

**A New Paradigm to Achieve Optimal Serum
LDL Cholesterol Levels**

Experiences with Ezetimibe

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Current Trend of Lipid Lowering Management

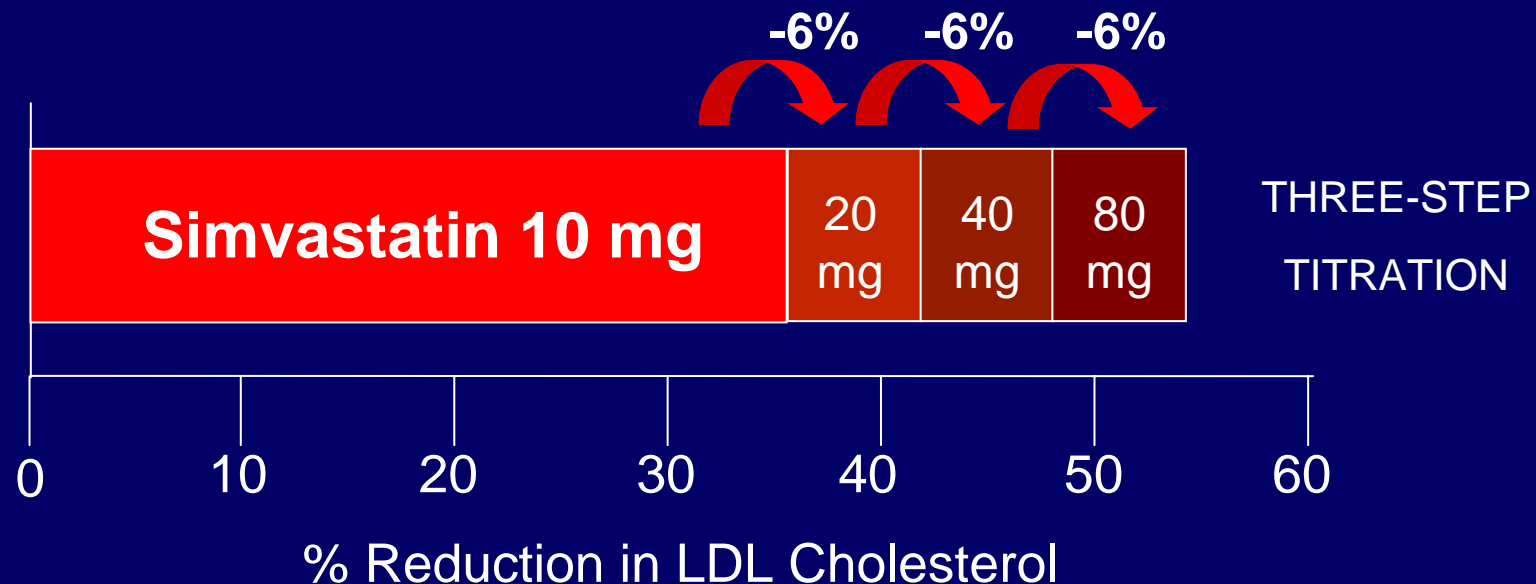
- Set up individual goal of serum LDL cholesterol levels based on **absolute global risk**
- LDL ; **Lower, the better.**

Human Being Has the Highest Serum Cholesterol Levels



Why are patients not reaching Goals?

Effect of Statin Therapy on LDL-C Levels: “The Rule of 6”



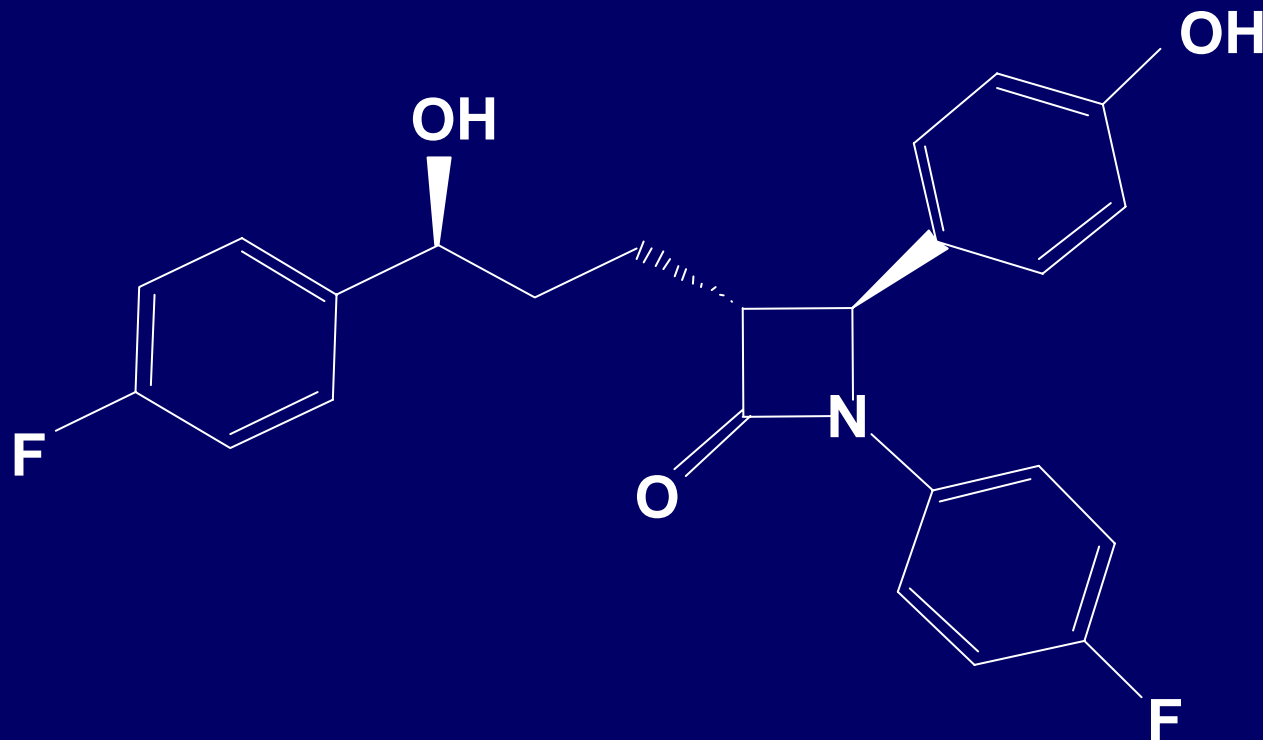
Despite Evidence-based Medicine, Physicians Generally use Lower Doses of Statins

- In Spain:
 - typical simvastatin dose 17.5 mg/day
 - typical atorvastatin dose 13 mg/day
 - typical pravastatin dose 17 mg/day

