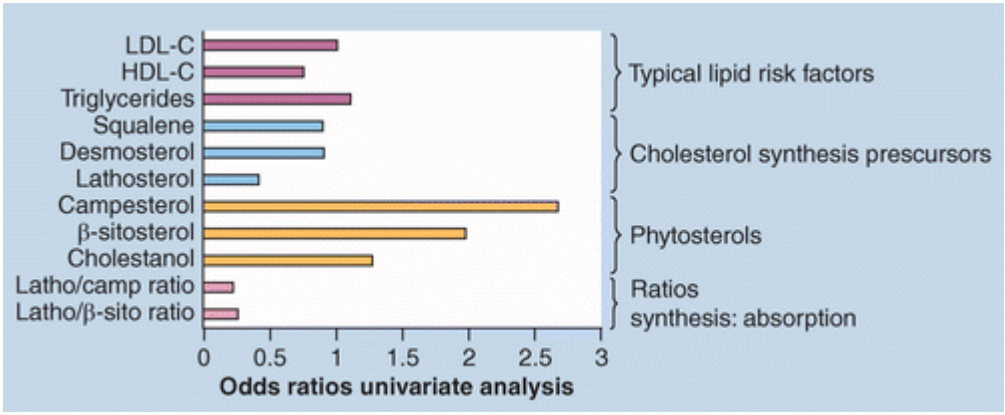
Adverse effects



Med Clin North Am. 2000; 84:23

Ezetimibe and Statin Effects on Cholesterol Precursors

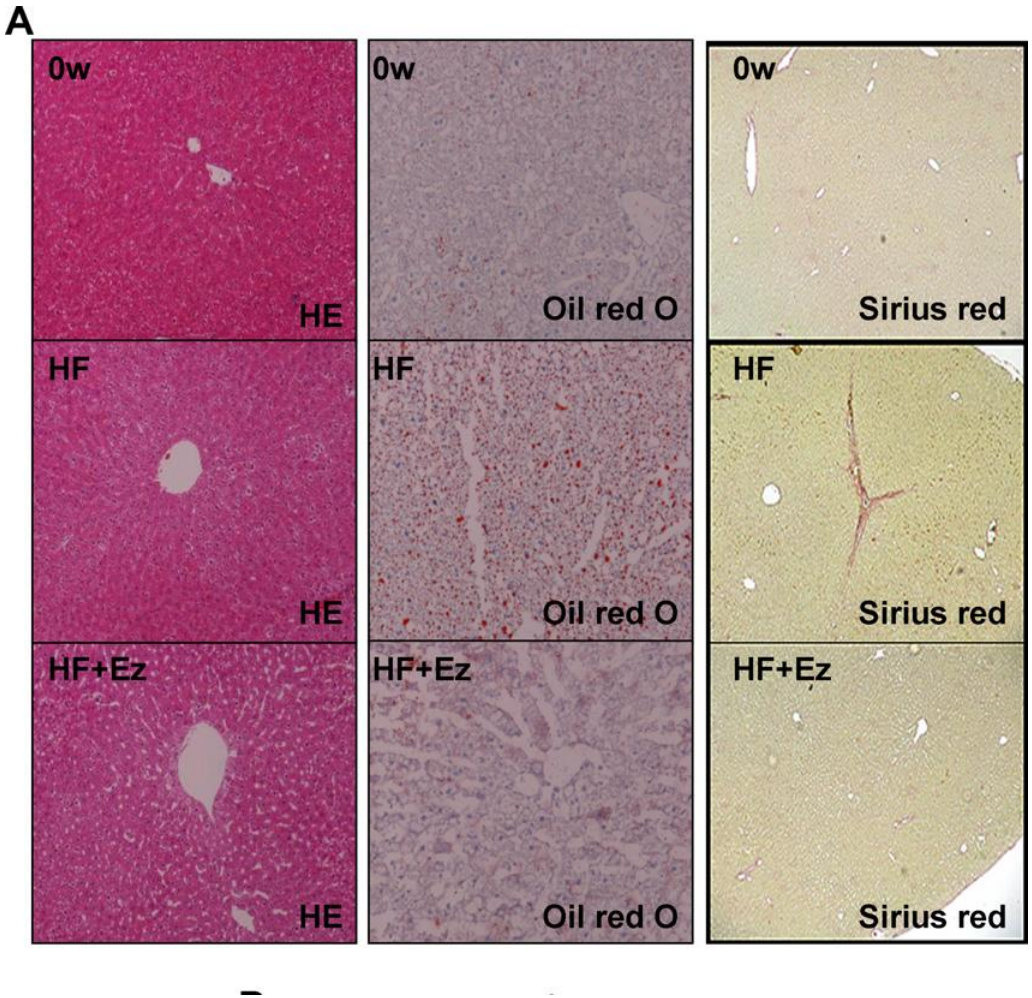




Sitosterol: marker of cholesterol absorption
Campersterol: marker of cholesterol synthesis

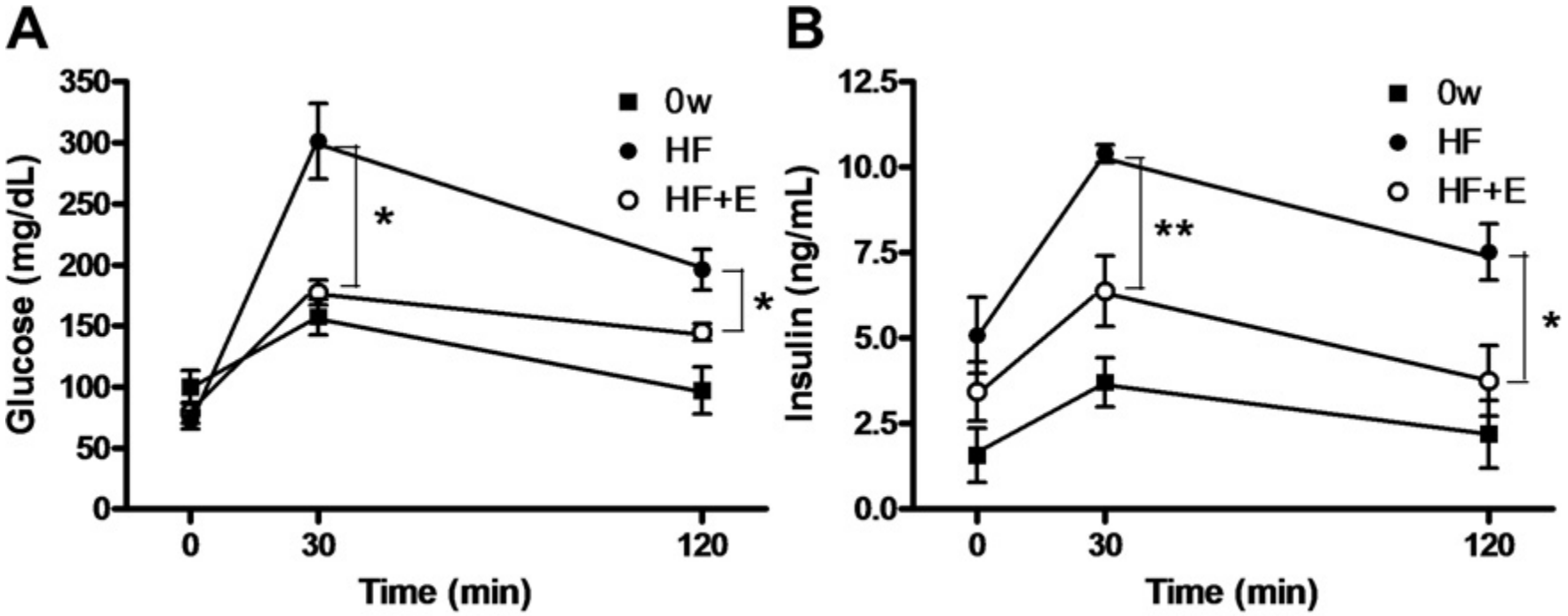
Expert Rev Cardiovasc Ther. 2008;6(4):447-470.

