Noncholesterol Sterols

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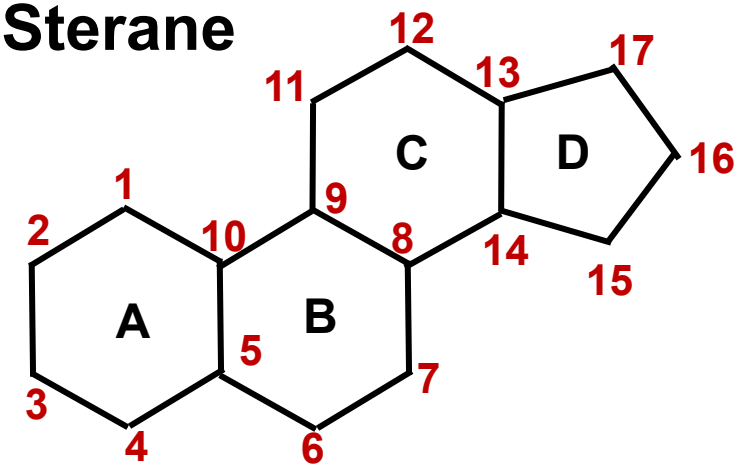
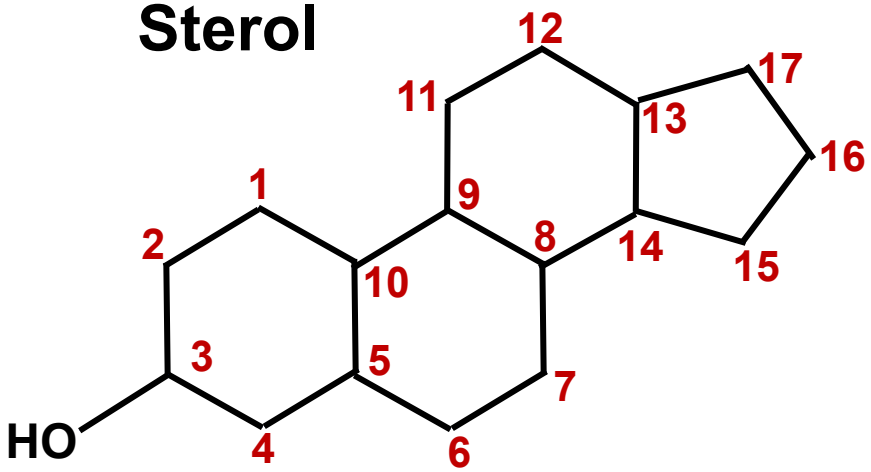
Steranes and Sterols

Steranes are a class of 4-cyclic compounds which constitute the core of all sterols and steroids.

Sterane

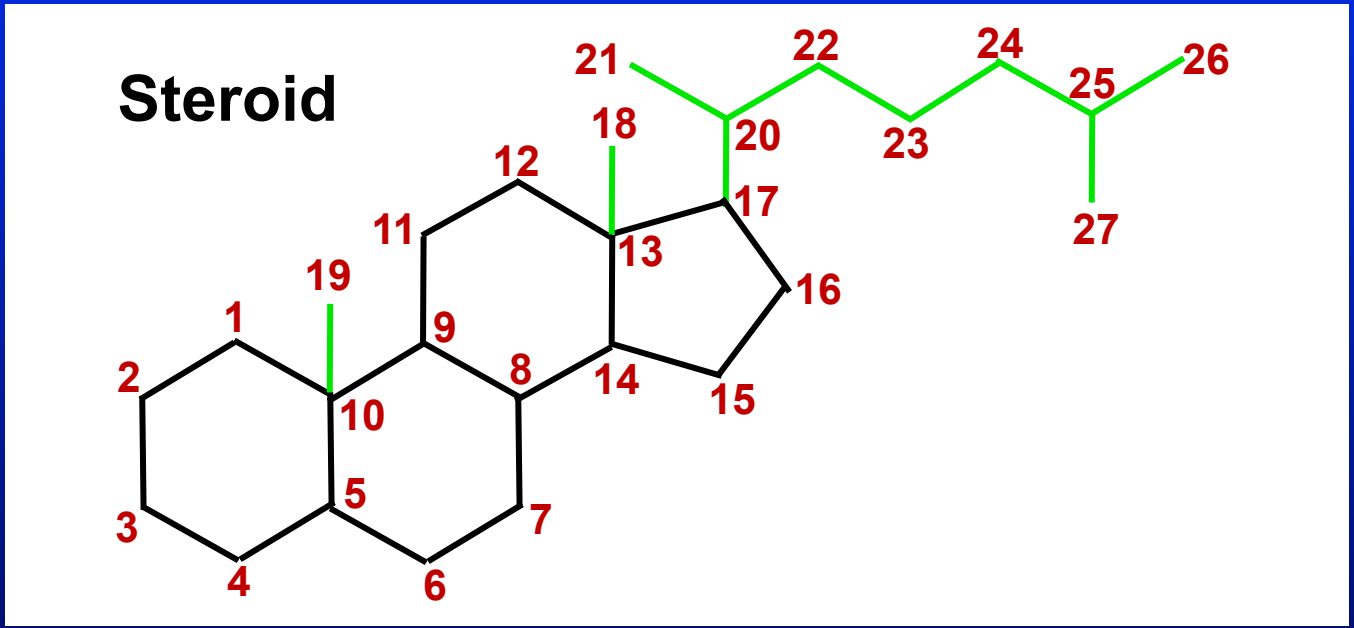


Sterol



Sterols are also known as **steroid alcohols**. They are steranes with a hydroxyl group at the 3-position of the A-ring. They are amphipathic lipids as the hydroxyl group on the A ring is polar. The rest of the aliphatic chain is non-polar. Sterols of plants are called phytosterols and sterols of animals are called zoosterols

Steroids



A steroid is a isoprenoid lipid characterized by its sterane or steroid nucleus: a carbon skeleton with four fused rings, generally arranged in a 6-6-6-5 fashion. Steroids vary by the functional groups attached to these rings and the oxidation state of the rings.

Noncholesterol Sterols

Exogenous

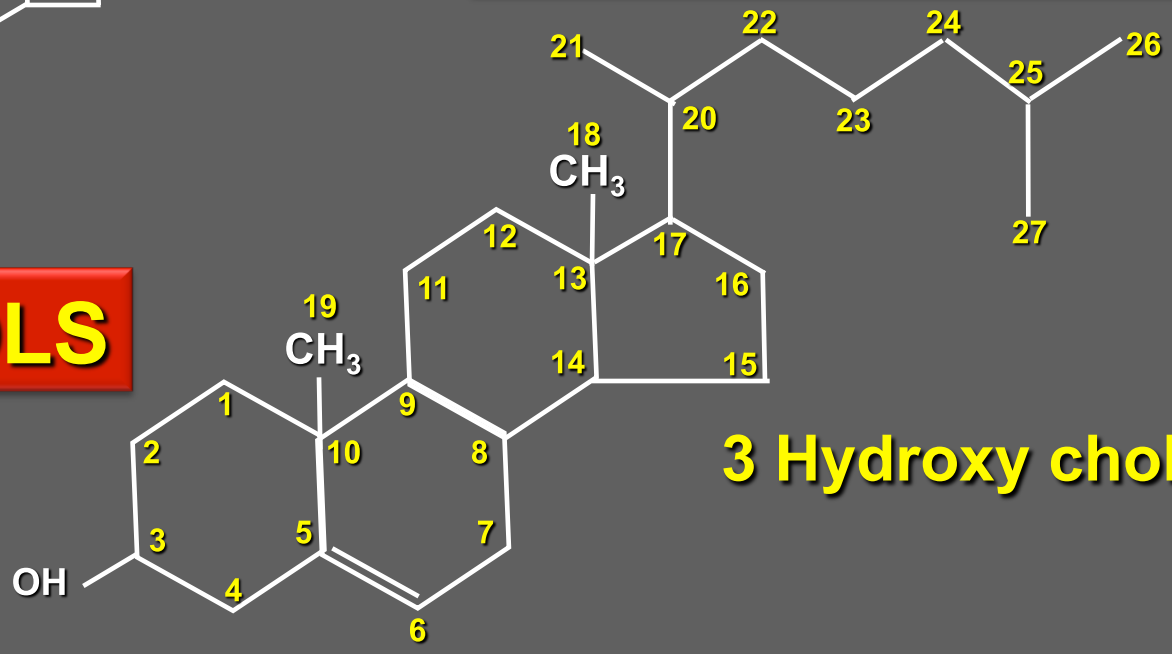
- Plant Sterols
  - Sitosterol
  - Campesterol
  - Brassicasterol
  - Avenosterol, etc.
- Yeast Sterols
  - Ergosterol, etc.
- Shellfish Sterols
  - Desmosterol
  - Fucosterol, etc

Endogenous

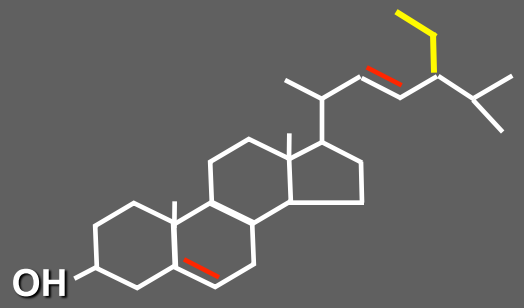
- Sterol Synthesis Intermediates
  - Desmosterol
  - Lathosterol
  - Cholestenol
- Metabolites
  - Cholestanol
  - Oxysterols

Noncholesterol Sterols

STEROLS



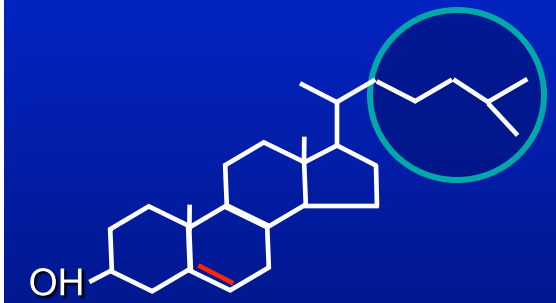
3 Hydroxy cholesterol



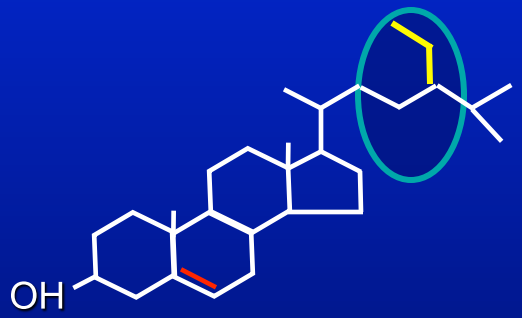
Stigmasterol

Cholesterol and Noncholesterol Sterols

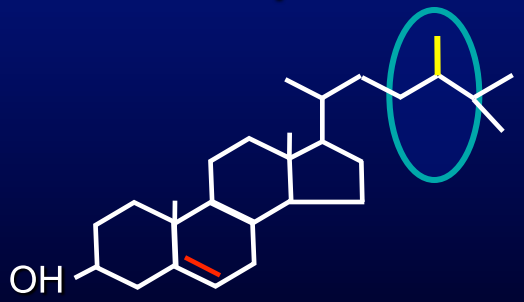
Cholesterol



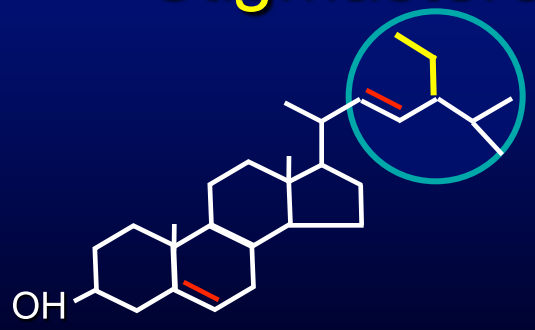
Sitosterol



Campesterol



Stigmasterol

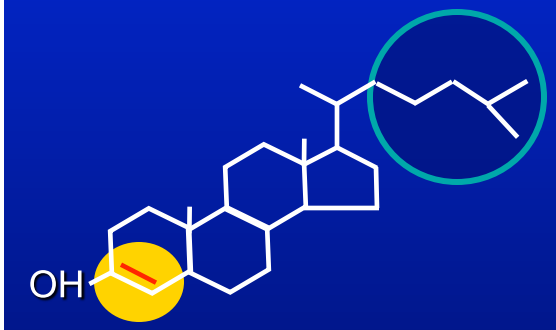


The majority of the differences are in the “R” tail with plant sterols having an extra methyl (campesterol) or ethyl (sitosterol) group at the C-24 position and different levels of desaturation