New LDL Lowering Drug ; Ezetimibe

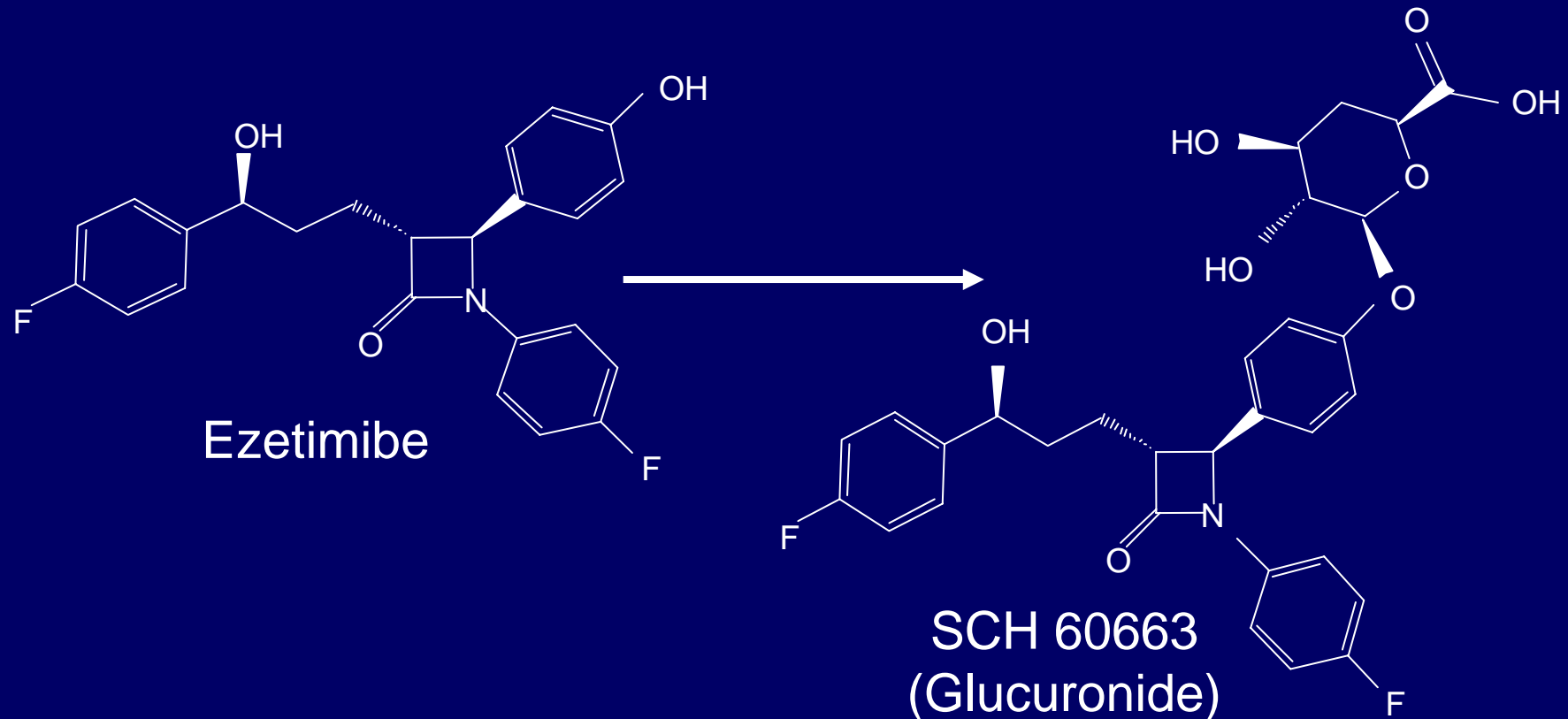
E-Z & Effective

Structure of Ezetimibe (SCH 58235)



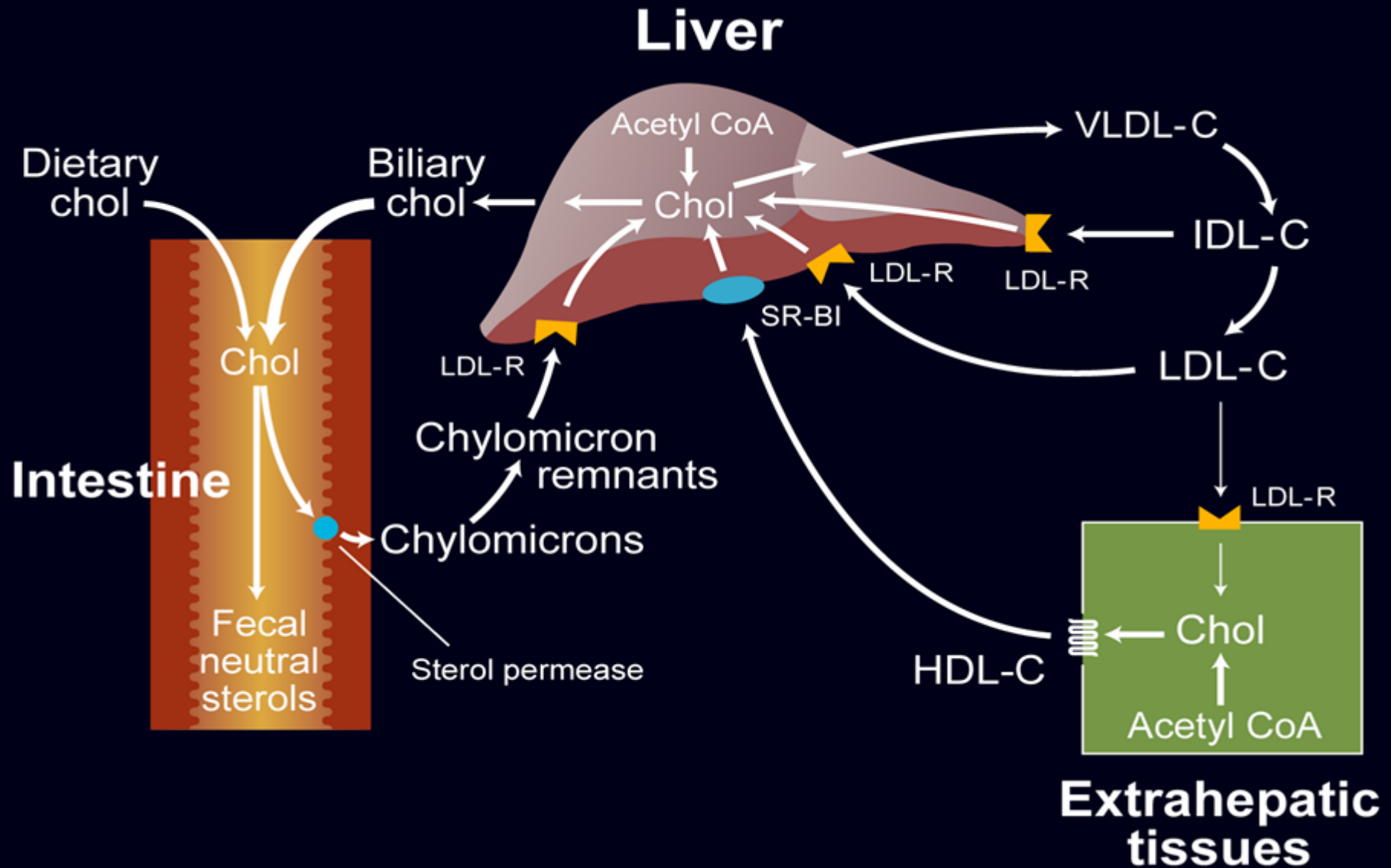
Ezetimibe is a potent and specific inhibitor of dietary and biliary cholesterol absorption

Ezetimibe and its Metabolite (SCH 60663)