Ezetimibe On Fatty Liver



FEBS Lett. 2007 Dec 11;581(29):5664-5670.

Ezetimibe On Insulin Sensitivity (1)



FEBS Lett. 2007 Dec 11;581(29):5664-5670.

Ezetimibe On Insulin Sensitivity (2)

This study registered 100 cases.

Of the cases, 50 [57.1 ± 11.1 years (24 (48%) females and 26 (52%) males)] were administered **40 mg/day pravastatin (group 1)** and 50 [53.2 ± 12.2 years (27 (54%) females and 23 (46%) males)] were administered **10 mg pravastatin + 10 mg ezetimibe (group 2).**

Results In group 1, total cholesterol fell from 231.1 ± 83.5 mg/dl to 211.3 ± 37.2 mg/dl ($p = 0.03$), triglyceride from 243.5 ± 96.8 mg/dl to 190.9 ± 55.2 mg/dl ($p = 0.003$), and LDL cholesterol from 165.7 ± 29.7 mg/dl to 133.4 ± 26.6 mg/dl ($p = 0.02$). In group 2, total cholesterol dropped from 250.9 ± 51.8 mg/dl to 187.9 ± 34.9 mg/dl ($p = 0.001$), triglyceride from 270.3 ± 158.9 mg/dl to 154.6 ± 60.7 mg/dl ($p = 0.001$), and LDL cholesterol from 158.1 ± 47.5 mg/dl to 116.9 ± 26.4 mg/dl ($p = 0.001$). **Insulin resistance decreased from 4.05 ± 2.31 to 3.16 ± 1.90 ($p = 0.07$) in group 1 and from 2.96 ± 1.50 to 2.05 ± 0.55 ($p = 0.009$) in group 2. High sensitive C-reactive protein fell from 6.69 ± 6.11 mg/l to 3.02 ± 1.70 mg/l ($p = 0.01$) in group 1 and from 6.36 ± 2.06 mg/l to 2.68 ± 1.69 mg/l ($p = 0.001$) in group 2.**

Inflammation. 2007 Dec;30(6):230-235.

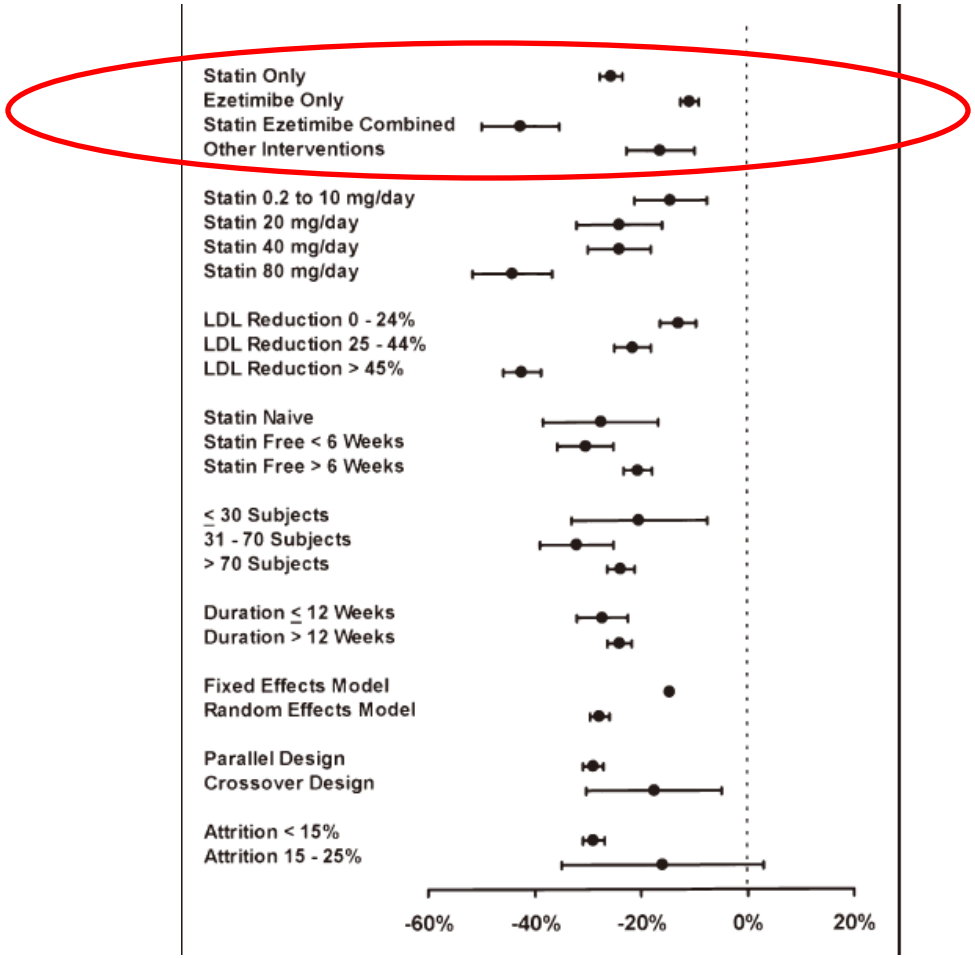
Ezetimibe On Insulin Sensitivity (3)

A randomized, double-blind, placebo-controlled clinical trial was carried out in **12 obese, dyslipidaemic patients,** independently of their basal insulin sensitivity. At the beginning of the study, a metabolic profile was measured, and insulin sensitivity estimated using the euglycaemichyperinsulinaemic clamp technique.

The volunteers were randomly assigned to receive ezetimibe (10 mg/day in the morning) or placebo for a period of 90 days. After intervention, a similar metabolic profile was measured and a second clamp study was performed.

*Results**: Ezetimibe administration for 90 days** decreased* total (6.0 ± 0.5 vs. 4.2 ± 0.9 mmol/L, *p = 0.011) and* low-density lipoprotein (4.0 ± 0.7 vs. 2.2 ± 0.8 mmol/L, *p=0.003) cholesterol* **concentrations without modification of insulin sensitivity (3.0 ± 0.6 vs. 2.9 ± 0.7 mg/kg/min, p = 0.345).**

Ezetimibe On CRP



(J Am Coll Cardiol 2007;49:2003–9)