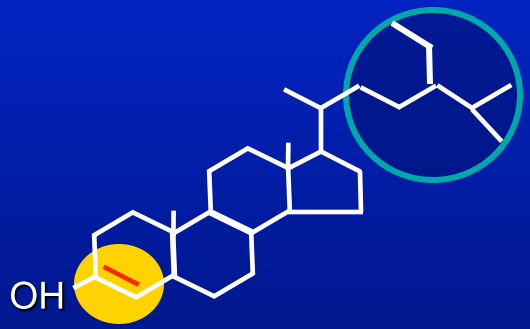
The more carbon atoms and desaturation, the less the intestinal absorption

Saturated Sterol Structures: Stanols

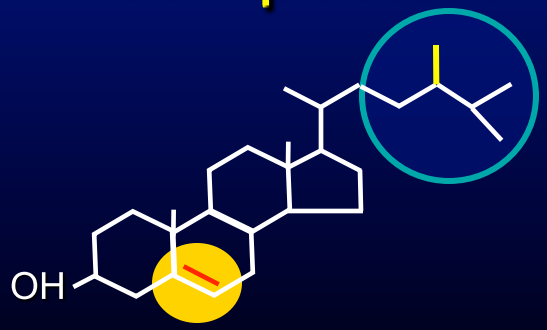
Cholestanol



Sitostanol



Campestanol



Saturation of the Δ 5 double bond of sterols by enzymes in the liver results in 5 α stanols

Stanols decrease cholesterol absorption by competing with cholesterol for incorporation into mixed micelles

Double bond at the Δ5 position

Esterification is necessary to solubilize plant stanols in fat (spreads)

Sterol Absorption

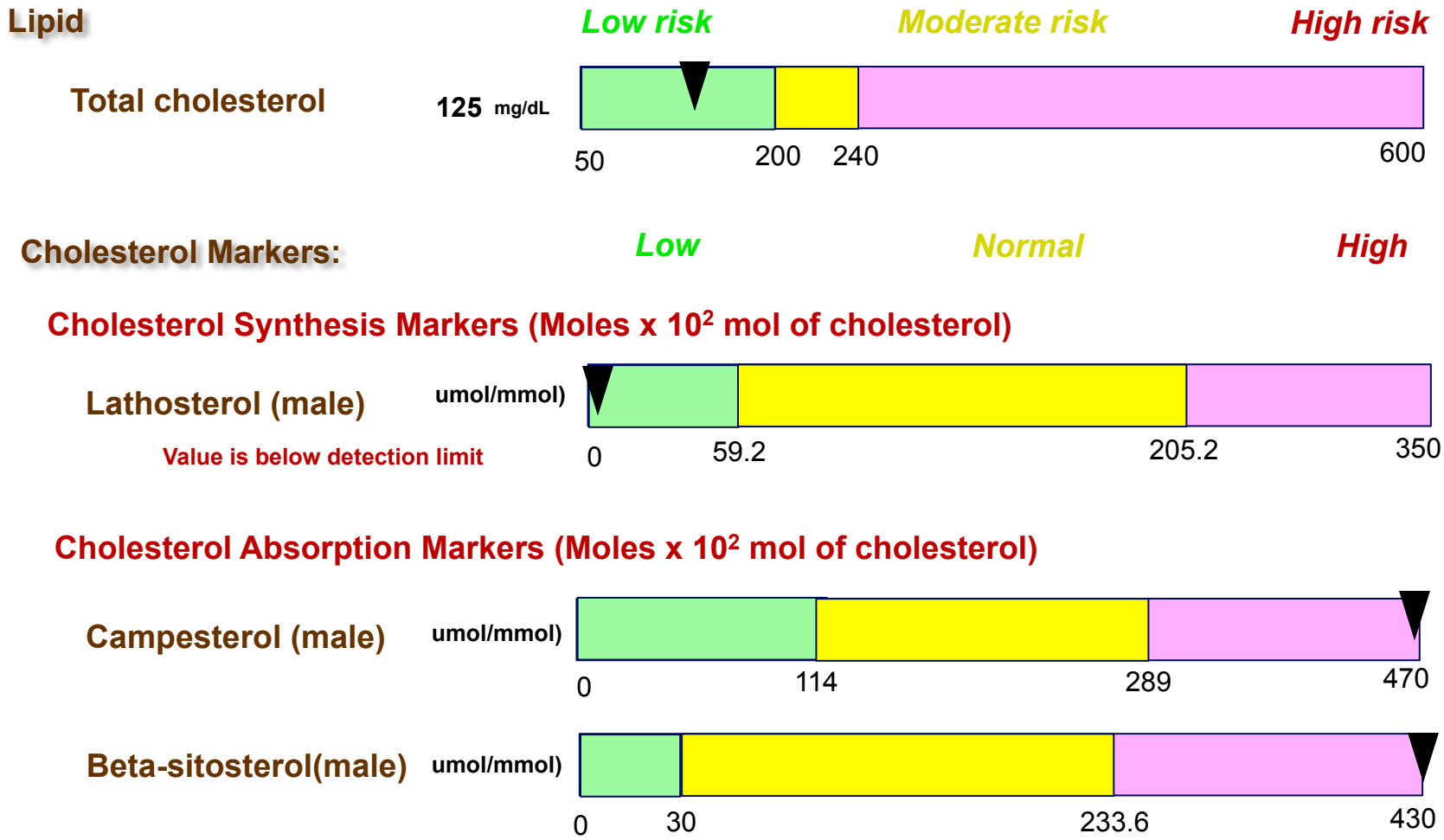
- The body can distinguish between sterols
- Plant sterols and stanols are not synthesized by animals or humans but are obtained in the diet
- Campesterol is absorbed to a greater extent than sitosterol (9-18%) which is absorbed to a greater extent than sitosterol (5-8%), although the absorption of all of these is much lower than that of cholesterol
  - The heritability of plasma noncholesterol sterol levels is stronger than that of cholesterol

Sterol Absorption

- Plant sterols and stanols can reduce the absorption of cholesterol.
- They mimic and displace cholesterol in micellar particles.
- Although they can constitute 50% of absorbed sterols, the body strictly limits their circulating amounts
- Non cholesterol sterols can be very damaging if physiologic defects allow them to circulate

Ira Tabas Cardiology Reviews 2004;21(7) (Suppl) p3.
Presented at ACC Annual Meeting New Orleans March 2004

Boston Heart Lab Cholesterol Balance



PROspective CArdiovascular Munster Study (PROCAM): Elevated Phytosterols and CHD

►A nested case-control study using stored samples from **male participants** in the Prospective Cardiovascular Munster (PROCAM) study was performed. Each of 159 men who suffered a myocardial infarction or sudden coronary death (major coronary event) within 10 years of follow-up in PROCAM was matched with 2 controls (N=318) by age, smoking status, and date of investigation

►Among men with an absolute coronary risk ≥ 20% in 10 years as calculated using the PROCAM algorithm, **high sitosterol concentrations were associated with an additional 3-fold increase in the incidence of coronary events** (P=0.032); a similar, significant relationship was observed between a high sitosterol/ cholesterol ratio and coronary risk (P=0.030).

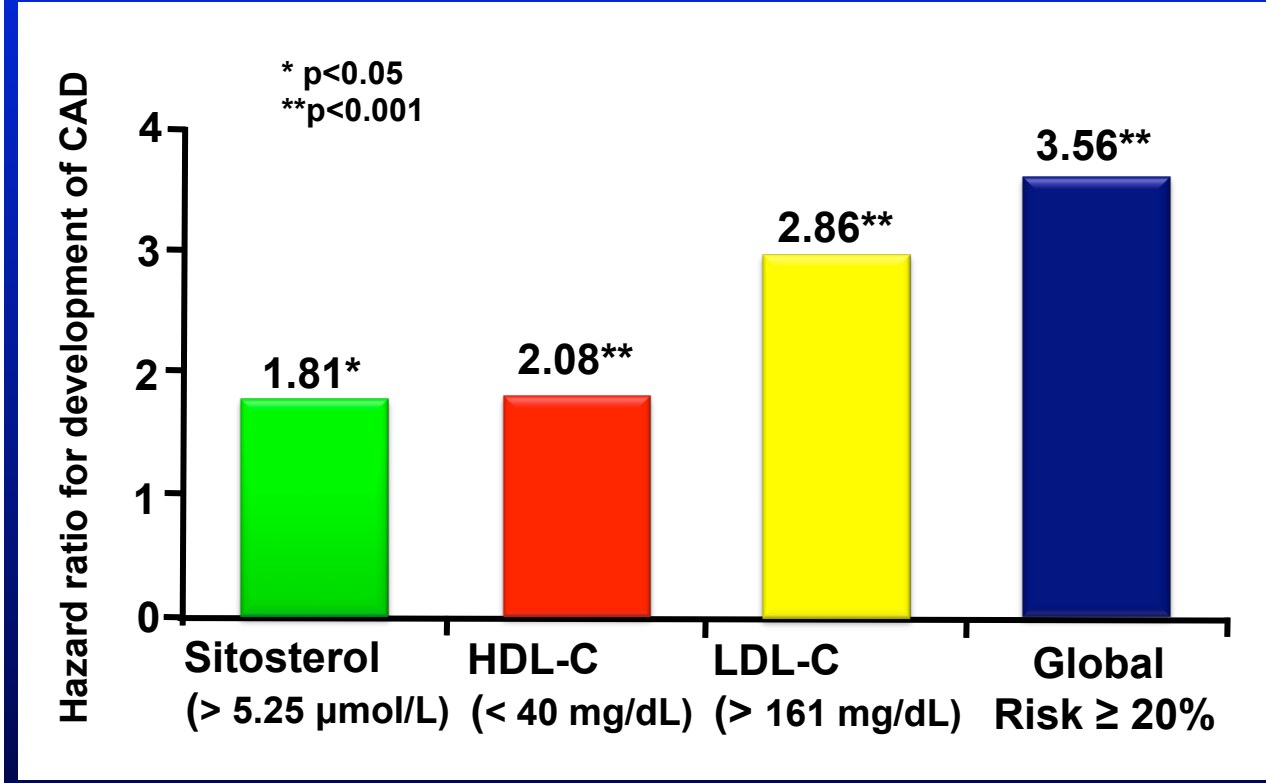
Assmann G et al. Nutrition, Metabolism & Cardiovascular Diseases (2006) 16, 13e21

PROspective CArdiovascular Munster Study (PROCAM): Elevated Phytosterols and CHD

- The PROCAM study was conducted before statins were available, and few participants were receiving other lipid-modifying medications when their blood samples were drawn
- Two potential explanations for these data are:
  - That sitosterol is somehow involved in the disease process
  - Sitosterol is a surrogate for some other factor or condition that is involved in atherogenesis.