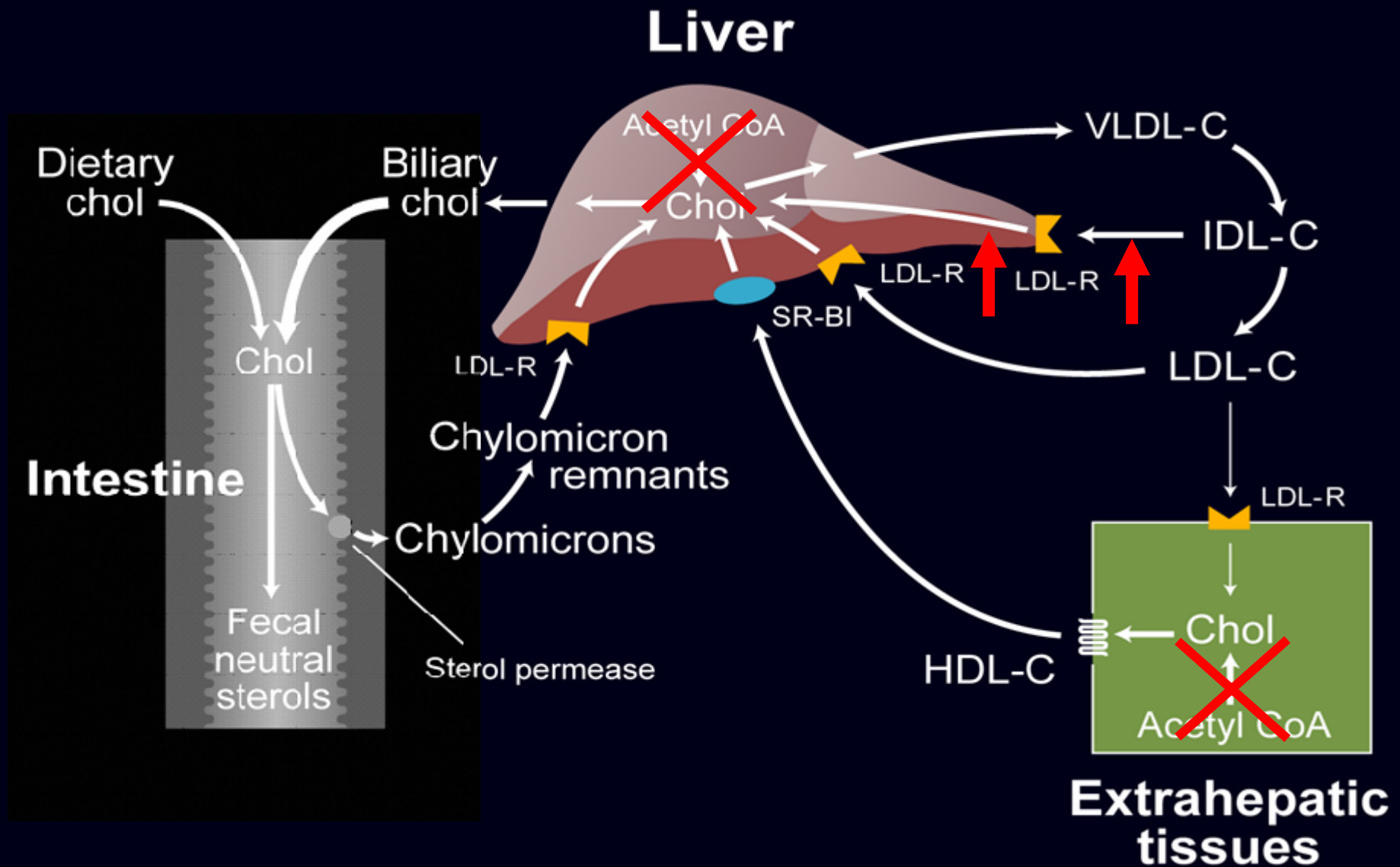


The main route of metabolism for ezetimibe is glucuronidation

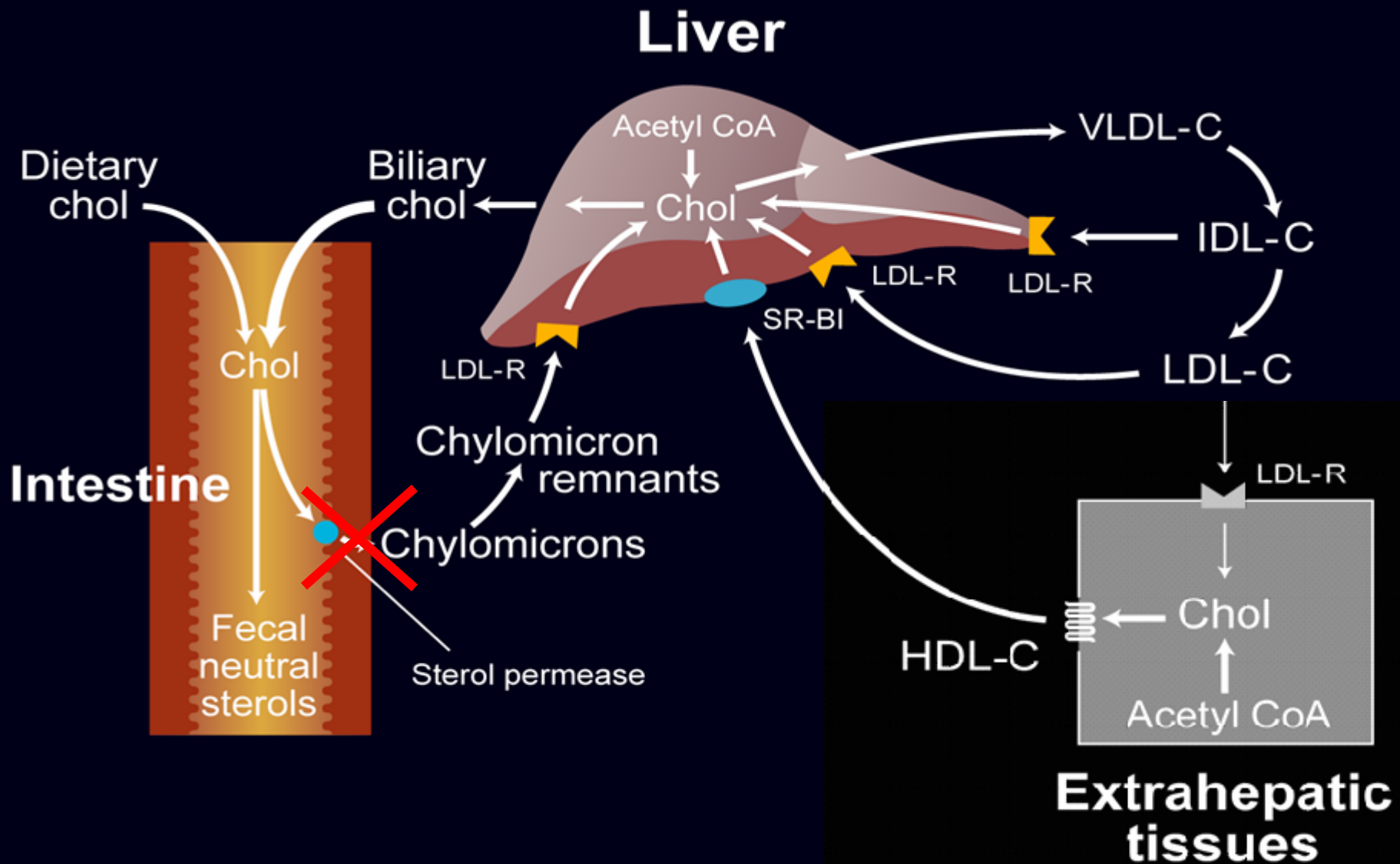
Overview of Cholesterol Transport



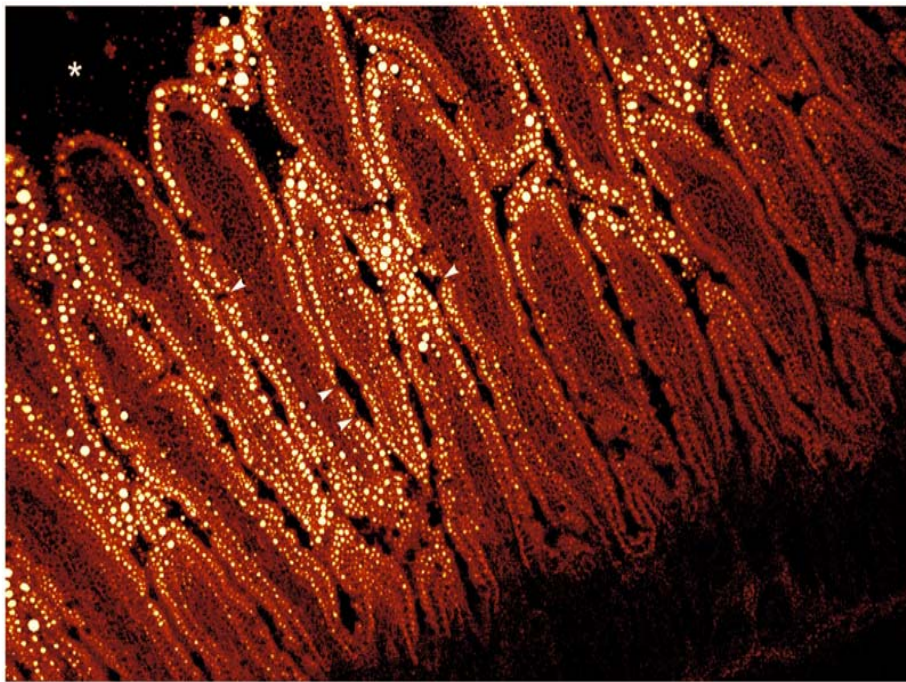
Action of Statins



Action of Ezetimibe



Ezetimibe Appears to Localize to the Site of Cholesterol Absorption

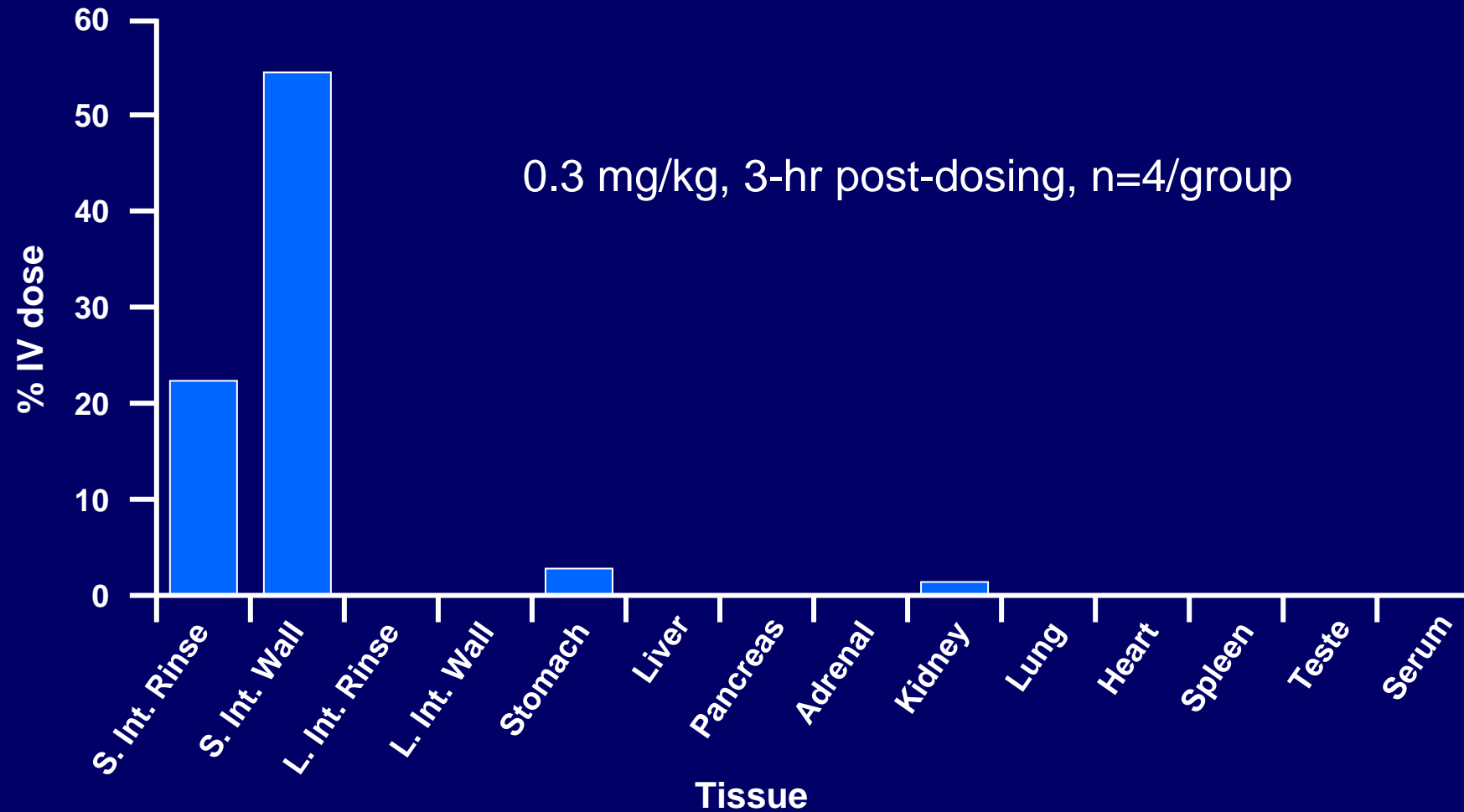


Uptake of a fluorescent cholesterol analog in hamster small intestine



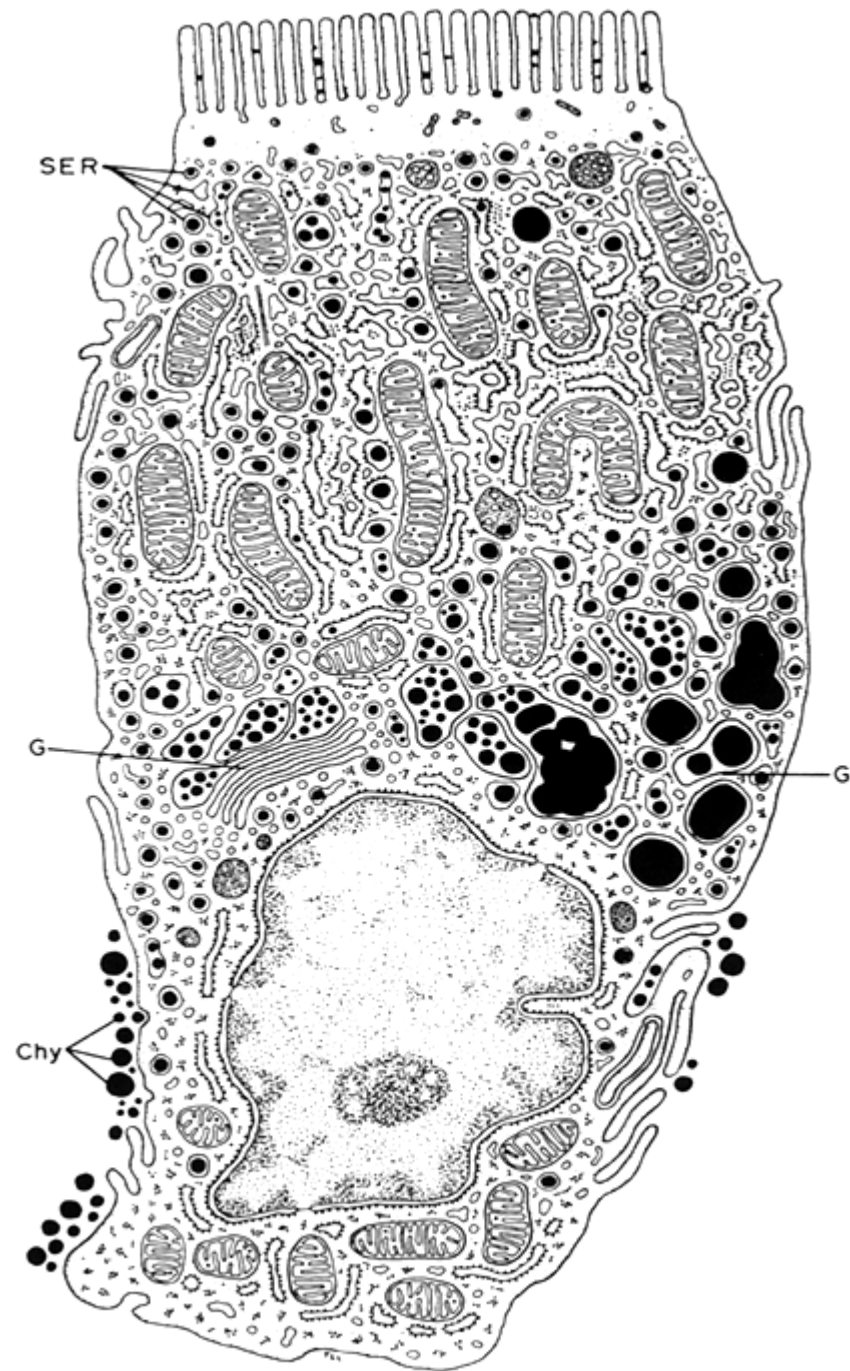