Change of CRP and Change of LDL

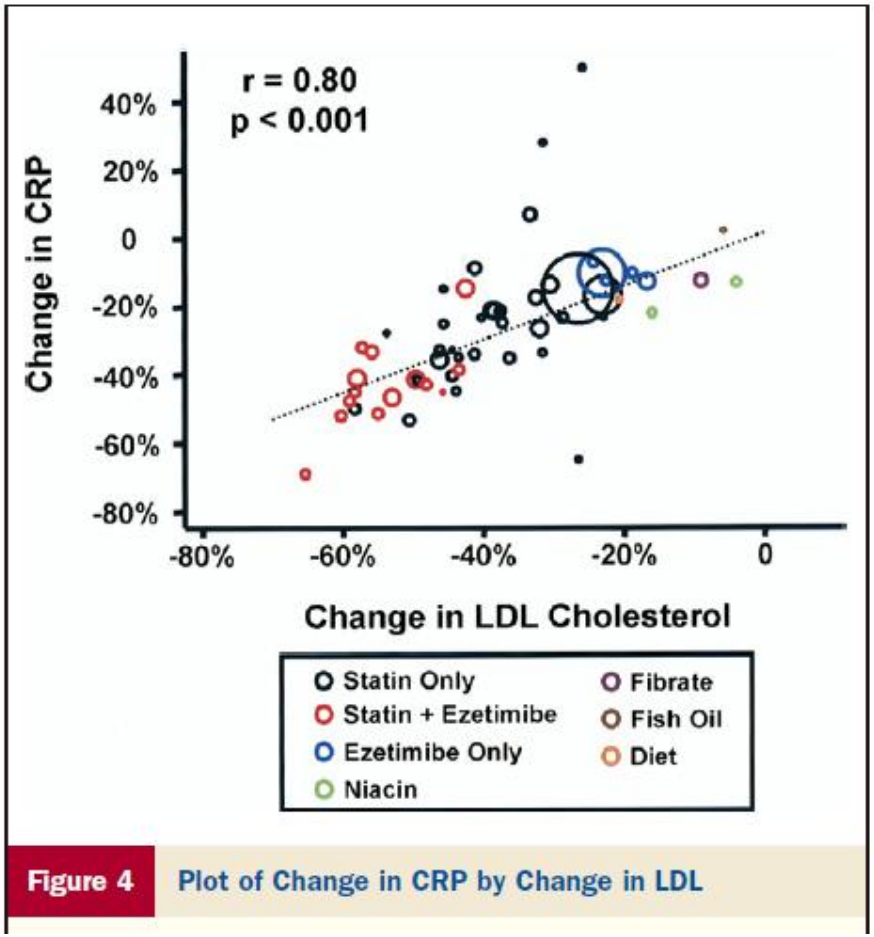


Figure 4 Plot of Change in CRP by Change in LDL

(J Am Coll Cardiol 2007;49:2003–9)

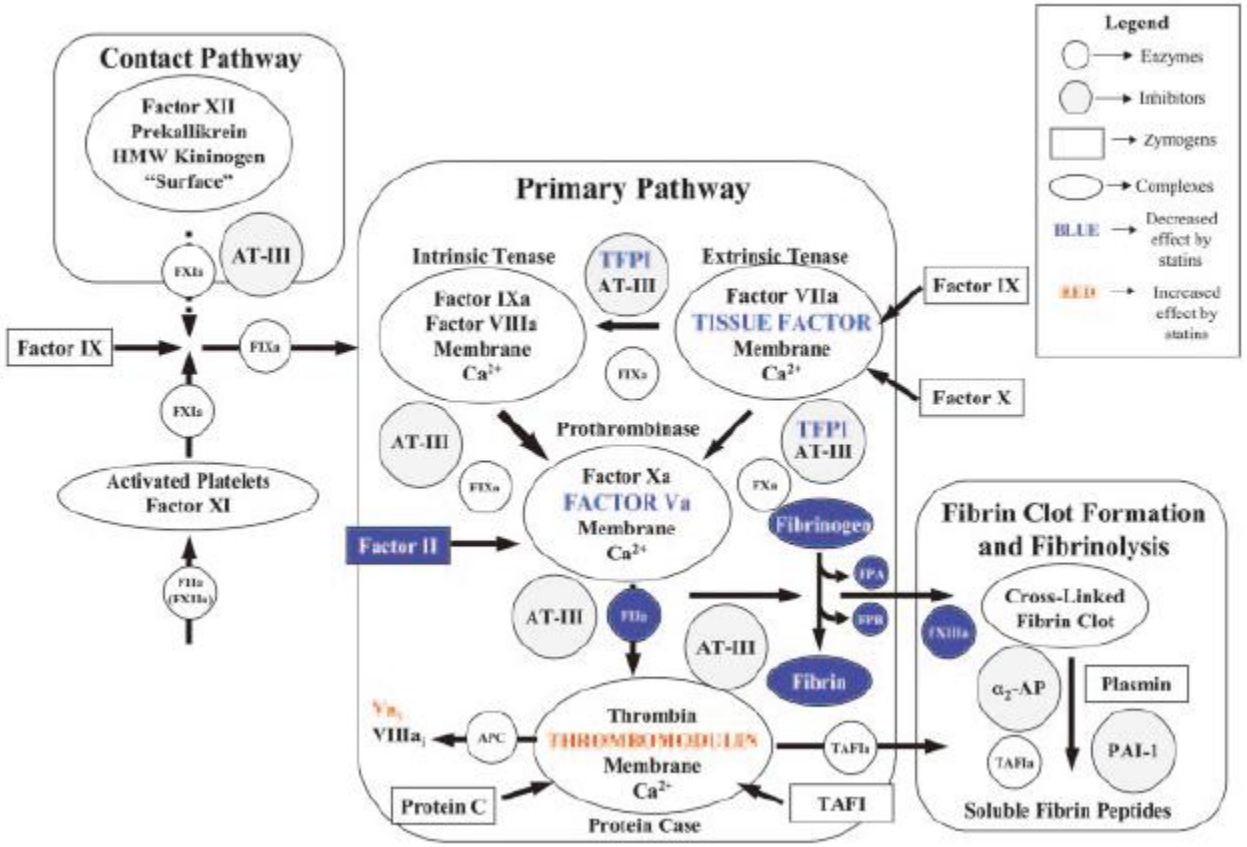
JUPITER
LDL reduction, hsCRP reduction, or both?

Minimal Correlation between change in LDL and change in hsCRP

	r value
Achieved LDLC, Achieved hsCRP	0.10
Percent change in LDLC, Percent change in hsCRP	0.15

Less than 2 percent of the variance in achieved hsCRP was explained by the variance in achieved LDLC

Statins on Coagulation



Arterioscler Thromb Vasc Biol. **2005;25:287-294.**

Rosuvastatin and Thromboembolism

End Point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard Ratio (95% CI)	P Value
	no. of patients	*no. of events/ 100 person-yr*	*no. of patients*	*no. of events/ 100 person-yr*		
Primary efficacy analysis*						
Venous thromboembolism						
Total	34	0.18	60	0.32	0.57 (0.37–0.86)	0.007
Unprovoked	19	0.10	31	0.17	0.61 (0.35–1.09)	0.09
Provoked	15	0.08	29	0.16	0.52 (0.28–0.96)	0.03
Pulmonary embolism	17	0.09	22	0.12	0.77 (0.41–1.45)	0.42
Deep-vein thrombosis only	17	0.09	38	0.20	0.45 (0.25–0.79)	0.004
Safety analysis†						
Venous thromboembolism						
Total	35	0.18	64	0.33	0.55 (0.36–0.82)	0.003
Unprovoked	20	0.10	34	0.18	0.59 (0.34–1.02)	0.06
Provoked	15	0.08	30	0.16	0.50 (0.27–0.93)	0.02
Pulmonary embolism	17	0.09	24	0.12	0.71 (0.38–1.32)	0.27
Deep-vein thrombosis only	18	0.09	40	0.21	0.45 (0.26–0.78)	0.003

* The primary efficacy analysis was performed on the basis of 94 cases identified by March 30, 2008.
† The safety analysis was performed on the basis of 99 cases that were identified before the study was unblinded.

N Engl J Med 2009;360.