Assmann G et al. Nutrition, Metabolism & Cardiovascular Diseases (2006) 16, 13e21

PROspective CArdiovascular Munster Study (PROCAM): Elevated Phytosterols and CHD



On univariate analysis, a high sitosterol concentration (>2.0) was significantly associated with a CHD risk (HR = 1.81; < 0.05) similar to that of hypertension, family CHD history, or metabolic syndrome

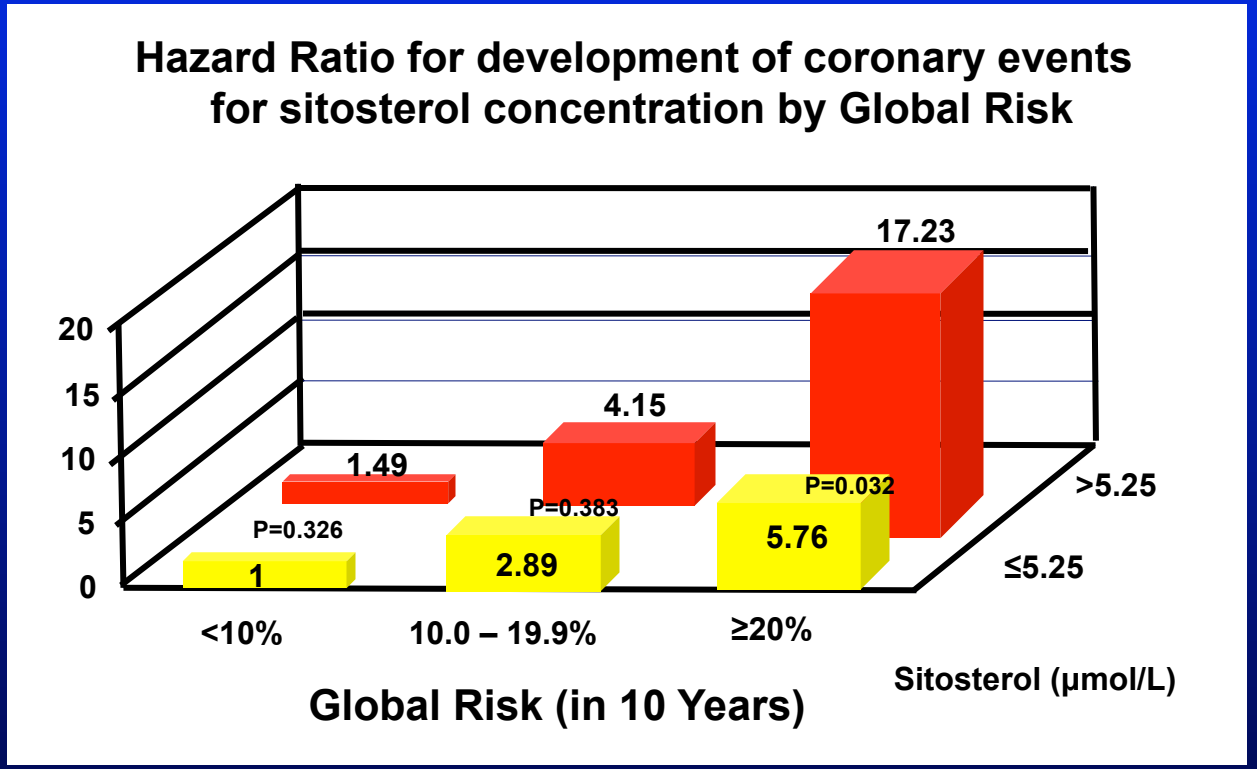
Of the univariate risk factors, only high LDL-C, low HDL-C and global risk > 20% (hazard ratio = 3.56) were associated with a greater relative risk of a major coronary event than elevated sitosterol.

Male Data

Assmann G et al. Nutrition, Metabolism & Cardiovascular Diseases (2006) 16, 13e21

PROspective CArdiovascular Munster Study (PROCAM): Elevated Phytosterols and CHD

Hazard ratios for development of coronary events according to sitosterol concentration (mmol/L) among men in different categories of 10-year global coronary risk (hazard ratio of 1 = global risk < 10% and sitosterol ≥ 5.25 mmol/L). The participants in the category with low global risk (< 10%) were divided into groups with low (≤ 5.25 mmol/L, 39 cases, 140 controls) and high (> 5.25 mmol/L, 17 cases, 46 controls) sitosterol concentrations.

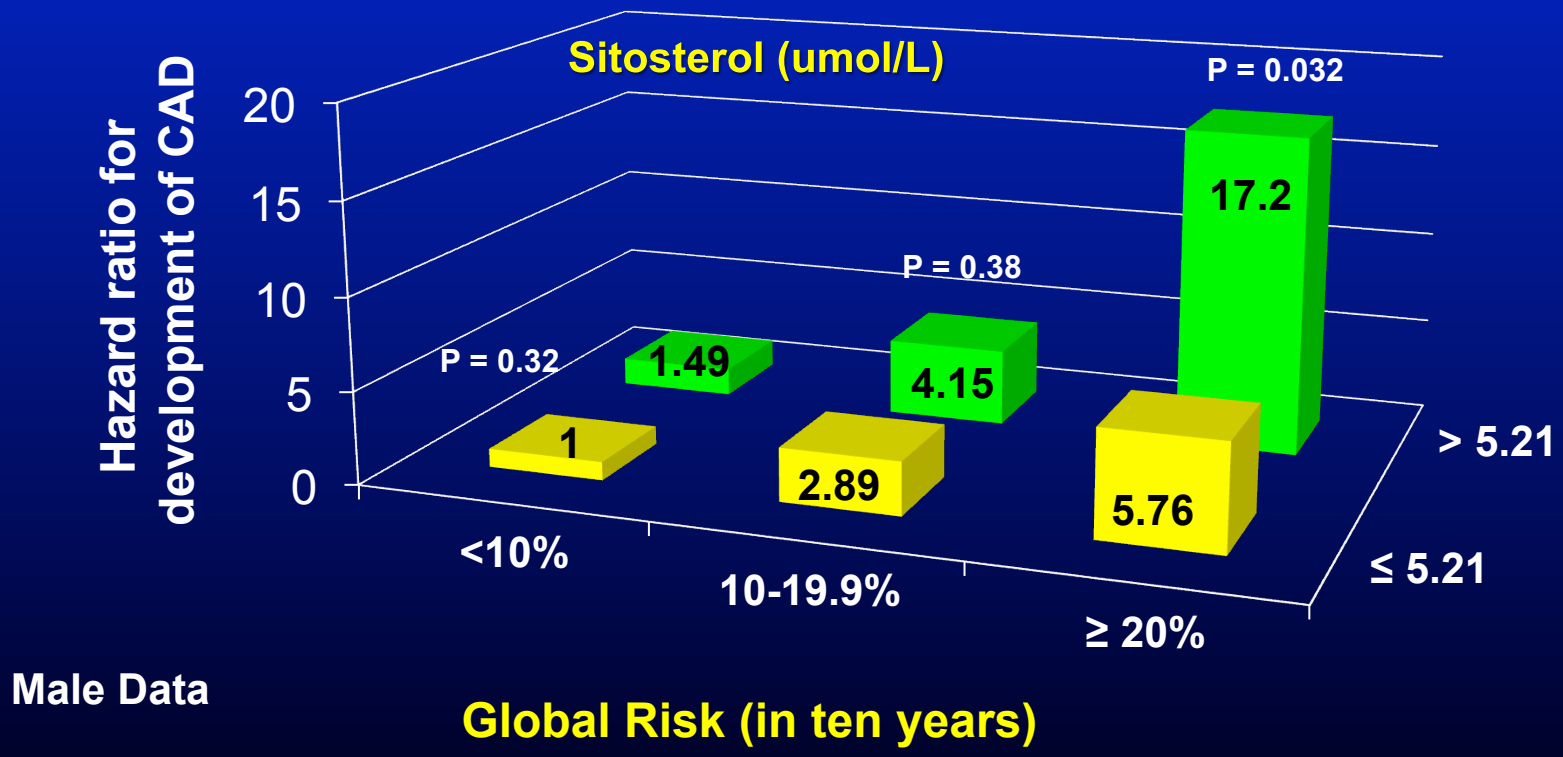


At medium level of global risk (10.0 - 19.9%), low sitosterol concentrations were observed in 29 cases and 53 controls and high sitosterol levels in 18 cases and 24 controls, while at high global risk (≥ 20%), low sitosterol levels occurred in 38 cases and 47 controls while high sitosterol levels were measured in 18 cases and 8 controls.

Assmann G et al. Nutrition, Metabolism & Cardiovascular Diseases (2006) 16, 13e21

PROspective CArdiovascular Munster Study (PROCAM): Elevated Phytosterols and CHD

Hazard ratio for Sitosterol concentration by Global Risk

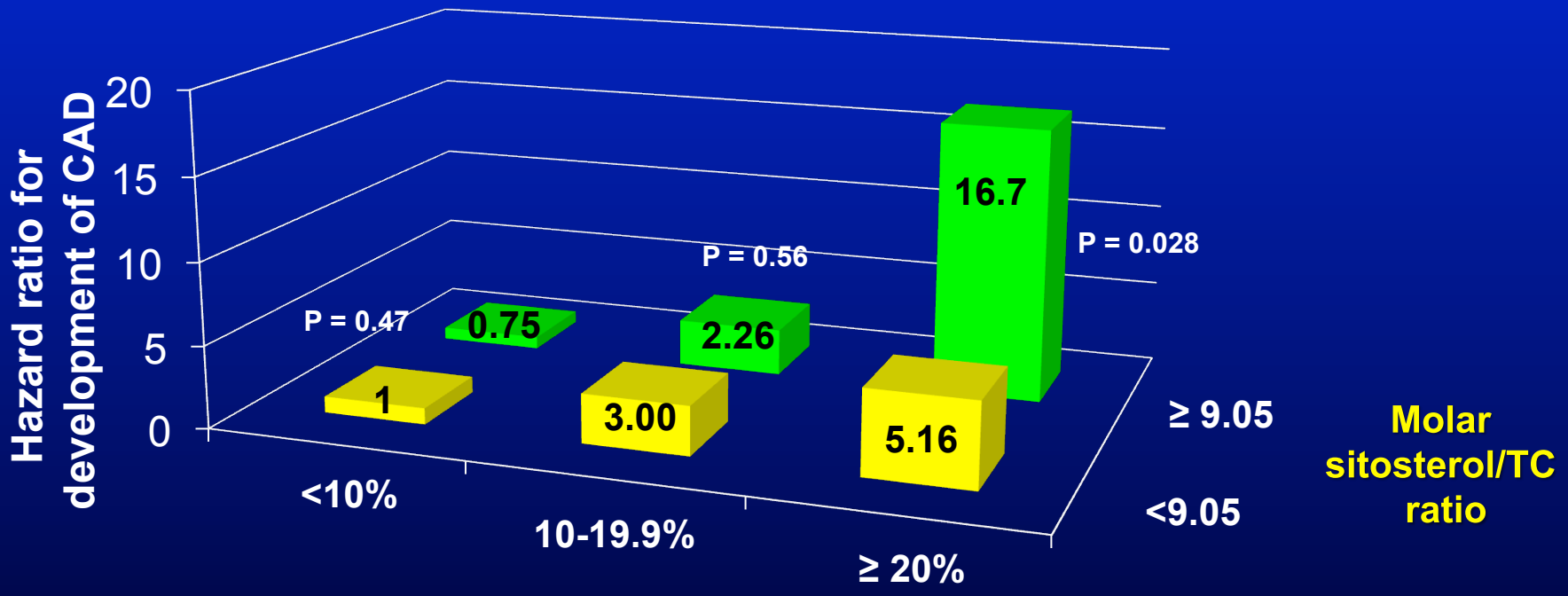


Male Data

Assmann G et al. Nutrition, Metabolism & Cardiovascular Diseases (2006) 16, 13e21

PROspective CArdiovascular Munster Study (PROCAM): Elevated Phytosterols and CHD

Hazard ratio for Sitosterol / TC ratio by Global Risk



Male Data

Global Risk (in ten years)