¹²⁵I-Gluc-Ezetimibe Delivered I.V. Localizes to the Intestinal Brush Border in Bile-Duct Cannulated Rats

Localization of IV-Dosed ^{125}I -Gluc-Ezetimibe (SCH 61209) in Normal Rats



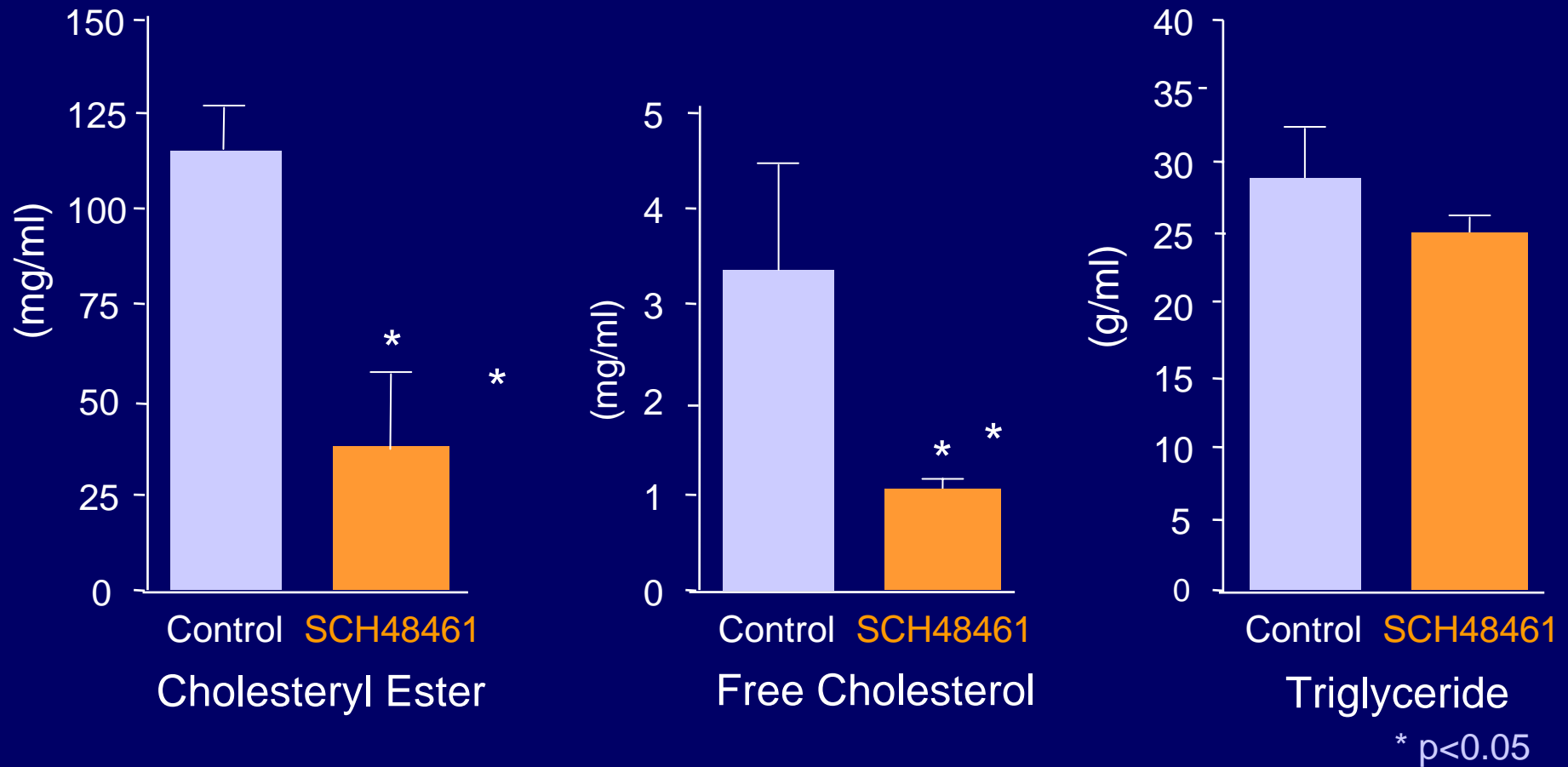
Steps of Cholesterol Absorption

- Emulsification
- Transfer ~~from~~ bile acid micelle to brush border
- Transport to endoplasmic reticulum
- Esterification (ACAT)
- Incorporation into chylomicrons
- Secretion from basolateral surface
- Movement into lymph