Ezetimibe on Surrogate Markers

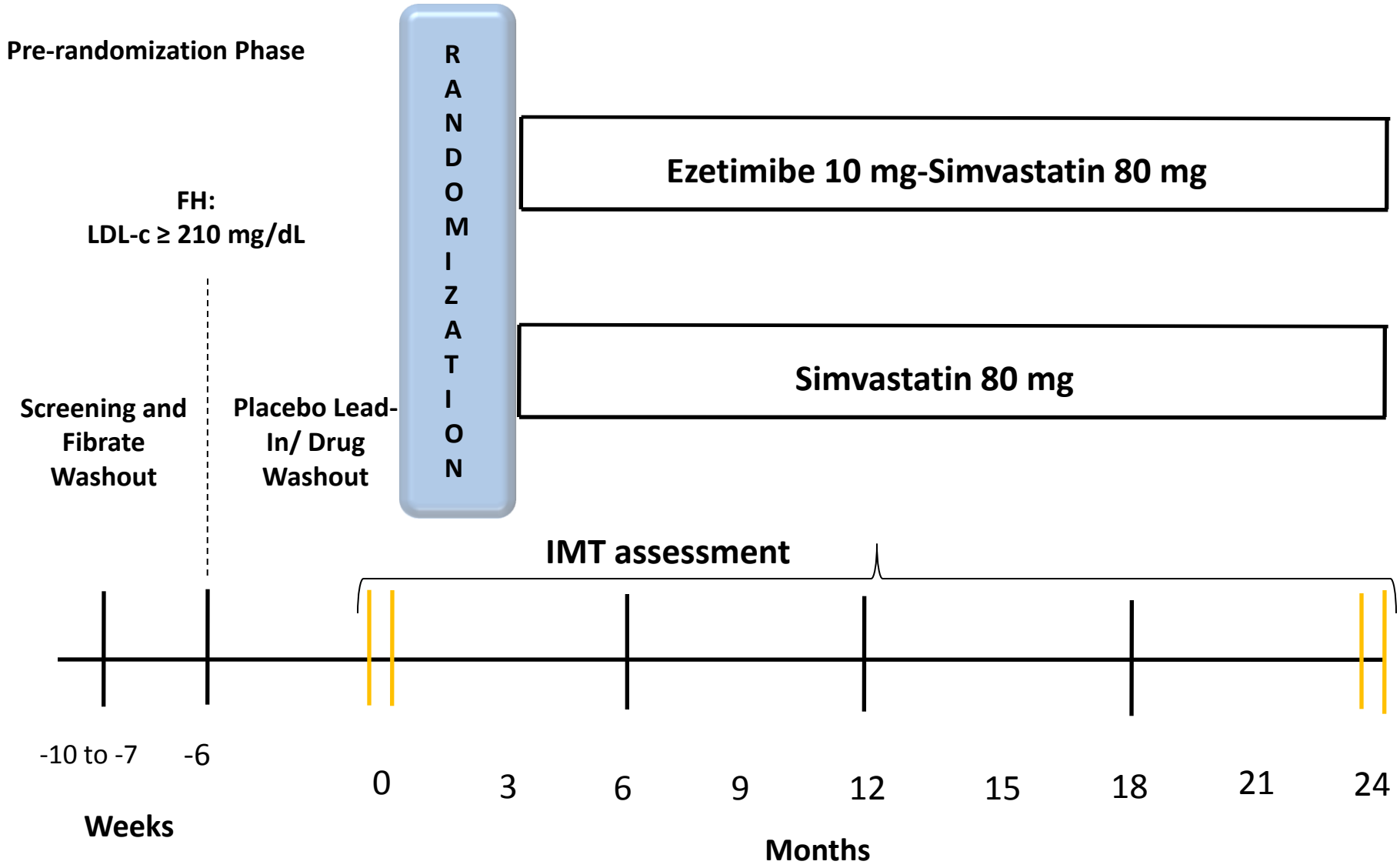
- 1 Carotid IMT
- 2 Endothelial function

The NEW ENGLAND JOURNAL of MEDICINE

Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

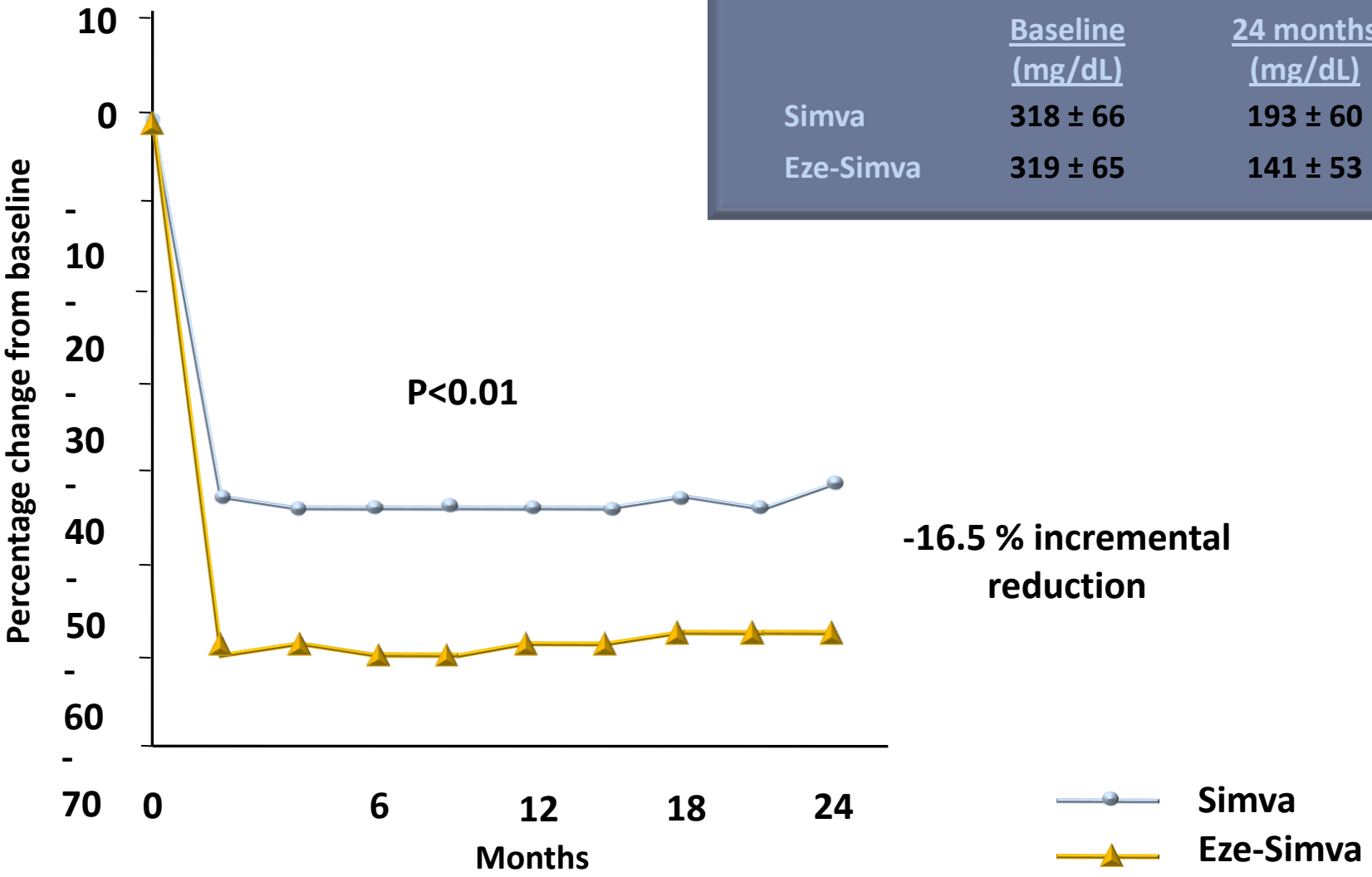
John J.P. Kastelein, M.D., Ph.D., Fatima Akdim, M.D., Erik S.G. Stroes, M.D., Ph.D., Aeilko H. Zwinderman, Ph.D., Michiel L. Bots, M.D., Ph.D., Anton F.H. Stalenhoef, M.D., Ph.D., F.R.C.P., Frank L.J. Visseren, M.D., Ph.D., Eric J.G. Sijbrands, M.D., Ph.D., Mieke D. Trip, M.D., Ph.D., Evan A. Stein, M.D., Ph.D., Daniel Gaudet, M.D., Ph.D., Raphael Duivenvoorden, M.D., Enrico P. Veltri, M.D., A. David Marais, M.D., Ph.D., and Eric de Groot, M.D., Ph.D., for the ENHANCE Investigators*