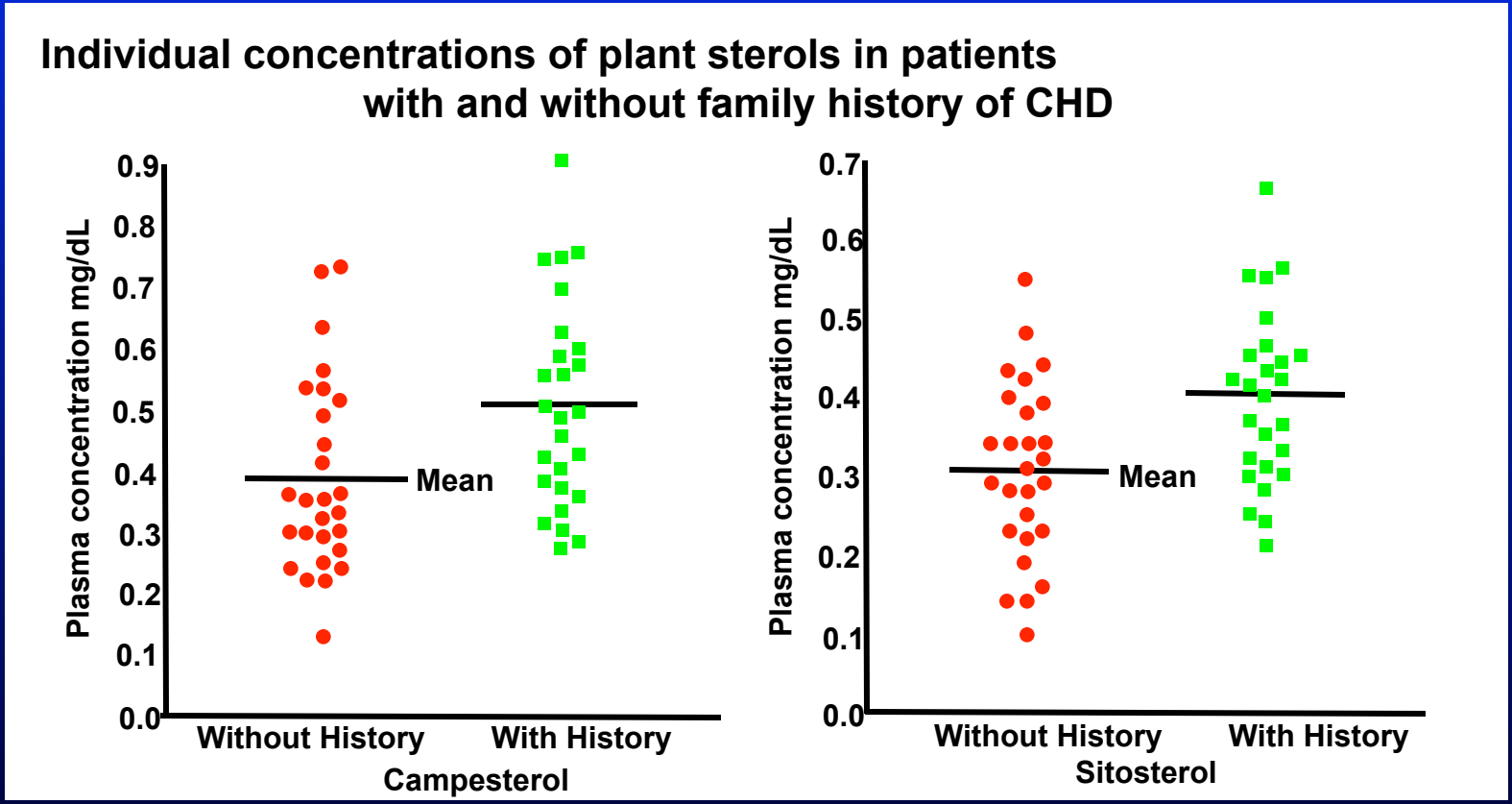
Assmann G et al. Nutrition, Metabolism & Cardiovascular Diseases (2006) 16, 13e21

Elevated Phytosterols and CHD

- Sitosterol and campesterol concentrations are higher in subjects with personal or family history of premature CHD
- 42% of probands' kindred had history of premature CHD vs 19% of the cohort
- Suggests plant sterol levels are genetically determined

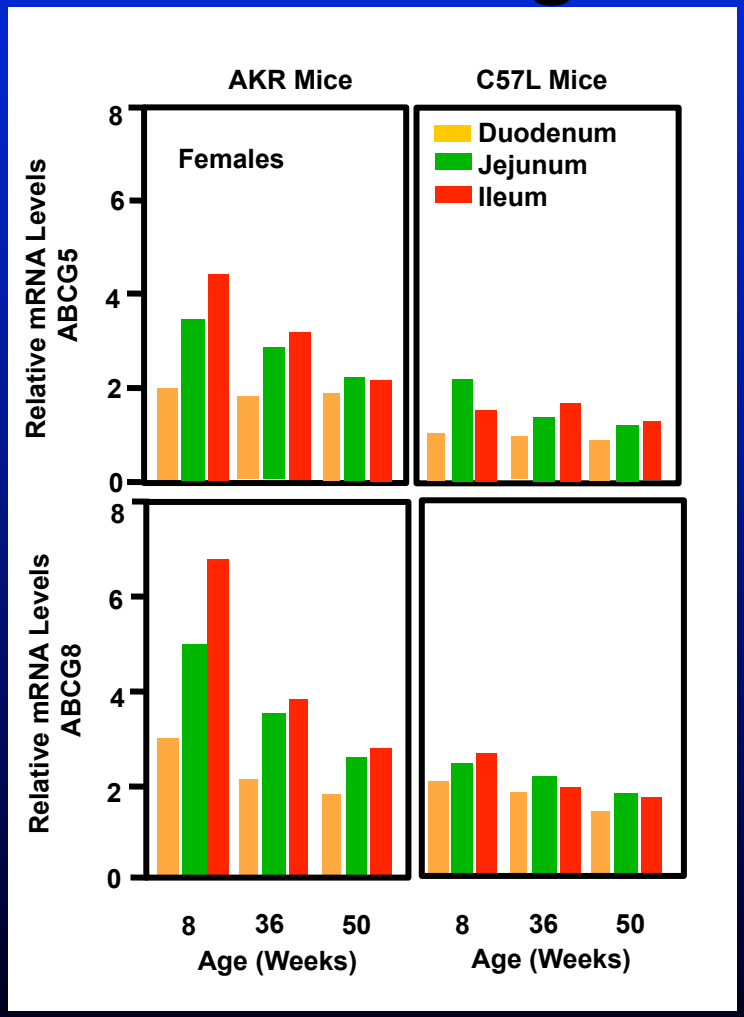
Glueck CJ et al Metabolism 1991;40:842-848

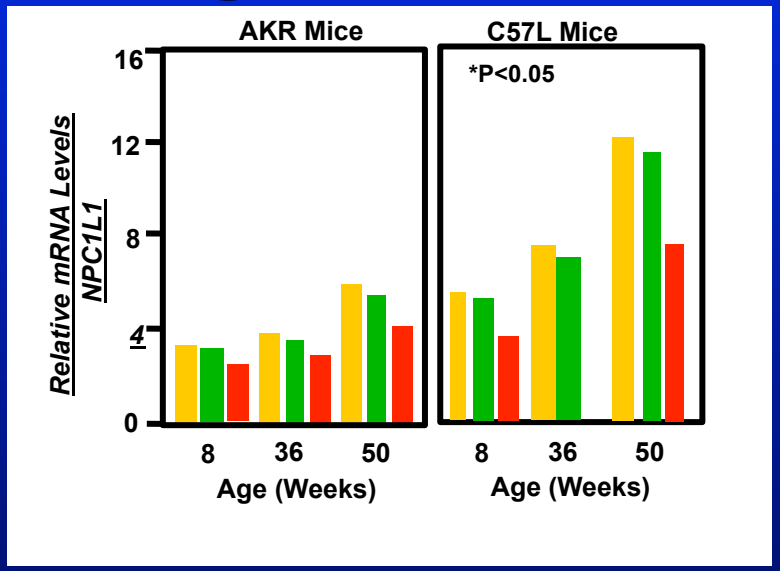
Phytosterols and Family History of Coronary Heart Disease



Sudhop T et al. Metabolism 2002;51:1519-1521

Role of intestinal sterol transporters ABCG5 G8 and NPC1L1 in cholesterol absorption in mice: gender and age effects



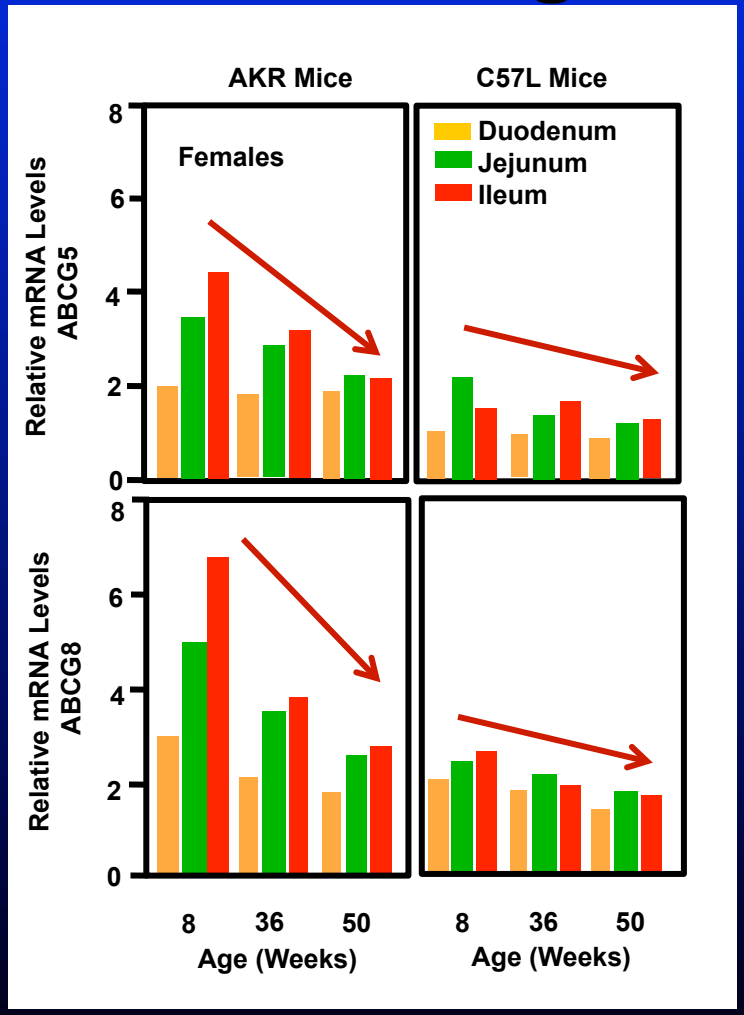


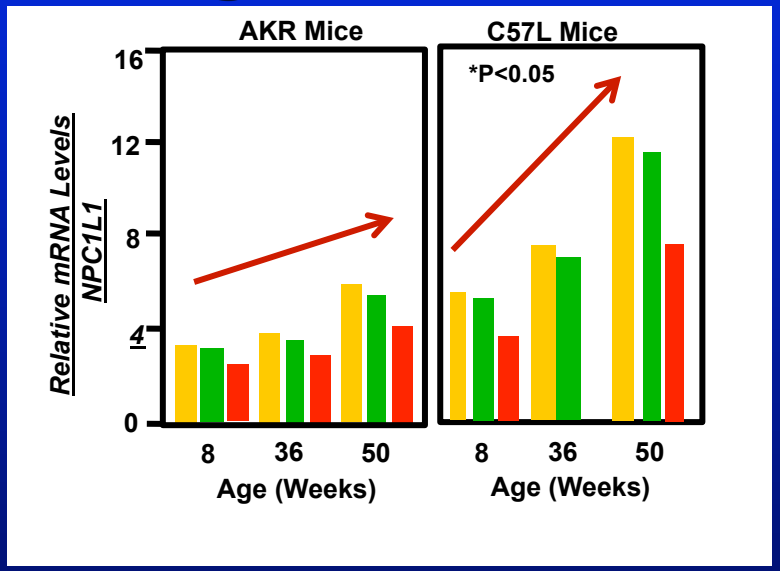
Of note is that the relative mRNA levels for duodenal ABCG5 and ABCG8 are essentially similar in mice of different ages.