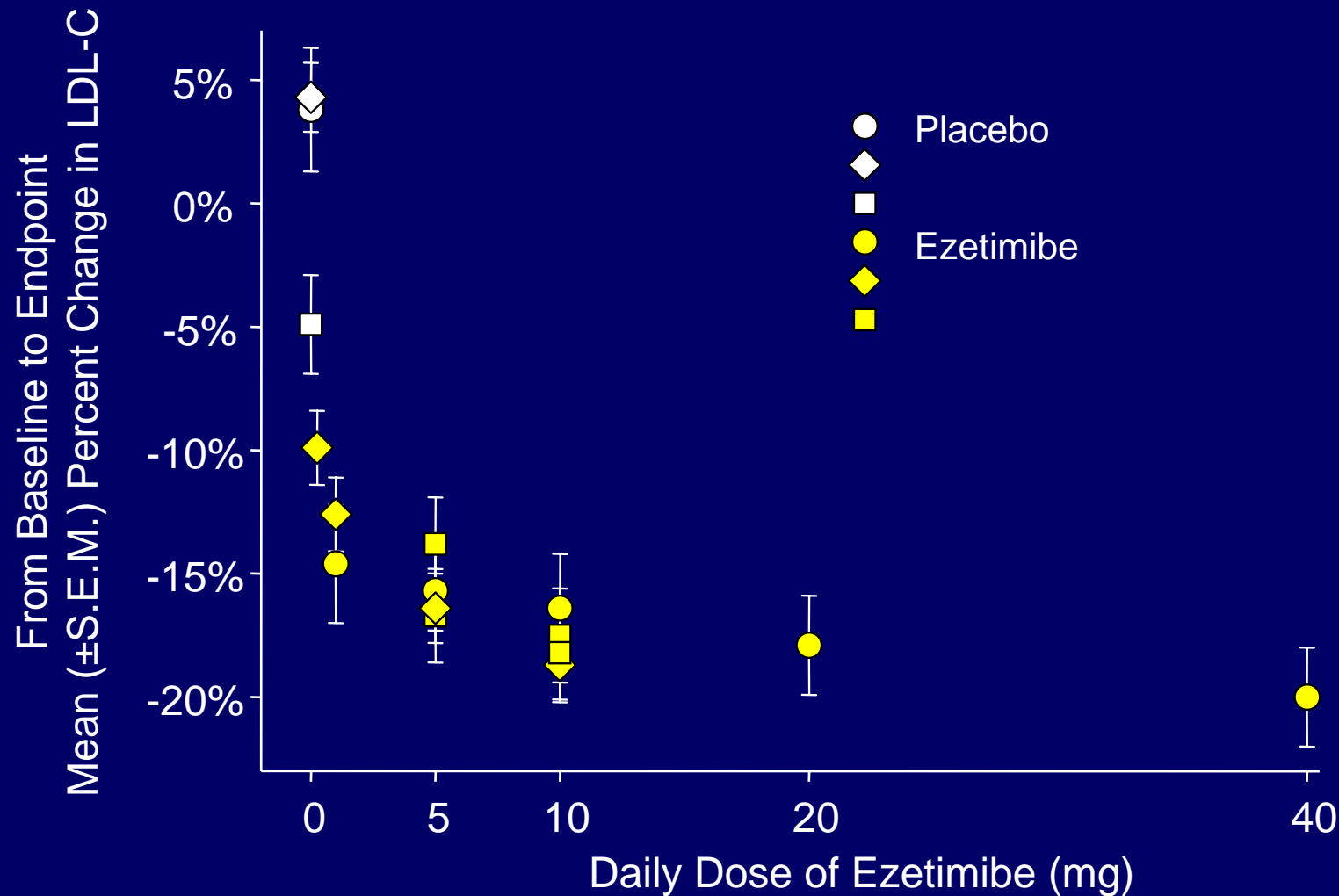
Depletion of Cholesterol from Postprandial Chylomicrons in Cynomolgus Monkeys

SCH 48461 (10 mg/kg/d)



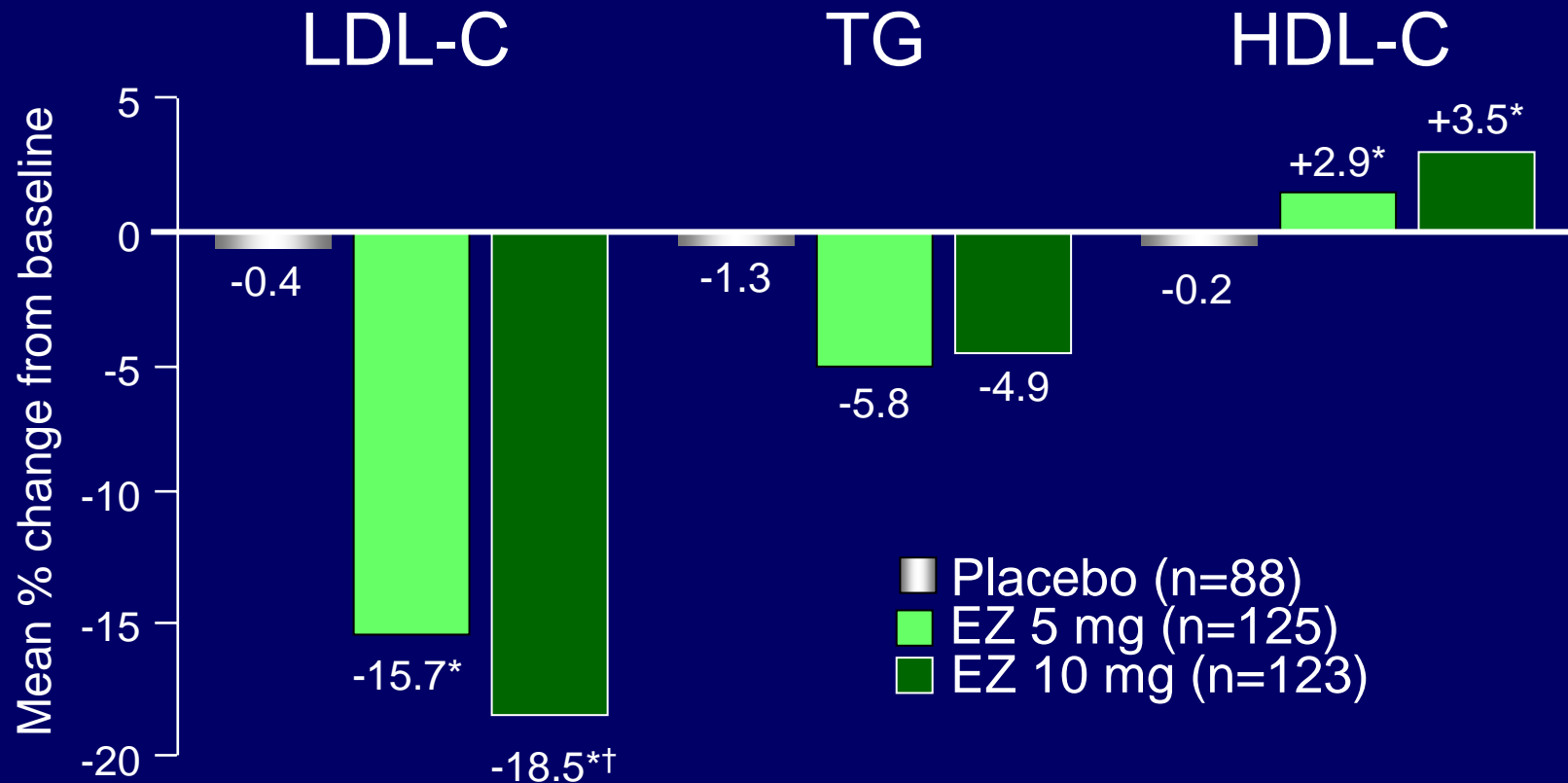
Relationship Between Dose of Ezetimibe and % Change in Plasma LDL-C