ENHANCE Study Design



LDL-cholesterol

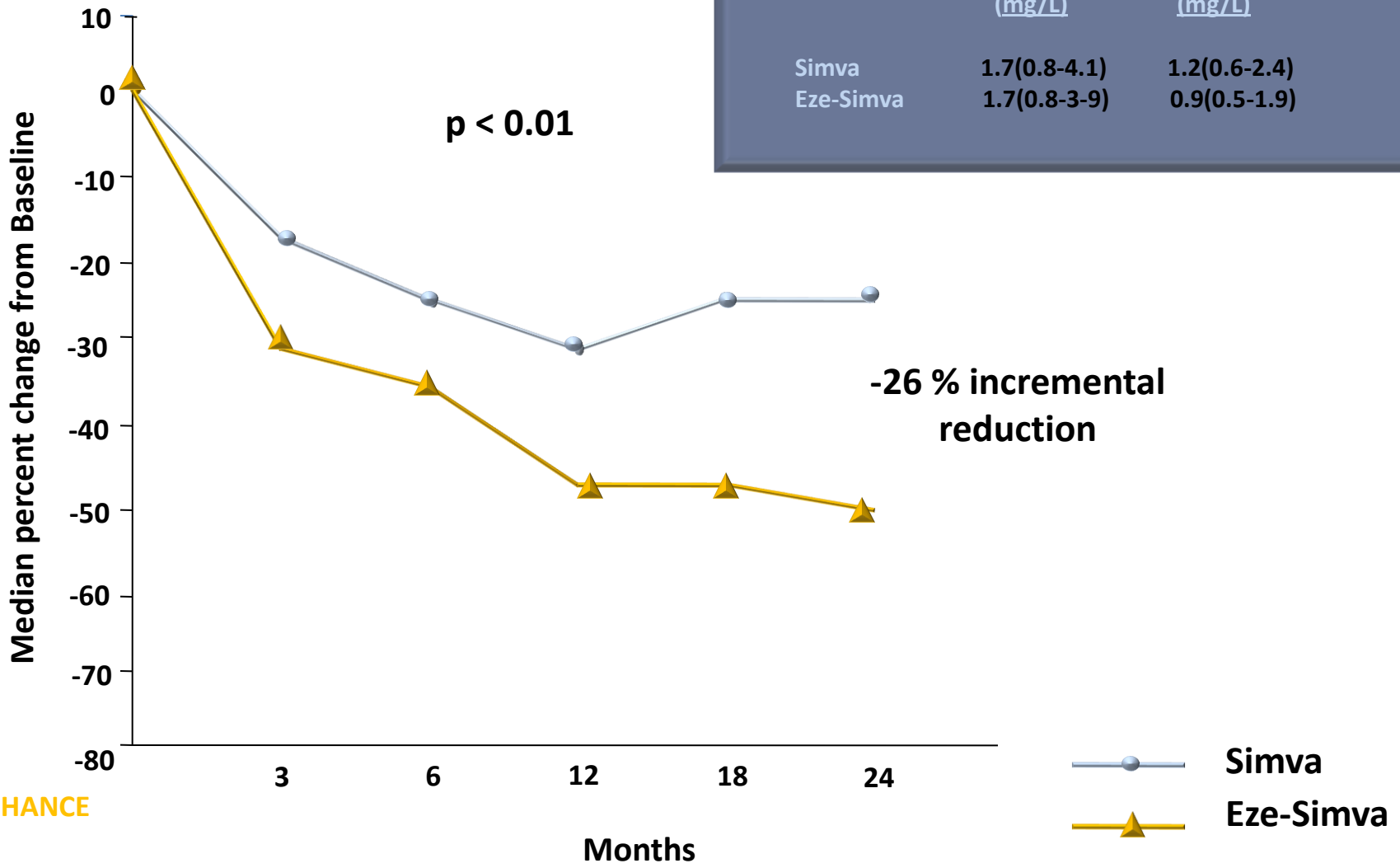
	Baseline (mg/dL)	24 months (mg/dL)
Simva	318 ± 66	193 ± 60
Eze-Simva	319 ± 65	141 ± 53



ENHANCE

hsCRP

	Baseline (mg/L)	24 months (mg/L)
Simva	1.7(0.8-4.1)	1.2(0.6-2.4)
Eze-Simva	1.7(0.8-3-9)	0.9(0.5-1.9)



ENHANCE

No significant changes in 1° or 2° endpoints

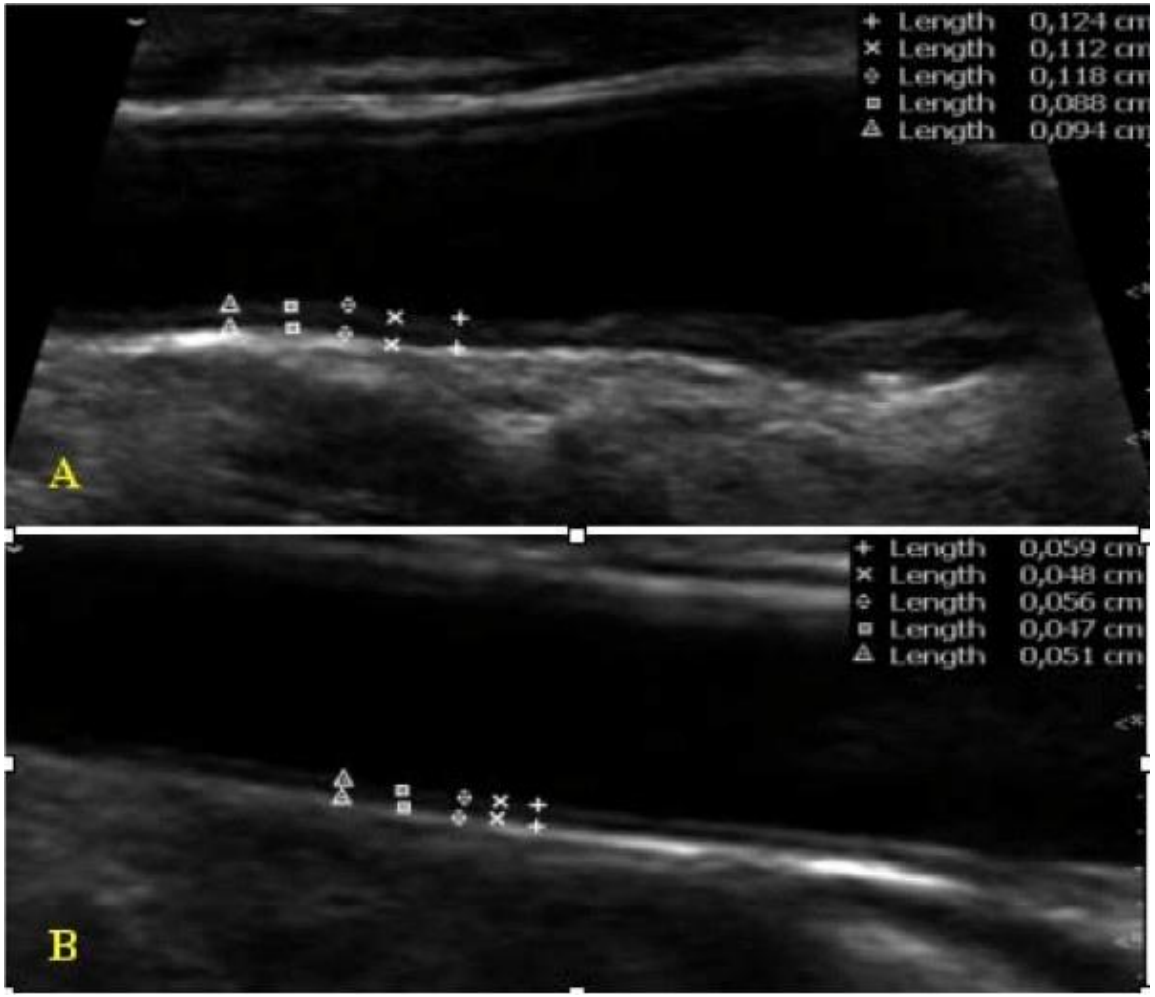
Variable	Simvastatin Monotherapy		Simvastatin plus Ezetimibe		P value (mean)
	Mean	Median	Mean	Median	
			Millimeters		
Baseline		n=342		n=338	
Mean cIMT	**0.70±0.13**	**0.69**	**0.69±0.13**	**0.68**	**0.64**
Mean maximum cIMT	**0.80±0.16**	**0.78**	**0.80±0.17**	**0.76**	**0.94**
24 months follow-up		n=320		n=322	
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**
Difference from baseline					
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