Aging significantly (P 0.05) increased expression levels of NPC1L1 in the duodenum and jejunum and to a lesser extent in the ileum, which is associated with increased intestinal cholesterol absorption

Li-Ping Duan, et al. Am J Physiol Gastrointest Liver Physiol 22006;90: G269–G276

Role of intestinal sterol transporters ABCG5 G8 and NPC1L1 in cholesterol absorption in mice: gender and age effects





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Li-Ping Duan, et al. Am J Physiol Gastrointest Liver Physiol 22006;90: G269–G276

Squalene & Sitosterol Concentrations in Menopausal Women with CHD

- Serum cholesterol precursors, including squalene, lanosterol and other methylated sterols, desmosterol and lathosterol, are positively related to cholesterol synthesis rate
- Plant sterols, solely of dietary origin, such as campesterol and sitosterol, and cholestanol, a metabolite of cholesterol, are related to cholesterol absorption efficiency
- Squalene and noncholesterol sterols in fasting sera were assessed in postmenopausal women with angiographically documented CAD and were compared to postmenopausal controls.

Radhakrishnan A. **et al. J AM Coll Cardiol 2000;35:1185-1191**

Squalene & Sitosterol Concentrations in Menopausal Women with CHD

- Menopausal women with CHD had higher levels of sitosterol and campesterol
- The plasma cholesterol levels did not differ
- Results remained significant after adjustment of other risk factors
- High serum plant sterols themselves are strongly atherogenic, especially in phytosterolemia

Radhakrishnan A. **et al. J AM Coll Cardiol 2000;35:1185-1191**

Squalene & Sitosterol Concentrations in Menopausal Women with CHD

- The present study revealed the independent associations of serum squalene, lathosterol, campesterol and sitosterol with the presence of angiographically documented CAD in postmenopausal women.
- Low lathosterol and high plant sterol ratios reflect low cholesterol synthesis rate and high cholesterol absorption efficiency in normal subjects
- Independent inverse association of lathosterol and positive associations of campesterol and sitosterol with CAD suggest that low synthesis and high absorption of cholesterol may be related to atherosclerosis in women independently of other lipid and nonlipid risk factors.

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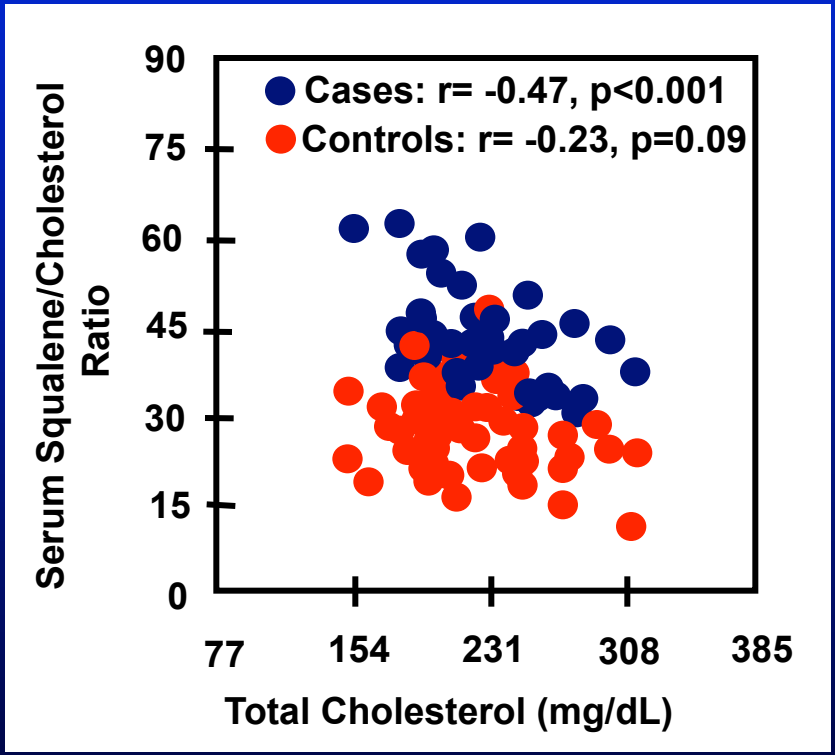
Squalene & Sitosterol Concentrations in Menopausal Women with CHD

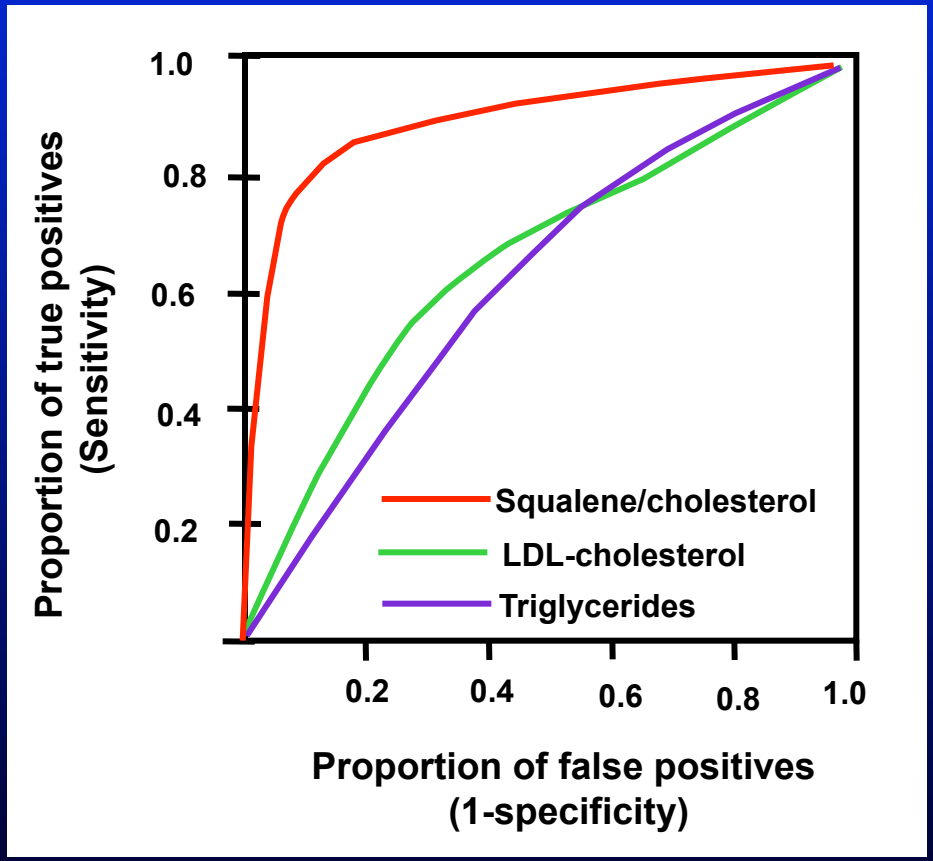


Association between serum squalene/ cholesterol ratio to serum total cholesterol (High ratios indicate over absorption of cholesterol)

The prevalence of CAD in menopausal women was independently and positively associated with the ratios of squalene, campesterol and sitosterol to cholesterol and inversely with the respective lathosterol value, suggesting that high absorption and low synthesis of cholesterol might play a significant role in the development of atherosclerosis.

Radhakrishnan A. **et al. J AM Coll Cardiol 2000;35:1185-1191**

Squalene & Sitosterol Concentrations in Menopausal Women with CHD

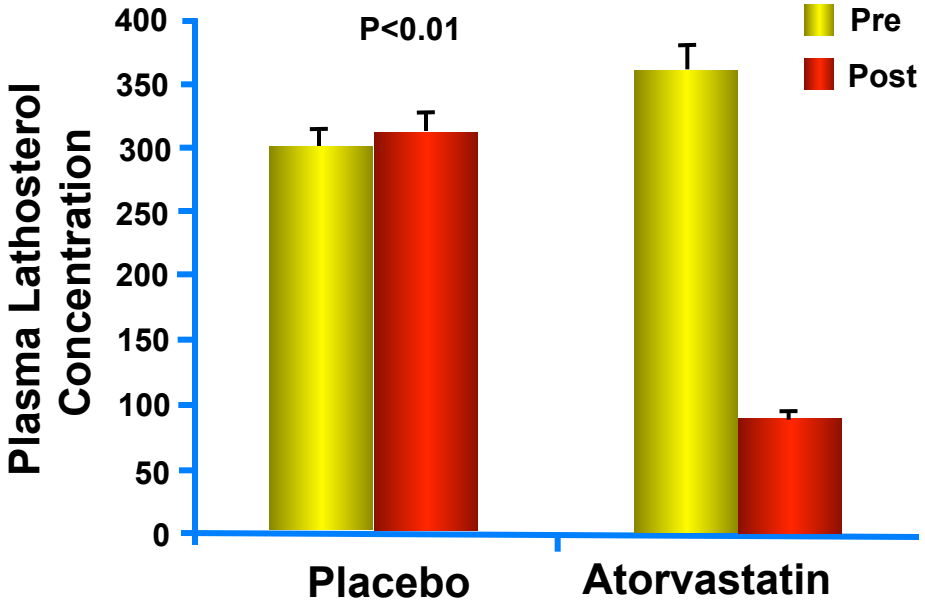


Receiver operating characteristic (ROC) curves for predicting the presence of coronary artery disease by squalene to cholesterol ratio, LDL cholesterol and serum triglycerides.

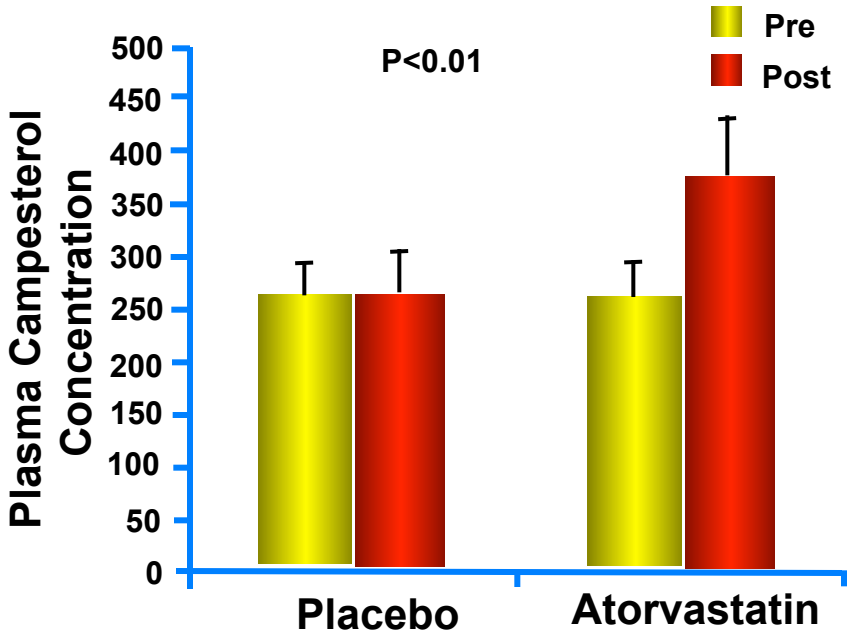
Area under the curve for the squalene ratio was 0.885; LDL cholesterol was 0.651 and serum triglycerides was 0.617.

Radhakrishnan A. **et al. J AM Coll Cardiol 2000;35:1185-1191**

Cholesterol Absorption & Synthesis
Effect of Statins



Cholesterol Synthesis



Cholesterol Absorption

Gylling, H. Int J Clin Prac 2004;58:859-866

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Lipids and Vascular Disease

Vascular Effects of Diet Supplementation With Plant Sterols

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Thomas Sudhop, MD,§ Klau
Hans-Joachim Schäfers, MD
Homburg/Saar, Bonn, Berlin,

Plant sterol supplementation impairs endothelial function, aggravates ischemic brain injury, effects atherogenesis in mice, and leads to increased tissue sterol concentrations in humans. In the light of the severe premature atherosclerosis in patients with phytosterolemia and epidemiological observations suggesting an association of plant sterols with increased vascular risk.