Results from three Phase II Clinical Therapy Trials



Effects of Ezetimibe (EZ) on serum LDL-C, Triglyceride (TG), and HDL-C

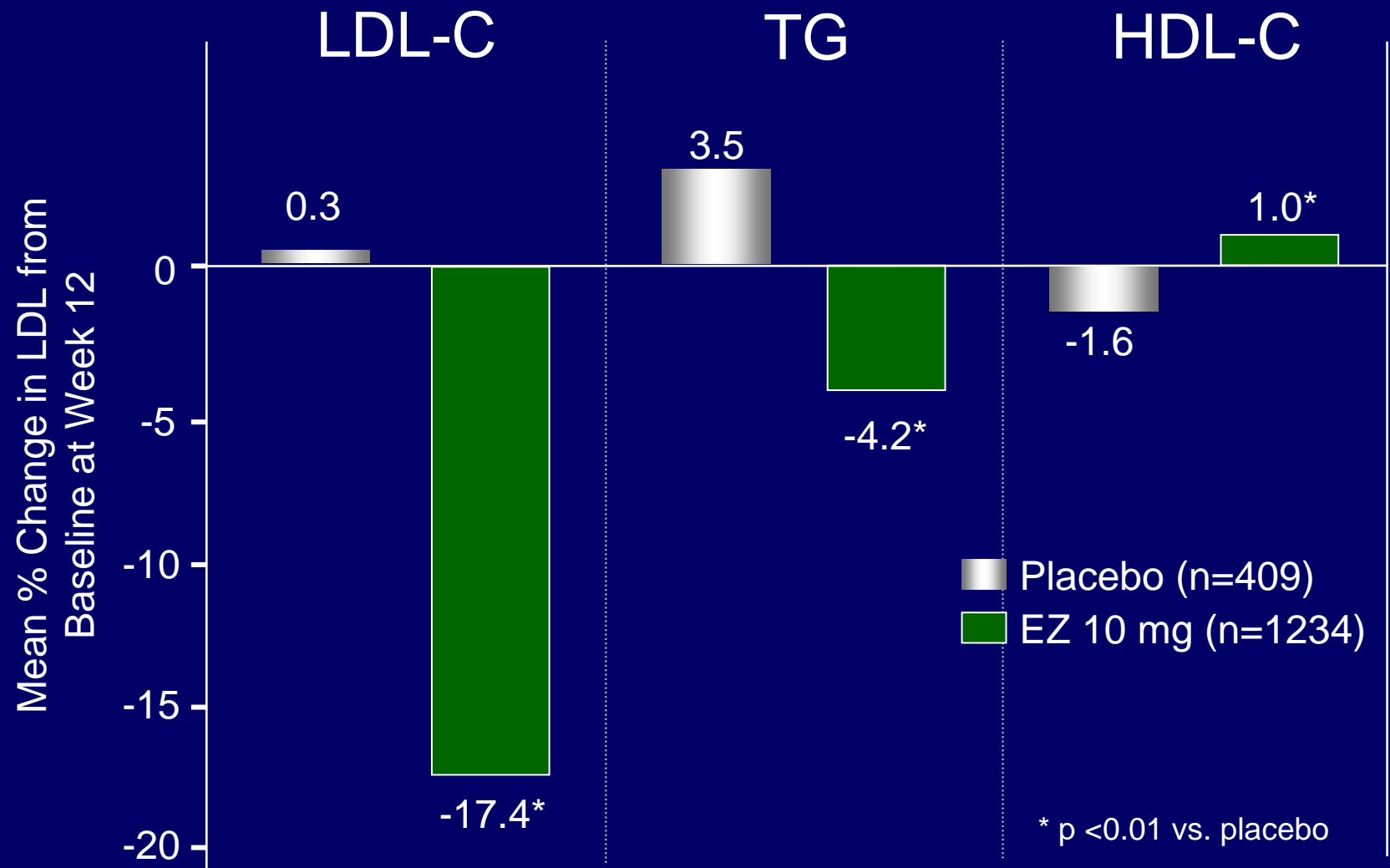
Results from three Phase II Clinical Therapy Trials



* p<0.05 vs placebo
† p<0.05 vs 5 mg EZ

Effects of Ezetimibe (EZ) on serum LDL-C, Triglyceride (TG), and HDL-C

Results from three Phase III Pooled Monotherapy Trials



Pooled Safety of Ezetimibe (EZ)

Results from three Phase III Pooled Monotherapy Trials

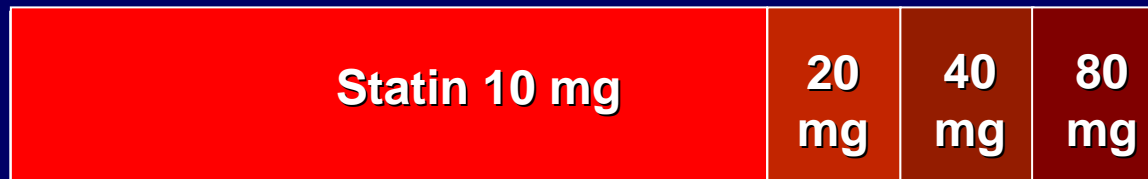
No. of Patients (%)	Placebo (n=431)	Ezetimibe (n=1288)
Adverse events	285 (66)	802 (62)
Gastrointestinal	93 (22)	230 (18)
DC 2° AE	11 (2.6)	51 (4)
Liver function tests (≥ 3 x ULN)		
ALT	2 (<1)	7 (<1)
AST	3 (<1)	6 (<1)
GGT	10 (2)	20 (2)
Total bilirubin	0	0
ALP	0	0
Creatine kinase (CK) elevations		
5-10 x ULN	0	8 (<1)
≥ 10 x ULN	1 (<1)	3 (<1)

Ezetimibe Phase II / III Program: Summary of Monotherapy Results

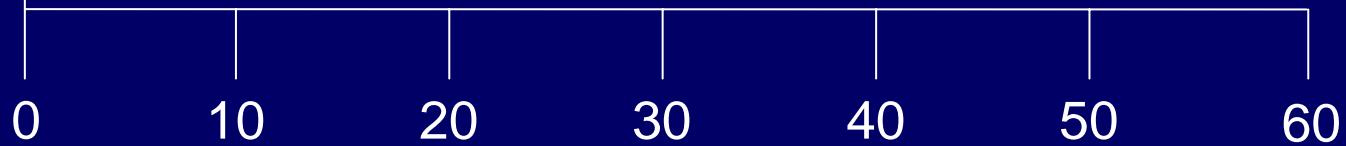
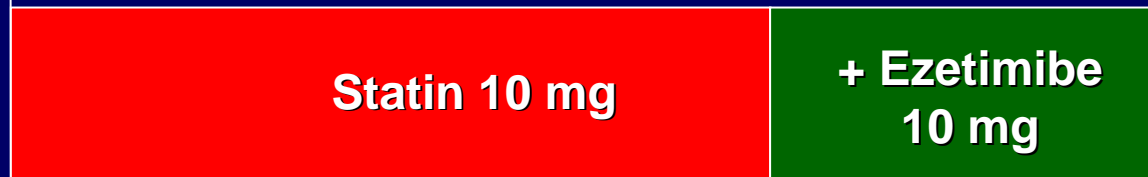
- Efficacy of EZ 10 mg QD relative to placebo:
 - LDL-C decreased by ~18%
 - TG decreased by ~7-8%
 - HDL-C increased by ~2-3 %
- LDL-C reduction occurred as early as 2 weeks
- EZ had excellent safety and tolerability, with an AE profile indistinguishable from placebo

One Step Move ; Ezetimibe on Statin

THREE-STEP TITRATION



ONE-STEP COADMINISTRATION



% Reduction in LDL-C

Summary of Follow-up Add-on Study

- The addition of **10 mg EZ to statins** resulted in

additional **LDL-C** reduction by 20 %

additional **TG** reduction by 10 %

additional **CRP** reduction by 10 %

70 % of subjects (who were not at optimal goal when randomized)
achieved optimal LDL-C levels