Why ENHANCE did not Enhance?

- 1 Does post treatment CIMT predict CV events?
- 2 Baseline CIMT

Carotid IMT


Length 0,124 cm
Length 0,112 cm
Length 0,118 cm
Length 0,088 cm
Length 0,094 cm
A
Length 0,059 cm
Length 0,048 cm
Length 0,056 cm
Length 0,047 cm
Length 0,051 cm
B

Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes

The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial

LDL<100

LDL<130

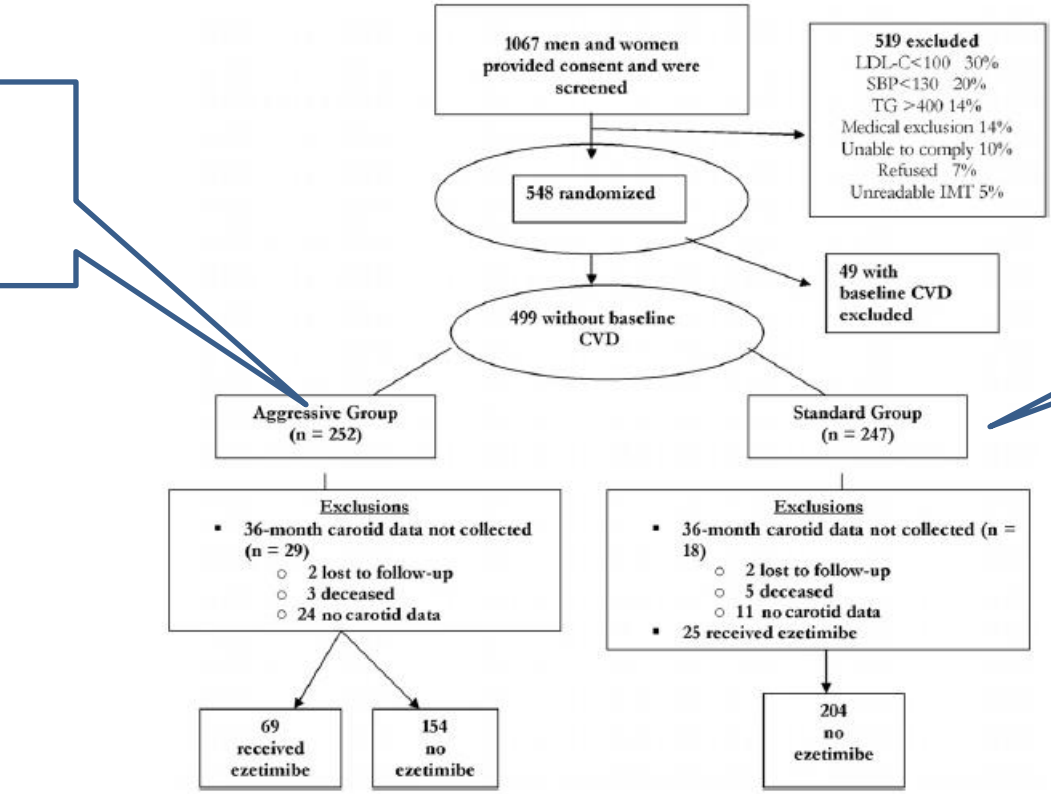


Figure 1 The SANDS Trial Participant Flow Diagram

The flow chart shows how participants were chosen and assigned to groups in the SANDS trial.
CVD = cardiovascular disease; IMT = intima-media thickness; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TG = triglyceride.

(J Am Coll Cardiol 2008)

Effect of Statins Alone Versus Statins Plus Ezetimibe on Carotid Atherosclerosis in Type 2 Diabetes

The SANDS (Stop Atherosclerosis in Native Diabetics Study) Trial

CIMT decrease in aggressive group
No matter ezetimibe or not

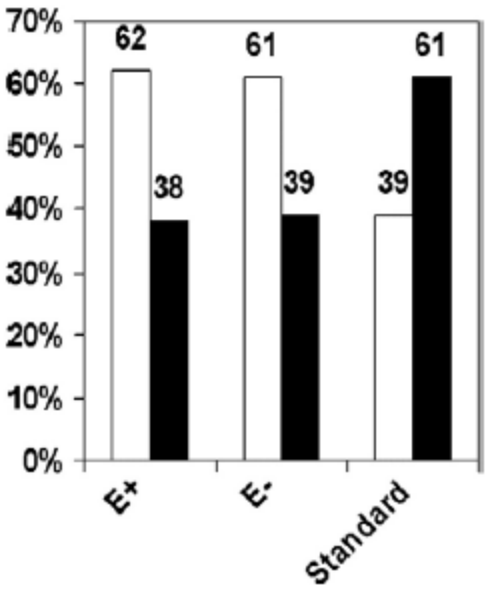


Figure 2 Categorical Change in CIMT in SANDS Subgroups

Numbers represent percentages of participants who experienced a decrease or no change **(open bars)** in common carotid artery intima-media thickness (CIMT) >0.01 mm versus an increase **(solid bars)**. The majority of both aggressive subgroups experienced a decline or no change in IMT, whereas the majority of the standard group showed an increase ($p < 0.0001$). E+ = statin plus ezetimibe; E− = statin alone.