Objectives The purpose

Background Plant sterol
tion, stroke,

Methods In mice, pla
sclerosis. Plasma and tissue sterol concentrations were measured by gas-liquid chromatography-mass spectrometry in 82 consecutive patients with aortic stenosis.

Results Compared with those fed with normal chow (NC), wild-type mice fed with NC supplemented with 2% PSE showed

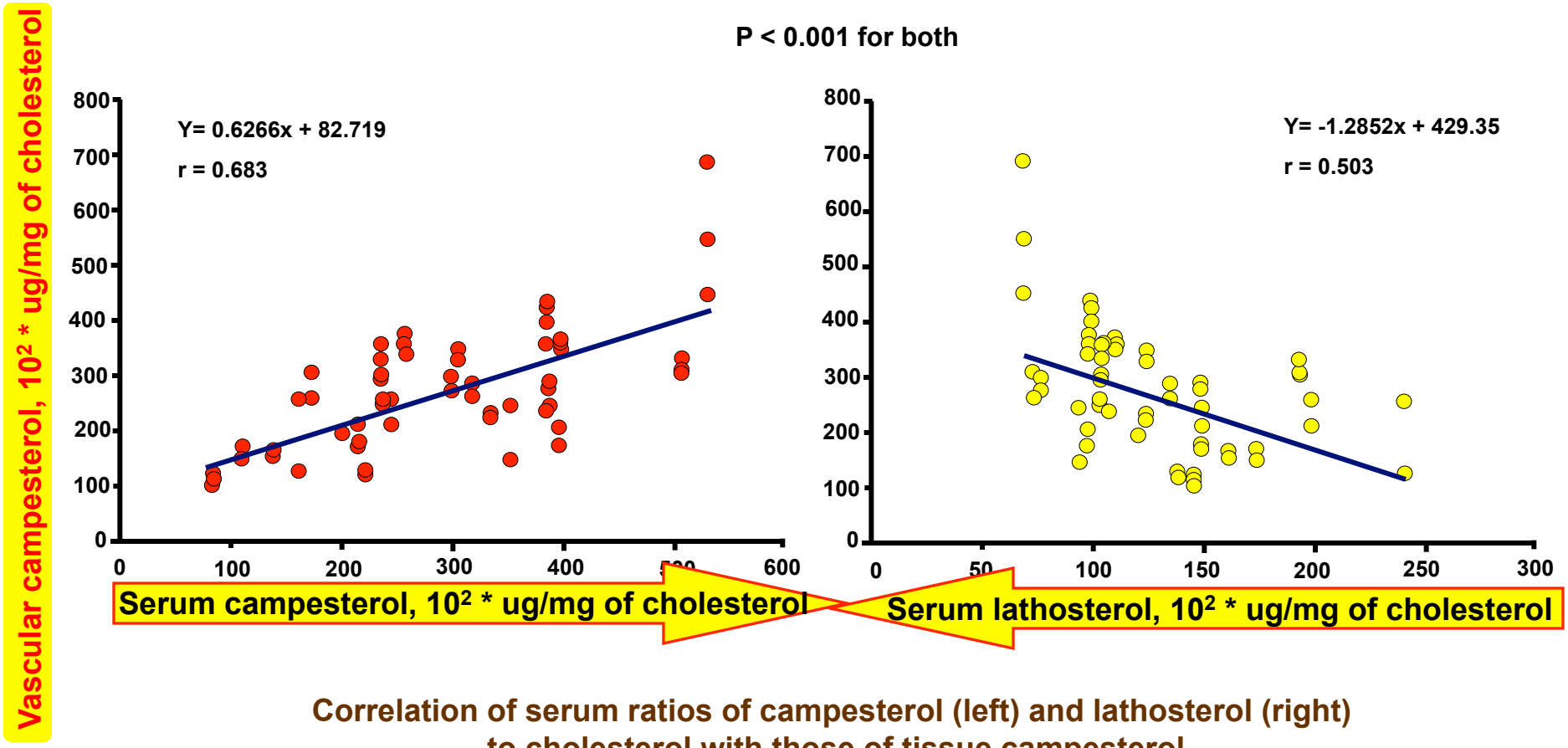
Long-term treatment with plant sterols and EZE conferred equal lowering of plasma cholesterol both in the presence of the high-fat, high-cholesterol WTD and the cholesterol-free normal chow groups. As expected, the substantial lipid-lowering by both treatment principles reduced lesion formation. However, despite equal plasma cholesterol concentrations, sterol ester supplementation was associated with twice the amount of plaque formation compared with EZE.

Conclusion

tion of Plant Sterols in Serum and Aortic Valve Cusps; NCT00222960) (J Am Coll Cardiol 2008;51:1553–61)

J Amer Coll Card. 2008;51:1553-61

Plant Sterols in Serum and Plaque of Carotid Endarterectomy Patients

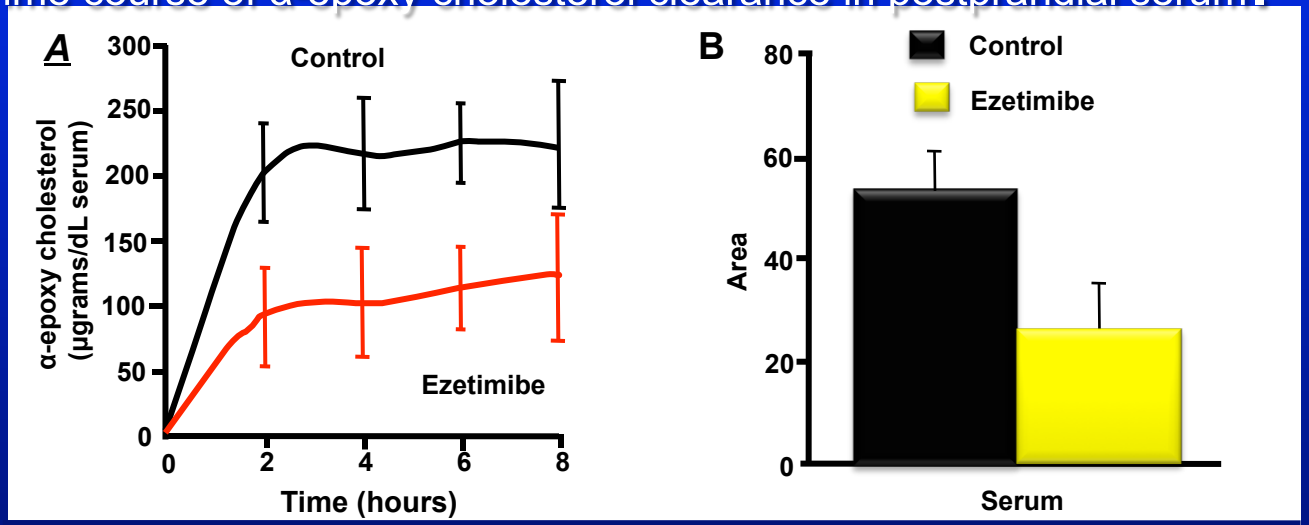


Correlation of serum ratios of campesterol (left) and lathosterol (right) to cholesterol with those of tissue campesterol

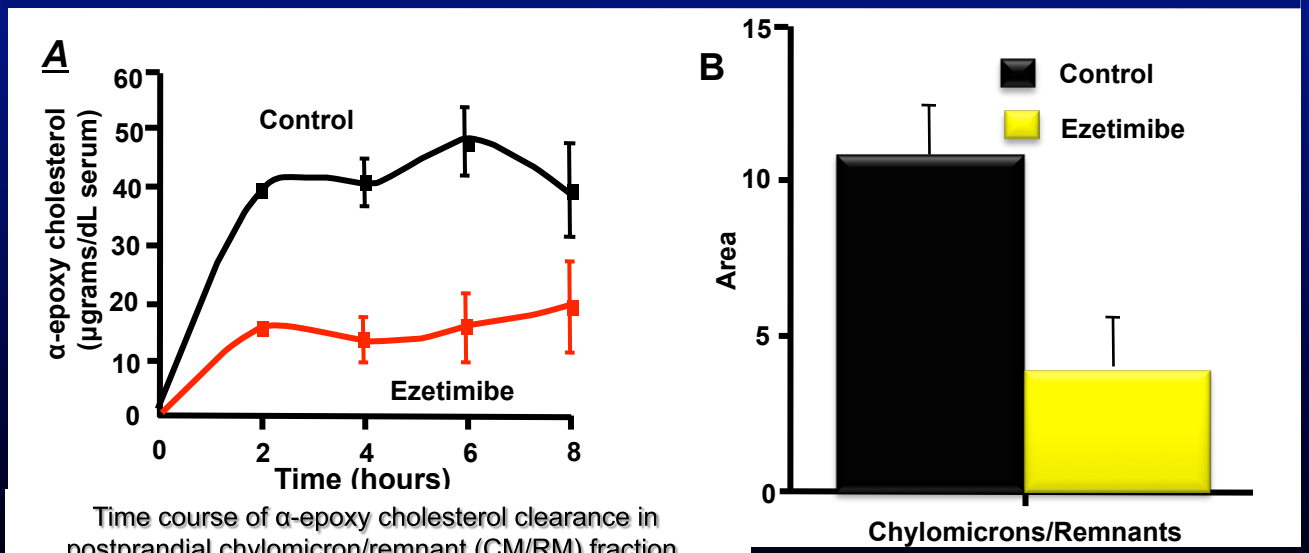
Miettinen, T et al. J Am Coll Cardiol 2005;45:1794-1801

Ezetimibe and Oxysterols

Time course of α-epoxy cholesterol clearance in postprandial serum.



A: Subjects were administered a test meal containing a-epoxy cholesterol (400 mg). The levels of a-epoxy cholesterol in serum were determined before and after treatment with ezetimibe (10 mg/ day for 30 days). B: The areas under the clearance curves were measured in arbitrary units, and the significance of the difference of areas under the curve was determined. P = 0.010.

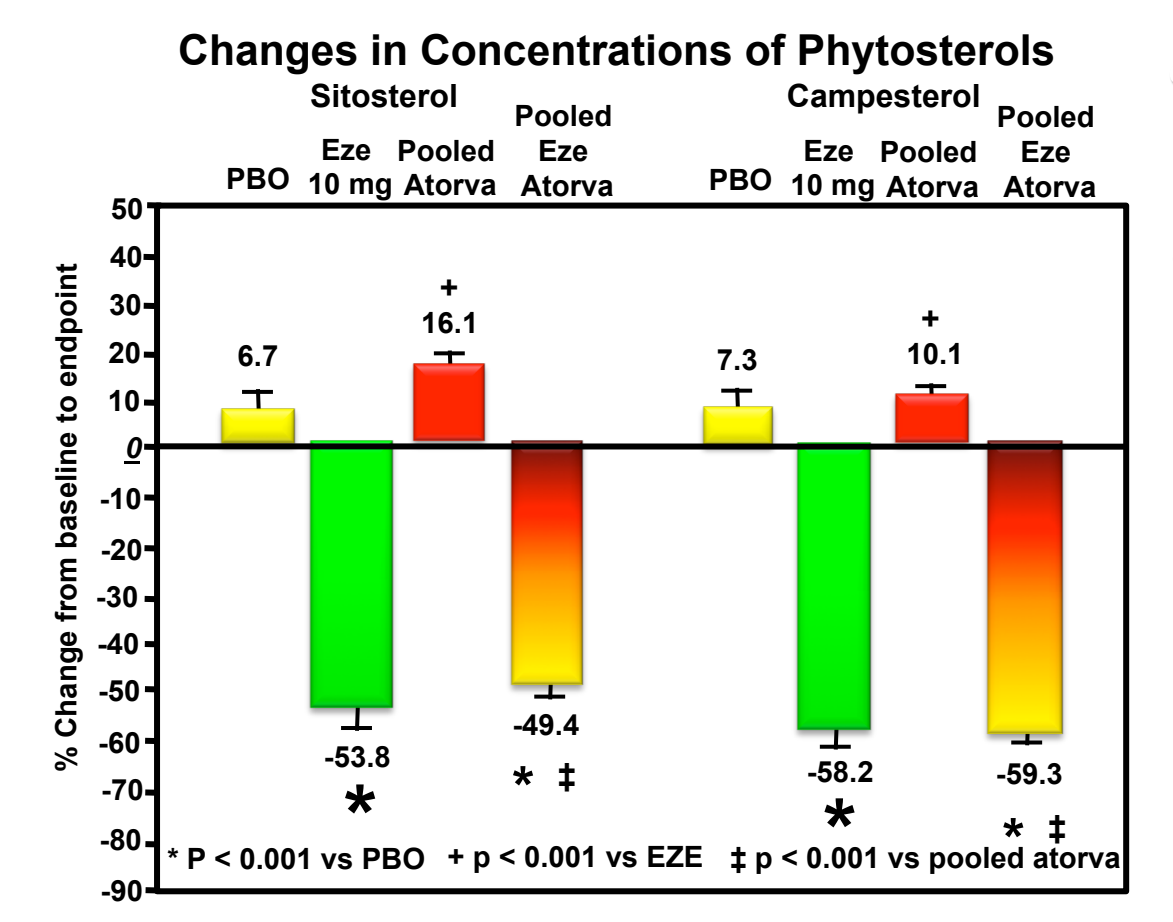


Time course of α-epoxy cholesterol clearance in postprandial chylomicron/remnant (CM/RM) fraction.