Co-administration of Ezetimibe and Statin

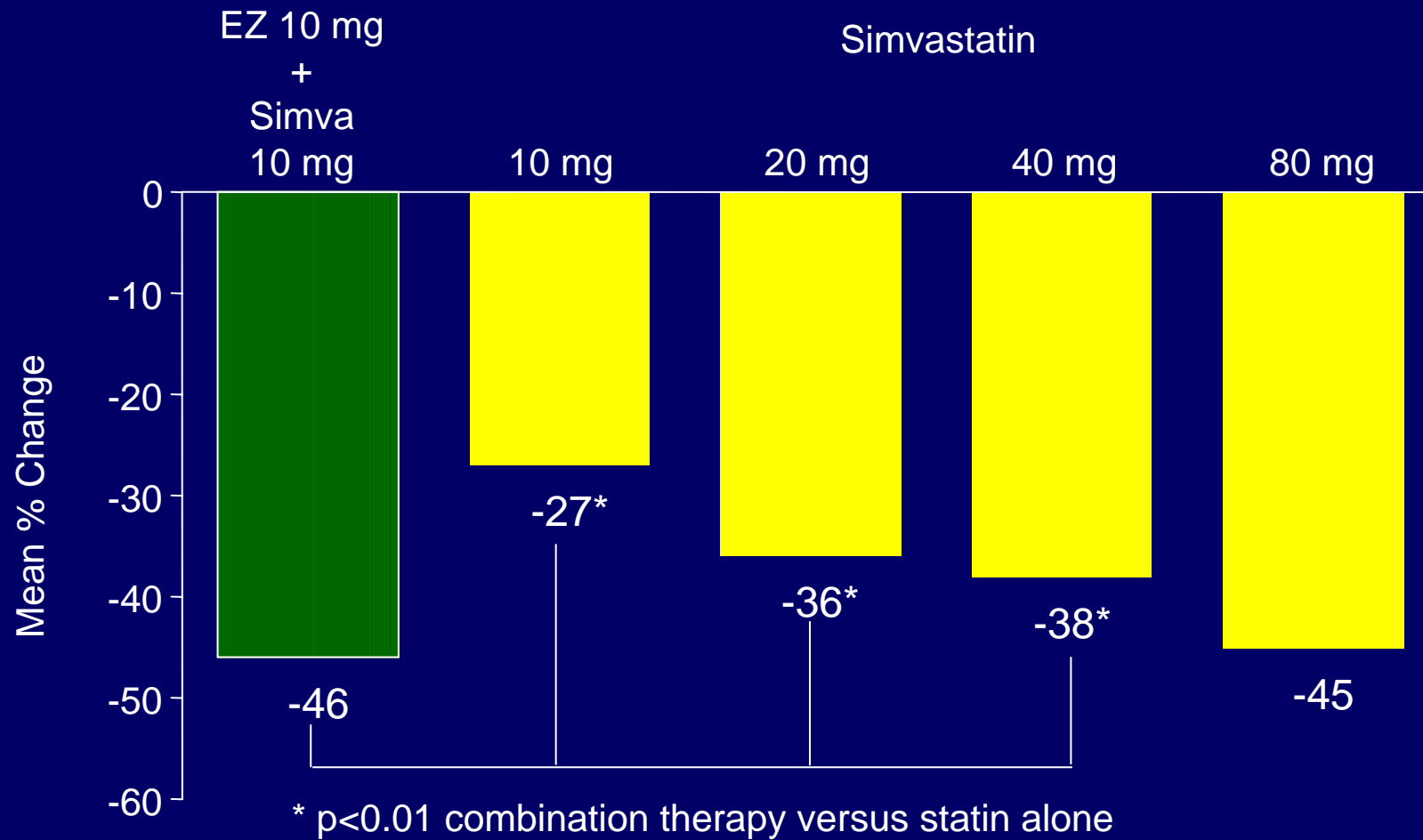
Dose (mg) of agent					<u>% Reduction</u>	
Rosuva	Atorva	Simva / EZ	Simva	Lova / Prava	TC	LDL-C
	5		10	20	22	27
	10		20	40	27	34
10	20		40	80	32	41
20	40	10 / 10	80		37	48
40	80				42	55

↓ ↓
Rule of 5s & 7s

Roberts WC. *Am J Cardiol.* 1997;80:106-107.

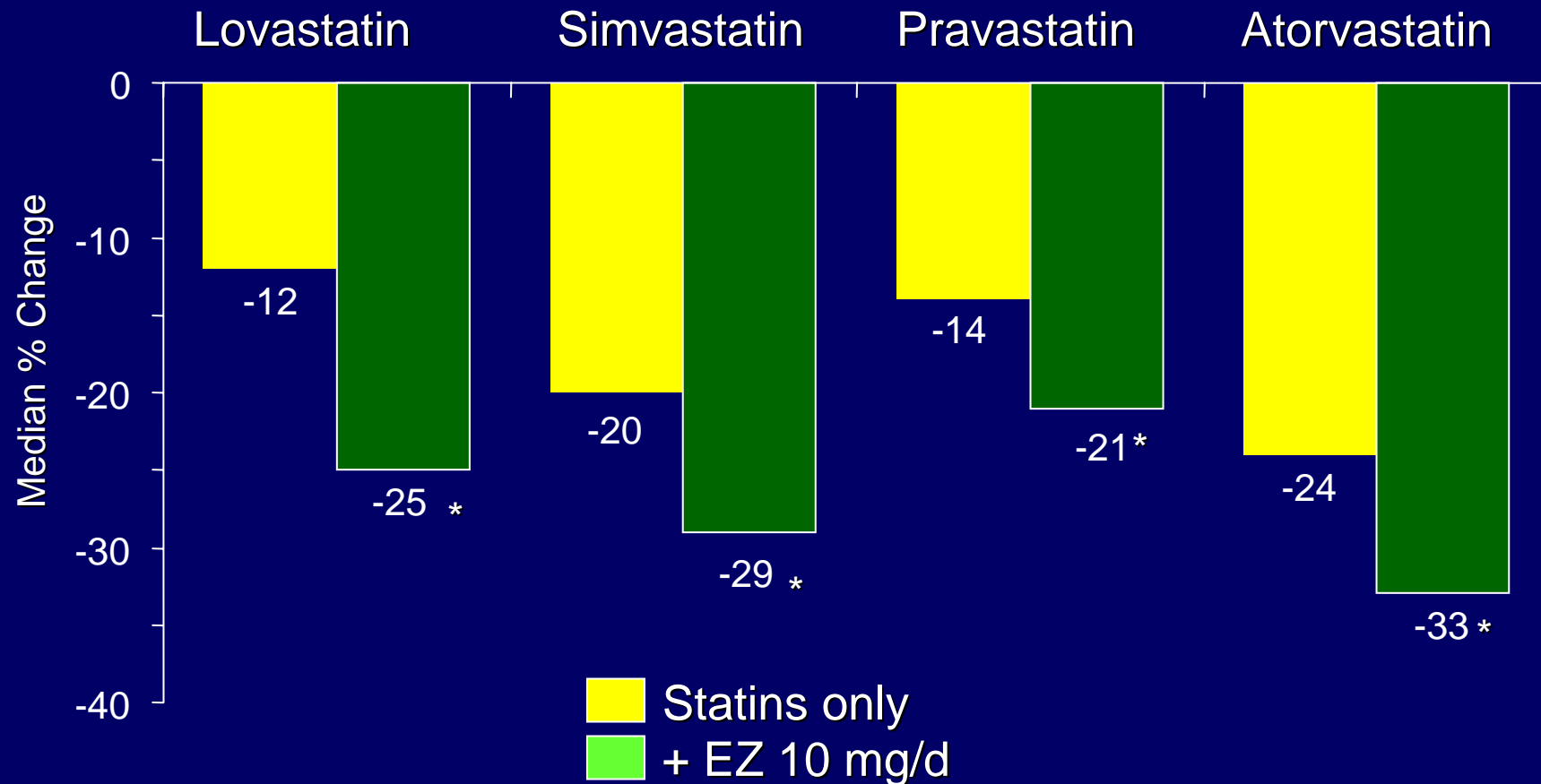
Stein E et al. *J Cardiovasc Pharmacol Therapeut.* 1997;2:7-16.