(J Am Coll Cardiol 2008)

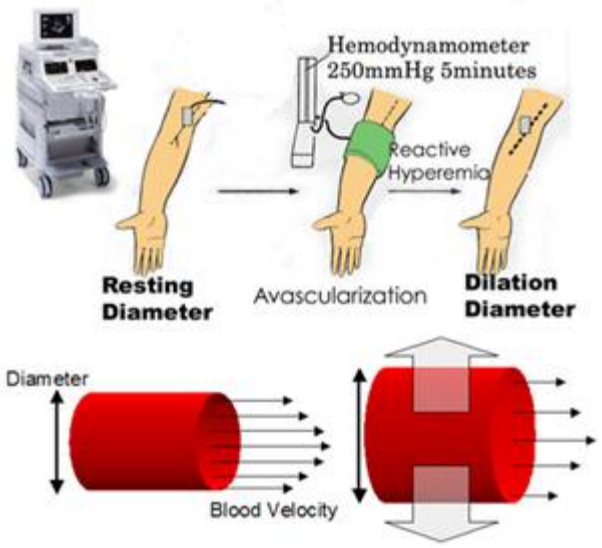
Endothelial Function

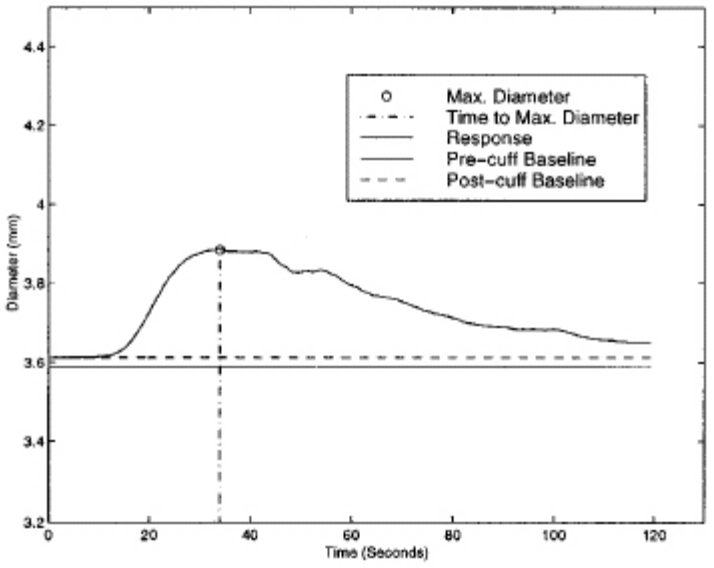
Reference	Patient population	Intervention	End points assessed	Findings	Conclusion	Study quality[b]
Settergren et al,[72] 2008	43 With stable CAD and DM or IGT	Simvastatin (10 mg) + ezetimibe vs simvastatin (80 mg)	FMD and FBF[c] after 6 wk	FMD increased in both groups (0.9% vs 1.5%; P=.39)	Lipid lowering rather than pleiotropic effects of statins is important for improvement in endothelial function	5
Fichtlscherer et al,[73] 2006	60 With stable CAD	Ezetimibe vs combination simvastatin (20 mg) and ezetimibe vs atorvastatin (40 mg)	FBF after 4 wk	Atorvastatin but not other therapies increased FBF (P<.05)	Ezetimibe in patients with stable CAD does not improve endothelial function	1
Landmesser et al,[74] 2005	20 With NYHA III CHF	Ezetimibe vs simvastatin (10 mg)	FMD after 4 wk	Simvastatin but not ezetimibe increased FMD	Ezetimibe in CHF lowers LDL-C levels but does not improve endothelial function	1
Maki-Petäja et al,[75] 2007	20 With RA	Ezetimibe vs simvastatin (20 mg)	FMD and aPWV after 6 wk[d]	Δ aPWV (0.60 vs 0.71) (P=.90); FMD increased 1.36% vs 2.55% (P=.10)	Ezetimibe and statins reduced LDL-C levels and improved endothelial function and aPWV	3
Efrati et al,[33] 2007	40 With hyper-lipidemia	Ezetimibe vs simvastatin (40 mg) vs combination simvastatin (40 mg) and ezetimibe vs simvastatin (80 mg)	AIx after 3 mo	Only simvastatin (40 mg) decreased AIx	Improved AIx with simva-statin in statin-naive patients but not with ezetimibe	1
Bulut et al,[76] 2005	14 (male) with MeTS with chest pain	Atorvastatin (40 mg) vs combination atorvastatin (10 mg) and ezetimibe	FBF after 8 wk	Atorvastatin + ezetimibe increased FBF more than ator-vastatin (40 mg)	Combination therapy is more potent in improving endothelial function	1

[a] AIx = augmentation index; aPWV = aortic pulse wave velocity; CAD = coronary artery disease; CHF = congestive heart failure; DM = diabetes mellitus; FBF = forearm blood flow; FMD = flow mediated dilatation; IGT = impaired glucose tolerance; LDL-C = low-density lipoprotein cholesterol; MeTS = metabolic syndrome; NYHA = New York Heart Association; RA = rheumatoid arthritis.
[b] Study quality assessed using the criteria outlined by Jadad et al.[8]
[c] We measured FMD noninvasively with ultrasonography; FBF was measured using venous occlusion plethysmography.
[d] Study design included crossover.

Mayo Clin Proc. 2009;84(4):353-361

Flow Mediated Dilatation





Cardiovascular Events

- SEAS

SEAS

Simvastatin + **E**zetimibe in **A**ortic **S**tenosis

A Randomized Controlled Study

Simvastatin + Ezetimibe in Aortic Stenosis

Primary Objective

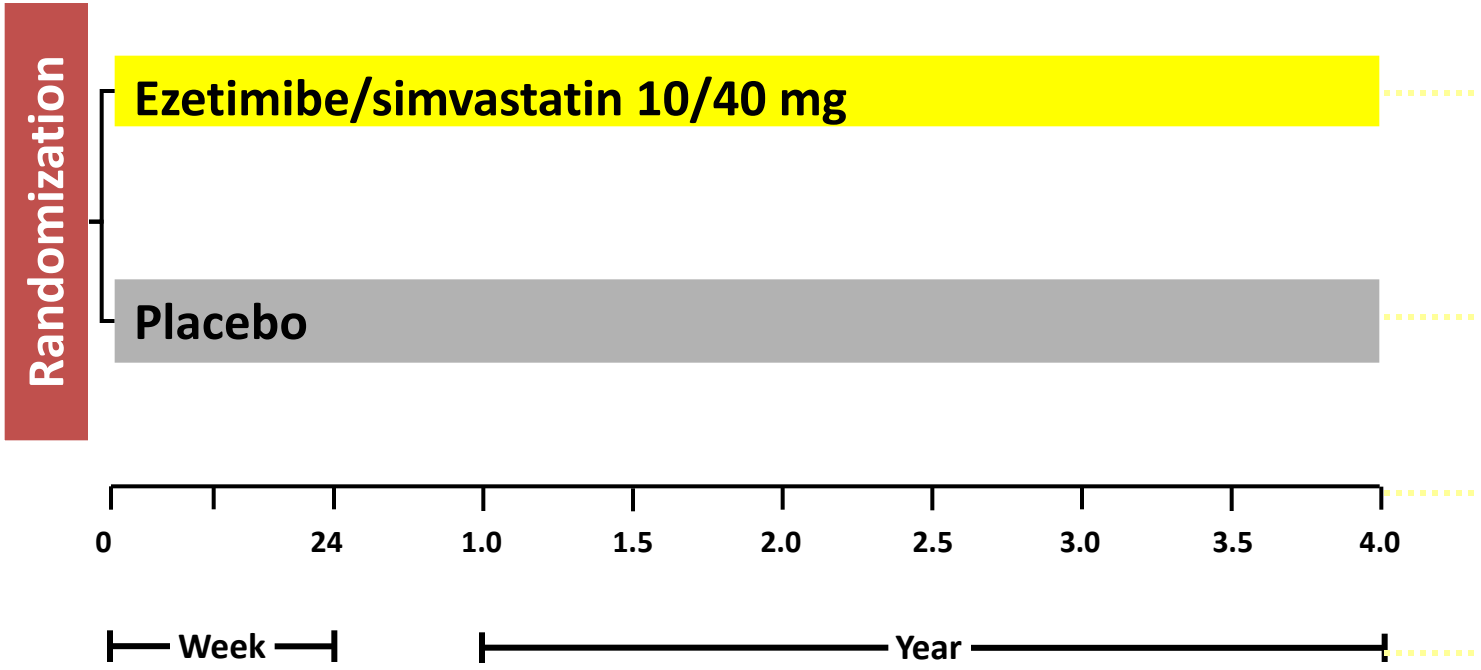
In patients with asymptomatic aortic stenosis, to evaluate whether treatment with ezetimibe 10 mg/day and simvastatin 40 mg/day compared to placebo will reduce the risk of:

Major cardiovascular events:

- **Cardiovascular death**
- **Aortic valve replacement surgery**
- **CHF as a result of progression of AS**
- **Non-fatal myocardial infarction**
- **CABG or PTCA**
- **Hospitalized UAP**
- **Non-hemorrhagic stroke**

SEAS: Treatment Randomization

Sample size : 1873 patients



173 Centers in: Norway, Sweden, Denmark, Finland, Germany, UK, Ireland

Results

	Ezetimibe 10mg+ Simvastatin40	Placebo	P value
Primary Endpoint			
Major CV Event	N=333	N=355	NS
Secondary Endpoint			
Aortic Valve Dx Events	N=308	N=326	NS
Atherosclerotic Events	N=148(15.7%)	N=187(20.1%)	p=0.02

22% Reduction

Adapted from press release 07-2009-VYT-2008-TW-7421-PR

LIPID/METABOLIC

Controversial ezetimibe trial's completion expected in June 2013

APRIL 1, 2010 | Michael O'Riordan

Durham, NC - The **Improved Reduction of Outcomes: Vytorin Efficacy International Trial** (IMPROVE-IT) study, testing the controversial cholesterol-lowering drug combination **ezetimibe/simvastatin** (Vytorin, Merck/Schering-Plough Pharmaceuticals), is expected to be completed in June 2013 [1].

The announcement of the anticipated completion date is based on statistical modeling that allows investigators to track enrollment rates, blinded aggregate event rates, treatment discontinuation rates, and other variables and is intended to shed light on a study that some experts believed might never be completed.

"There has been a great deal of speculation about when the trial will end," **Dr Robert Harrington** (Duke University, Durham, NC), one of the IMPROVE-IT investigators, told **heartwire**. "We take an educated guess at the beginning of a trial, using a lot of assumptions, as to when we'll complete enrollment and when we think we'll accumulate the required events. . . . The models we use suggest, based on all the things we're observing, that the trial will end in 2013, and as the trial continues to go on for the next year or two, we'll continue to update those models."

> We think being pretty certain about the effect of ezetimibe is important.

In a recent editorial accompanying the **Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis** (ARBITER 6-HALTS) study, **Drs John Kastelein** (Academic Medical Center, Amsterdam, the Netherlands) and **Michel Bots** (University Medical Center, Utrecht, the Netherlands) raised concerns about whether IMPROVE-IT would ever reach completion [2]. Similarly, **Dr Steven Nissen** (Cleveland Clinic, OH) questioned whether the trial would be completed because more than 5000 hard clinical end points are needed for the study to reach statistical significance, an unusually high number given that past studies required a few hundred events.

10 Most Recent heartwire

Still no answers in largest review on clopidogrel/PPIs
APR 13, 2010 17:00 EDT

CME Previews

LIPID/METABOLIC
Emerging CV Genetic Markers
RELEASE DATE: 31 MAR 2010

Genetic markers for accessing CV risk: has the time come? With Drs. Ballantyne, Cannon, Roberts, and Sacks.
WATCH PREVIEW | VIEW PROGRAM NOW

LIPID/METABOLIC
Lipid Insights from AHA 2009
RELEASE DATE: NOV 20, 2009

Join Drs. Michael Davidson, Christie Ballantyne, Vera Bittner, and Roger Blumenthal for a discussion that advances our knowledge of cardiovascular risk assessment.
WATCH PREVIEW | VIEW PROGRAM NOW

Featured CME

Side Effects

- No increased liver or muscle injury as compared with statin or placebo.
- No increased cancer incidence.

Price /Efficacy Comparison for Lipid Lowering Agents

Product	VYTORIN (ezetimibe/ simvastatin)		Zocor		Lipitor		Lescol		Mevalotin		Crestor	
Efficacy / Cost	Reduce LDL-C%	Price NT$	Reduce LDL-C%	Price NT$	Reduce LDL-C%	Price NT$	Reduce LDL-C%	Price NT$	Reduce LDL-C%	Price NT$	Reduce LDL-C%	Price NT$
10mg					-37%	28.9					-46%	30.8
20mg	-52%	51										
40mg			-42%	32	-48%	49.1			-30%	36.6		
80mg							-33%	27				
衛生署適應症	原發性高膽固醇血症、同型接合子家族性高膽固醇血症 REMARKS : VYTORIN 為一複方產品，內含有 20mg simvastatin 及 10mg ezetimibe 經由**雙重抑制**作用，一方面利用simvastatin **控制體內膽固醇生合成**，一方面再利用ezetimibe**經由腸胃道抑制膽固醇的吸收**，以達到降低膽固醇的目的。		高膽固醇血症， 高三酸甘油酯血症 降低冠心病高危險群及冠心病患者的心血管事件發生率及冠心病致死率		高膽固醇血症、 高三酸甘油脂血症		原發性高膽固醇血症、 原發性混和型血脂異常 預防冠心病病人， 在接受穿皮血管整形術(PTCA)後的重大心臟血管不良事件		原發性高膽固醇血症、 合併高膽固醇血症及 高三酸甘油脂血症 初發性預防:心肌梗塞， 冠狀動脈心臟病 再發性預防:心血管發作，腦血管發作		高膽固醇血症、 高三酸甘油脂血症	

Reference : Am J Cardiol 2003;92:152–160
AHJ 2005;149:464-73
** FDA –Lescol /Crestor IPC *** Taiwan -IPC

Conclusions (1)

- Ezetimibe reduce LDL by inhibit cholesterol absorption in small intestine (both from food and bile juice).
- Because Ezetimibe has a long half life (22hr) which makes the block of cholesterol absorption more complete and convenient.
- Used alone, it could reduce LDL by 17. 2-22.3%.
- It may reduce insulin resistance and fatty liver, hs-CRP but not thromboembolism.
- It may have positive effect on endothelial function but not on carotid IMT.
- It may reduce the coronary ischemic event although not sure.
- It did not cause serious liver and muscle injury as statin and it did not increase cancer risk.
- Taking all the above and the rules of the health insurance system in Taiwan , It may be helpful when statin is not tolerable or not effective.

Conclusion (2)

- Vytorin (Ezetimibe 10mg + Simvastatin 20 mg) may be used as 1st line lipid-lowering agents as statins (according to the rules of the health insurance system in Taiwan).
- It may reduce LDL by 52% (similar or better than Atorvastatin 40mg, Rosuvastatin 10 mg.)
- However, there is no strong and consistent evidence of the positive effect of Ezetimibe or Vytorin on cardiovascular events yet.