A: Five control subjects were administered a test meal containing a-epoxy cholesterol. The levels of α-epoxy cholesterol in CM/RM were determined before and after treatment with ezetimibe (10 mg/ day for 30 days). B: The areas under the clearance curves were measured in arbitrary units, and the significance of the difference of areas under the curve was determined. P 5 0.019.

Staprans I et al. J. Lipid Res. 2006. 47: 2575–2580

Noncholesterol Sterols



Ezetimibe monotherapy (10 mg daily) significantly lowered plasma concentrations of both sitosterol and campesterol from baseline compared with placebo (–53.8% and –58.2%, respectively; both p < 0.001.

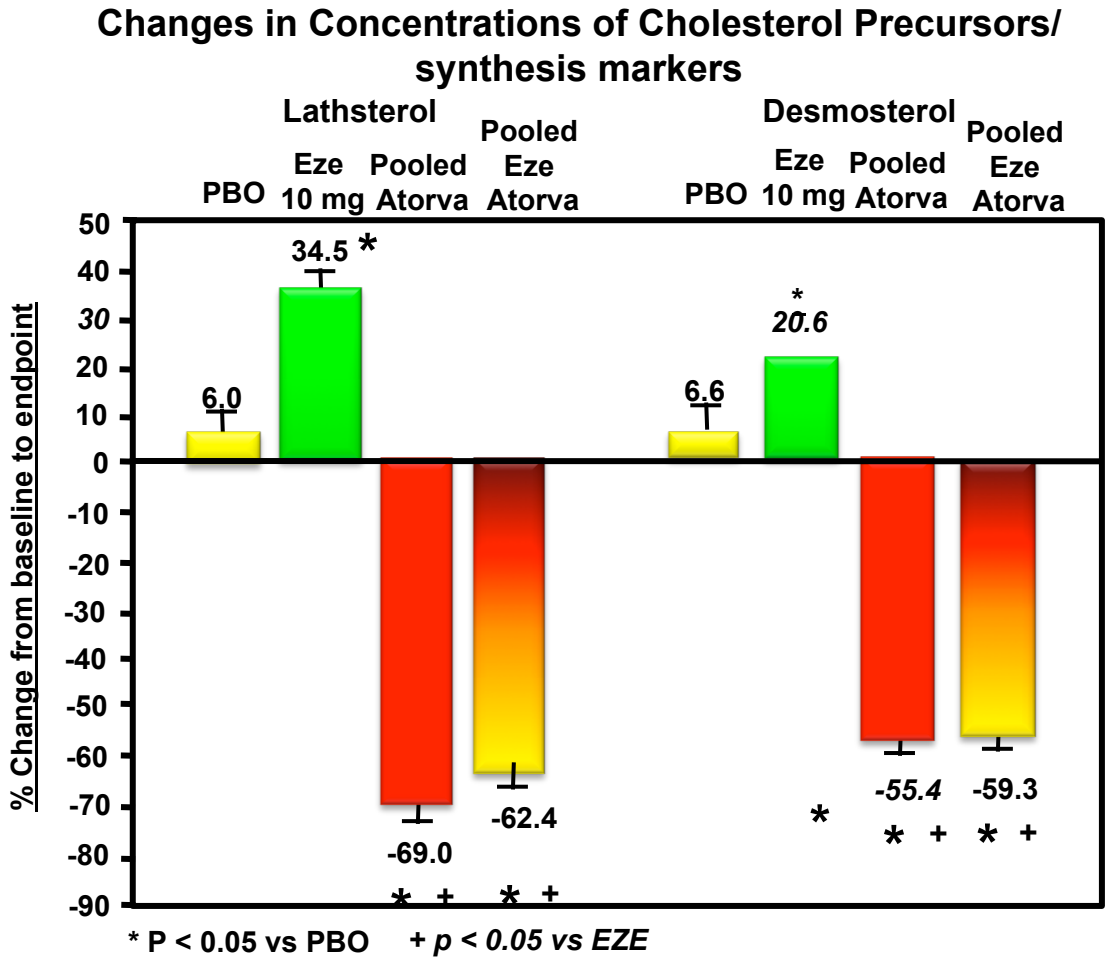
With atorvastatin monotherapy, there was a modest numerical increase in sitosterol and campesterol (16.1% and 10.1%, respectively;

Ezetimibe 10 mg plus atorvastatin (pooled across doses) produced decreases in phytosterols from baseline of a similar magnitude: –49.4% for sitosterol and –59.3% for campesterol (both p < 0.001 vs. placebo and atorvastatin monotherapy).

Overall,the decreases in phytosterol concentrations observed with ezetimibe co-administered with statins were of similar magnitude to those observed with ezetimibe monotherapy.

Assmann G et al. Curr Med Res & Opin 2008;24:249-259

Cholesterol Precursor Molecules



Assmann G et al. Curr Med Res & Opin 2008;24:249-259

Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR)

In order to gain more insight into the effects of intensive statin therapy on changes in markers of cholesterol synthesis and absorption, we measured plasma sterols in a subset of 135 participants of the STELLAR study.

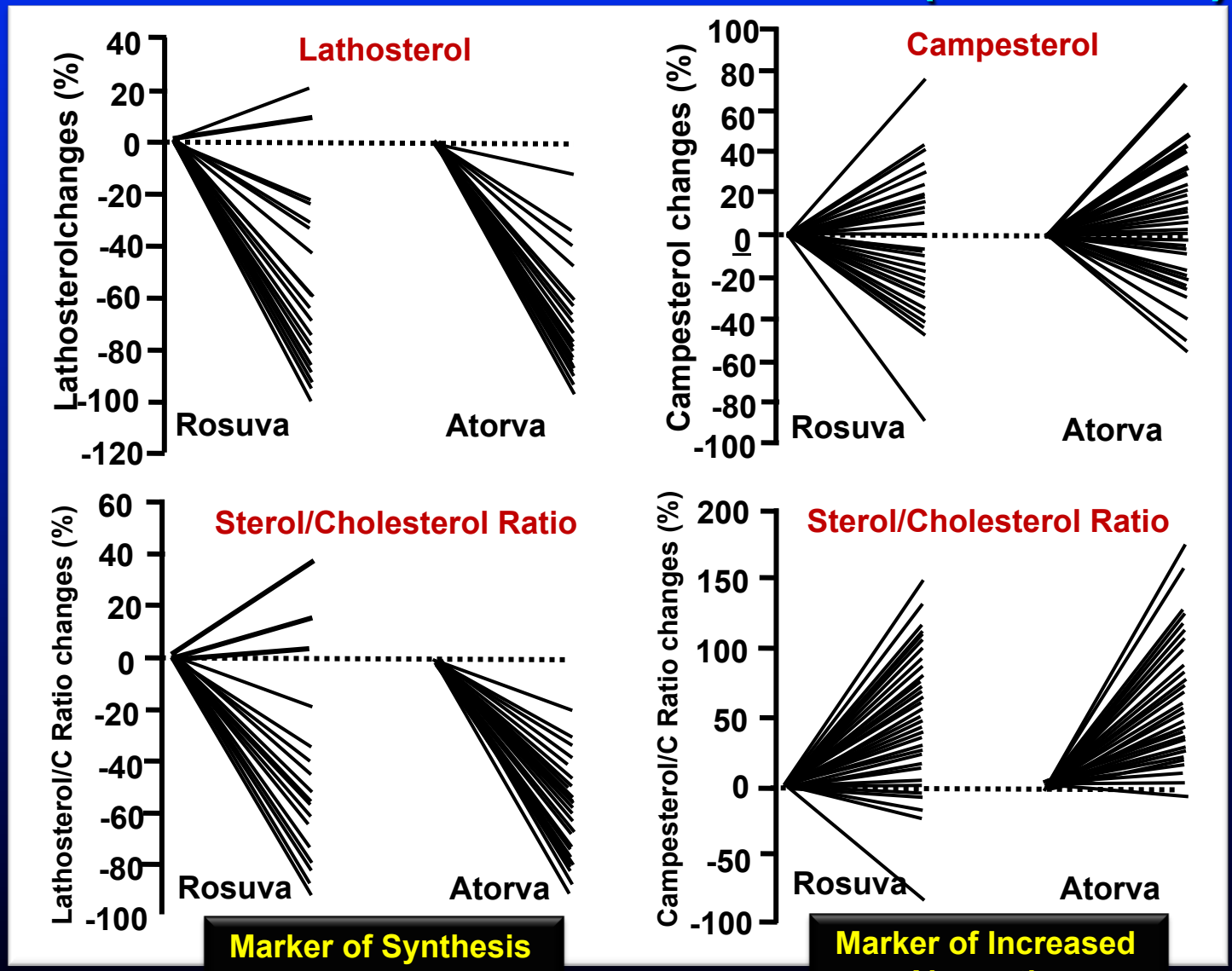
Our data indicate that the greatest total cholesterol and LDL-C reductions were achieved in subjects with the greatest reduction in lathosterol, and no increase in cholesterol absorption markers, as compared with subjects in whom the converse was true.

The data are consistent with the concept that cholesterol synthesis and absorption seem to be inversely linked in maintaining a constant cholesterol balance (i.e., when absorption increases, synthesis decreases, and visa versa)

The major effect of statins is to reduce cellular cholesterol synthesis, resulting in an up-regulation of LDL receptor activity, enhanced fractional clearance of LDL from plasma, and reduction in plasma LDL cholesterol levels. However these effects may be offset by an up-regulation in cholesterol absorption..

van Himbergenet al. J Lipid Res 2009;50:730-739

Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR)



van Himbergen et al. J Lipid Res 2009;50:730-739

Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR)

In summary, statins significantly decreased cholesterol synthesis and increased markers of fractional cholesterol absorption. This study strengthens the hypothesis that successful lipid-lowering depends on the synthesis/absorption status of the patient.