EZ + Simvastatin Study: Efficacy on LDL-C



EZ + Statin Studies: Efficacy on TG

Pooled Results

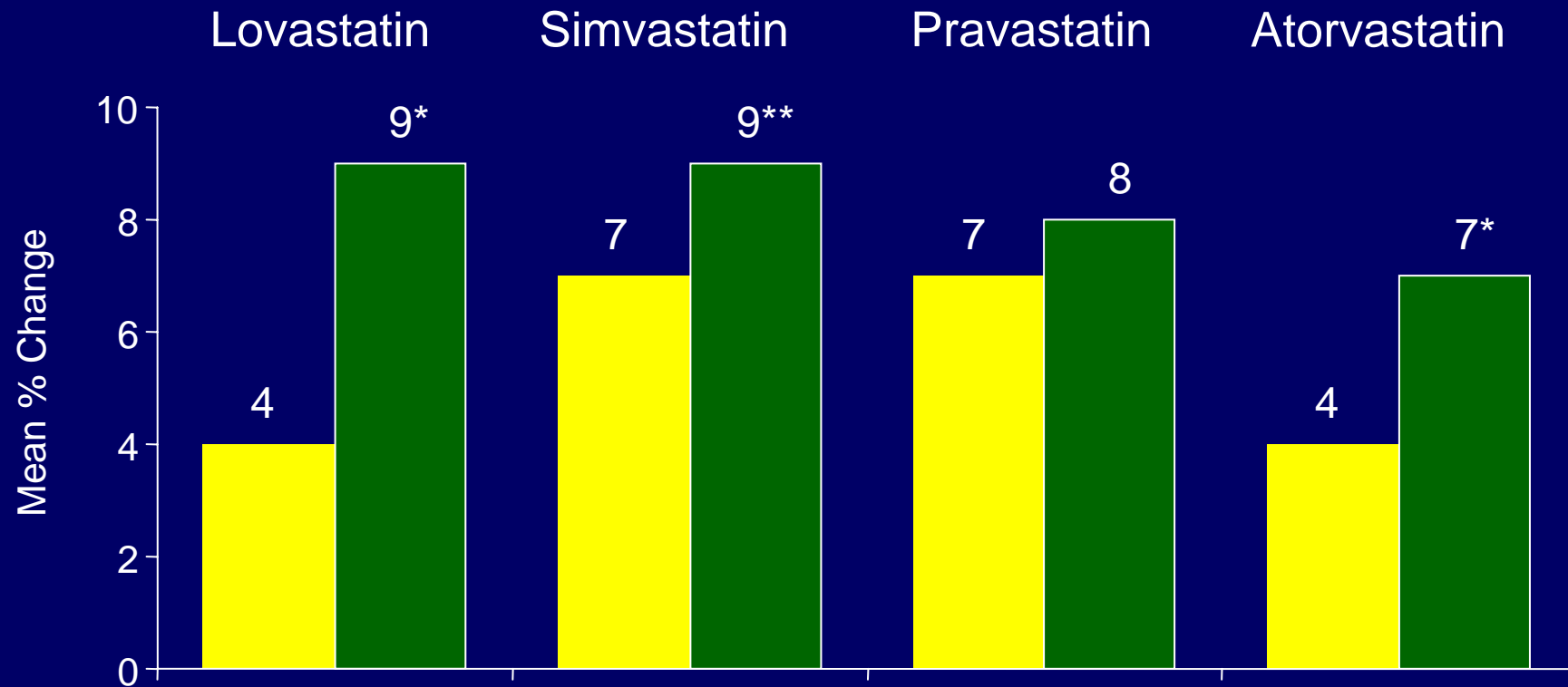


* p<0.01 combination therapy versus statin alone

Davidson M et al. ACC 2002: Abstract.
Ballantyne C et al. ACC 2002: Abstract.
Melani L et al. WCC 2002: Abstract.
Lipka L et al. WCC 2002: Abstract.


Ezetrol + Statin Studies: Efficacy on HDL-C

Pooled Results



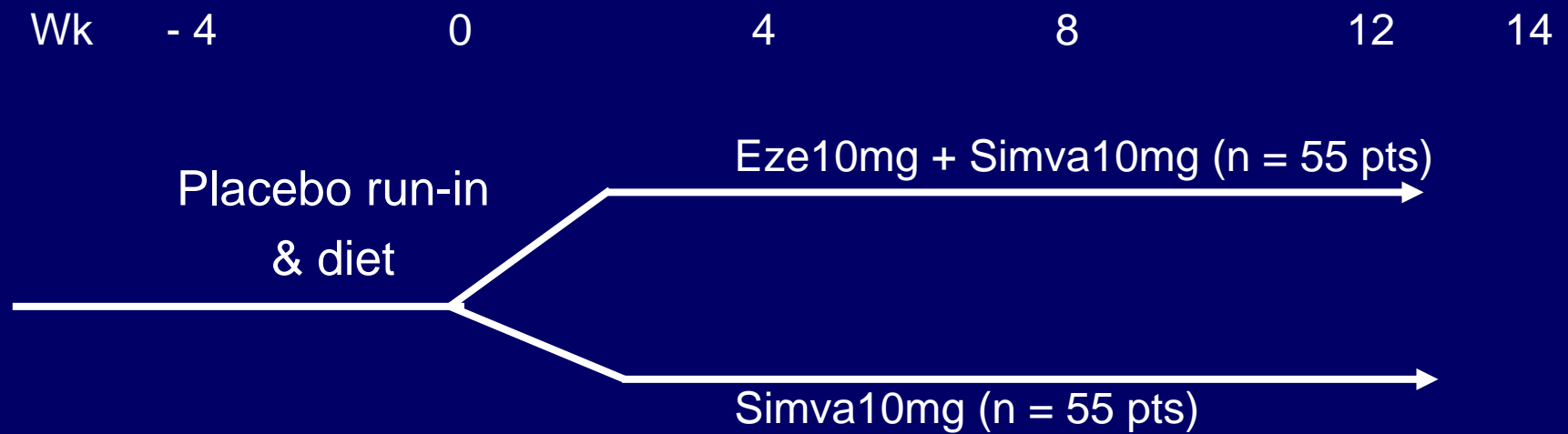
* $p < 0.01$ combination therapy versus statin alone

** $p = 0.03$ combination therapy versus statin alone

 Statins only
 + EZ 10 mg/d

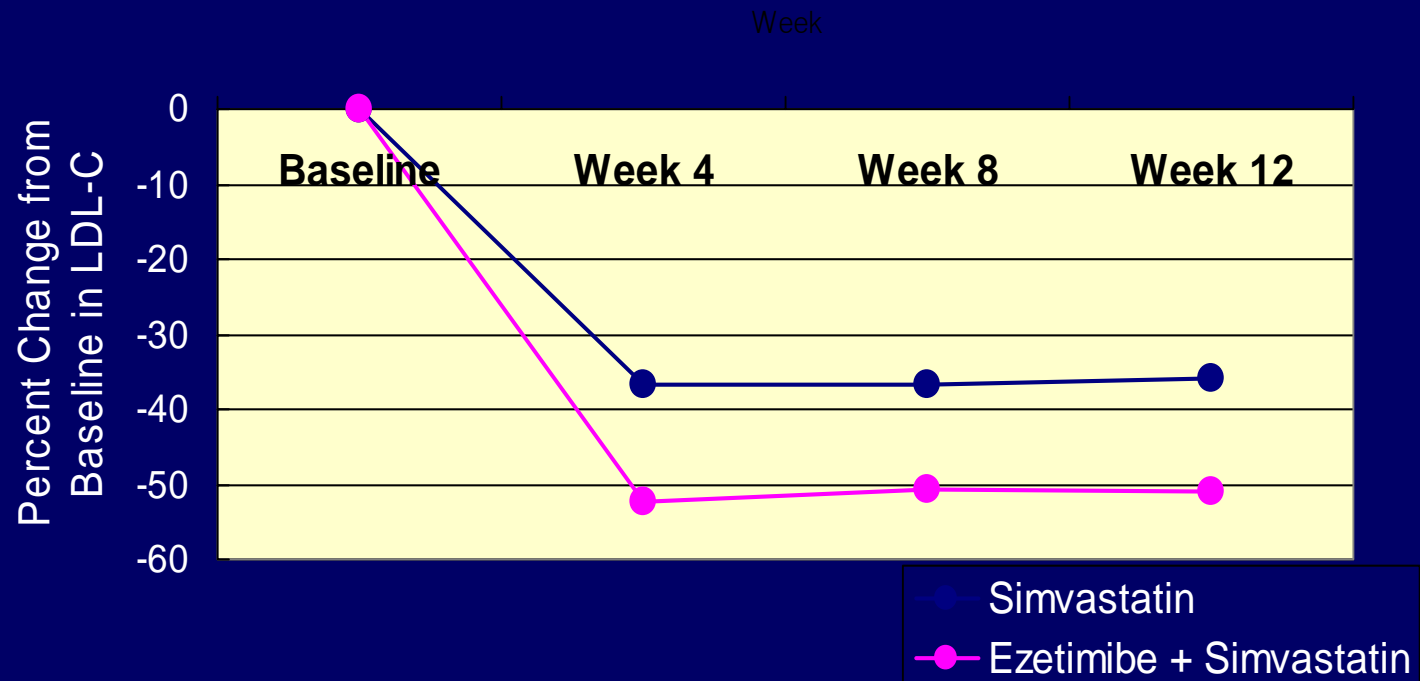
Davidson M et al. ACC 2002: Abstract.
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Ezetimibe in KOREANS



Ezetimibe in KOREANS (2)

Figure 2. Plot of LS Mean Percent Change from Baseline in LDL-C over Time: Modified Intention-to-Treat Approach



Number of Patients Treated With Ezetimibe (as of March 2002)

- Total patients exposed to Ezetimibe: **over 5700**
- Total patients exposed for ≥ 6 months: **over 2100**
- Total patients exposed for ≥ 12 months: **over 1600**
- Total patients exposed for ≥ 18 months: **980**
- Ongoing exposure: **up to 27 months**
- Ongoing exposure to ezetimibe + statins: **up to 23 months**

Ezetimibe Mechanism of Action

- Ezetimibe is a highly potent and specific inhibitor of dietary and biliary cholesterol absorption
 - Ezetimibe prevents cholesterol uptake at the level of the intestinal wall and is localized on the brush border membrane
 - Onset of action is rapid, <90 minutes
 - Ezetimibe may act on a cholesterol transporter (subject of ongoing research)

Ezetimibe: Dosage and Administration

- Recommended dose of ezetimibe is 10 mg once daily
- Ezetimibe can be administered at any time of the day, with or without food
- Ezetimibe may be administered concurrently with a statin for incremental effect
 - For convenience, the daily dose of ezetimibe may be taken at the same time as the statin, according to the dosing recommendations for the statin
- No important drug interaction with commonly used drugs

Conclusion

- The co-administration of Ezetimibe and any statin enables dual inhibition to address both liver-synthesized and intestinally-absorbed cholesterol
- Ezetimibe reduced LDL-C by an additional 19% to 23% when co-administered with a statin
- Co-administration of Ezetimibe with 10 mg of any statin provides an LDL reduction equal to 80 mg of that statin
- For patients on a statin and not at goal when Ezetimibe is added to their therapy, 72% reach goal
- The safety profile of co-administration therapy with Ezetimibe is similar to that of the statin alone
- Ezetimibe has a safety and tolerability profile similar to placebo