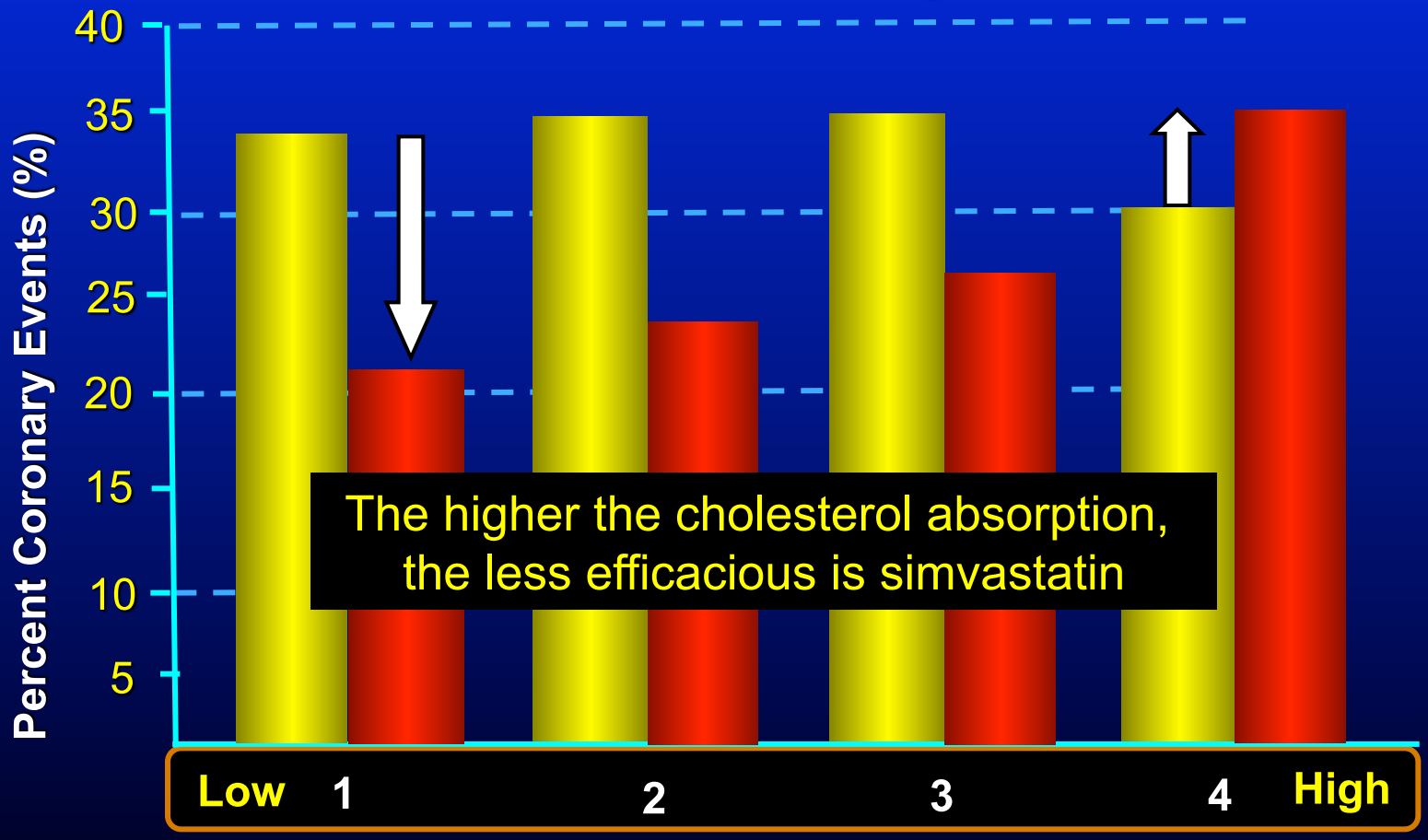
Because ezetimibe very significantly reduces intestinal cholesterol absorption, but increases synthesis, and because statins have the opposite effect, it would appear that combination therapy would be ideal.

In addition, because statin therapy is often long term, measuring sterols may prove to be a useful tool for optimizing therapy and reducing CHD risk.

van Himbergen et al. J Lipid Res 2009;50:730-739

Scandinavian Simvastatin Survival Study (4S)

Simvastatin Efficacy: Relationship to Cholesterol Absorption



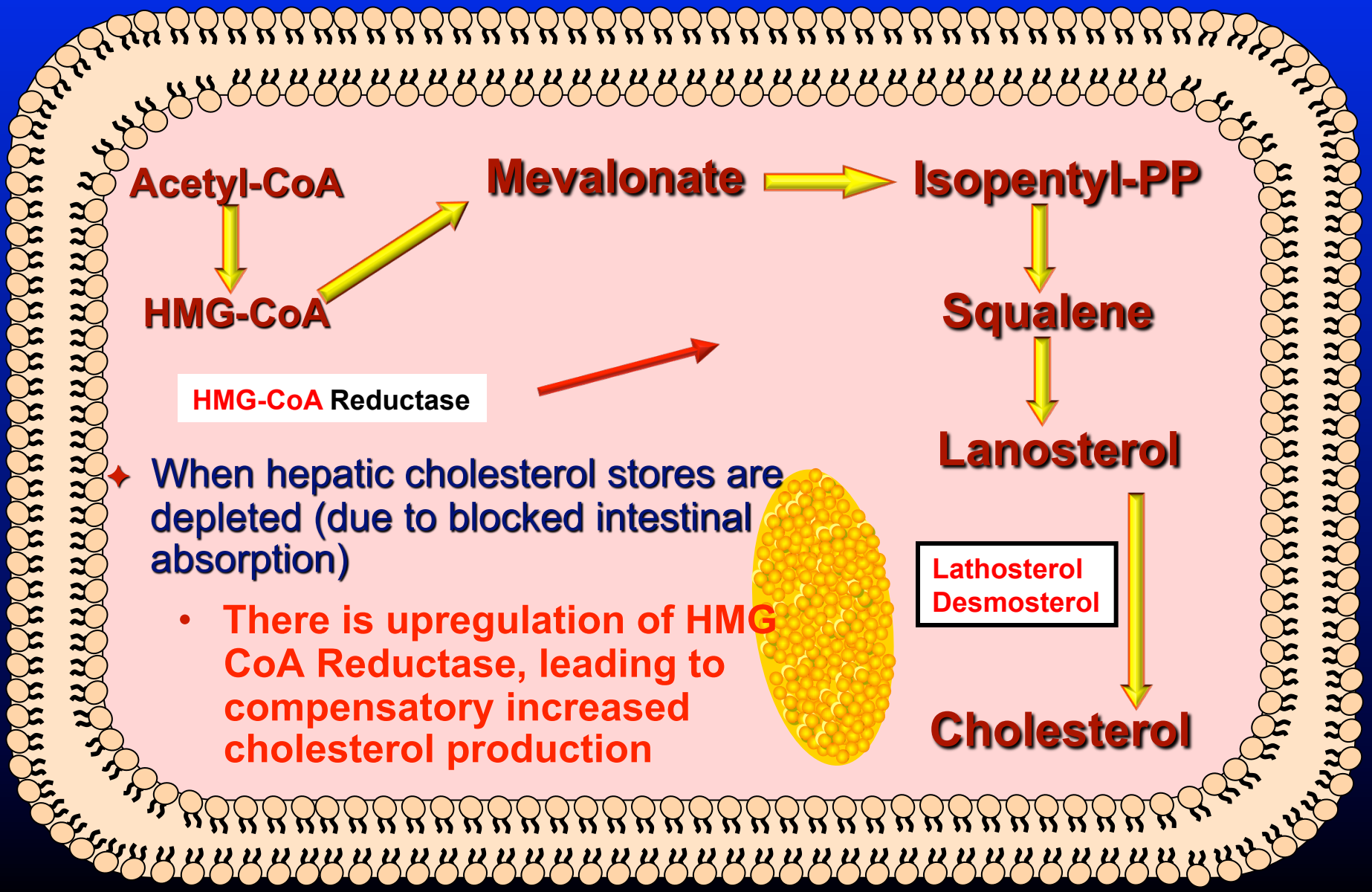
Miettinen TA et al. BMJ 1998;315:1127-30

Scandinavian Simvastatin Survival Study (4S)
Baseline Cholestanol as Predictor of Recurrent Events

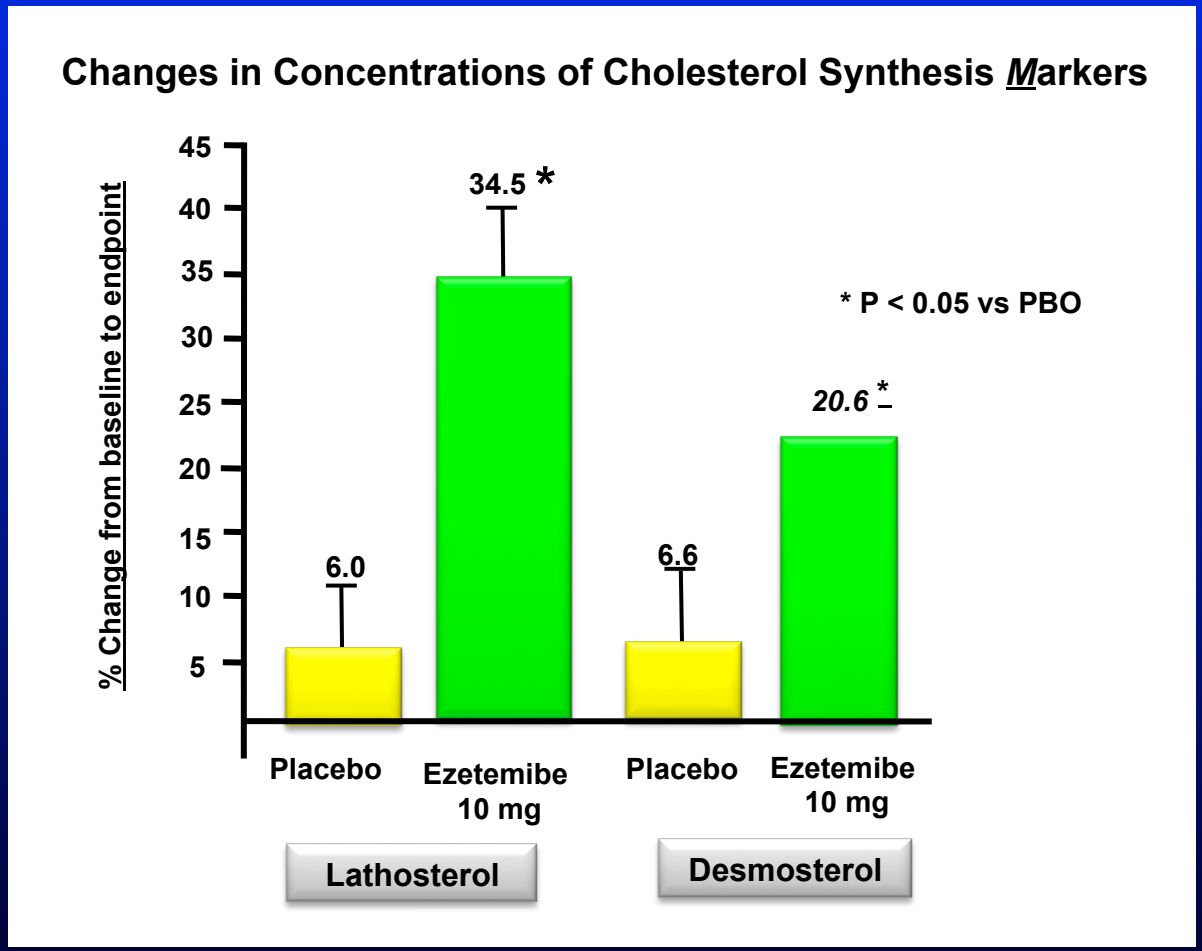
- Increasing quartiles of cholestanol:cholesterol ratio, reflecting decreased synthesis of cholesterol, were related to recurrent events
- Coronary patients with high baseline cholesterol and plant sterol ratios to cholesterol appear to be clinically resistant to the lowering of coronary recurrence by simvastatin
- Statin treatment is associated with further increase of plant sterols
  - High plant sterols are strongly atherogenic

Miettinen TA et al. BMJ 1998;315:1127-30

Ezetimibe and HMG CoA Reductase



Ezetimibe & Cholesterol Synthesis Markers



Lathosterol and desmosterol are cholesterol precursor sterols and are used clinically as markers of cholesterol synthesis as

Assmann G et al. Curr Med Res & Opin 2008;24:249-259