

# **Bile Acids and Bile Acid Sequestrants**

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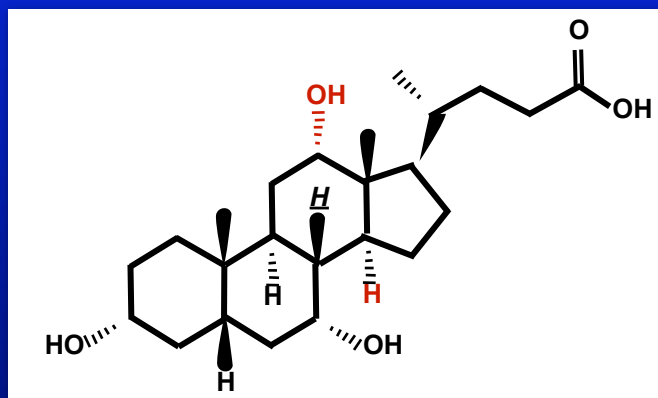
**North Jersey Institute of Menopausal Lipidology  
New Jersey**

**Wayne,**

# Bile Acids

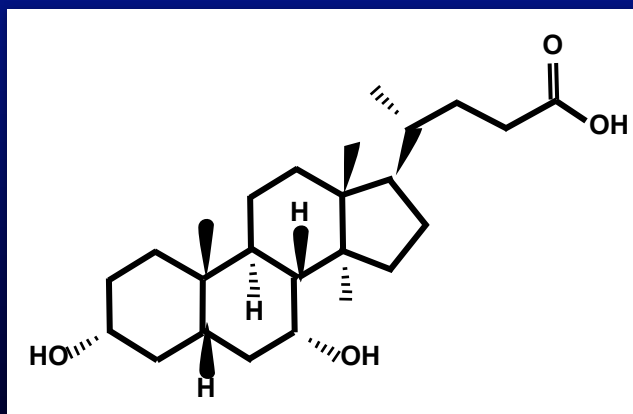
## Primary Bile Acids

Converted from cholesterol by 7  $\alpha$ -hydroxylase



### Cholic acid (Trihydroxy bile salt)

Cholic acid, along with chenodeoxycholic acid, is one of two major bile acids produced by the liver where it is synthesized from cholesterol. Of the two major bile acids, cholates represent approximately eighty percent of all bile acids.



### Chenodeoxycholic acid (Dihydroxy bile salt)

This compound, when altered by bacteria in the colon, will result in conversion to its secondary bile acid known as lithocolic acid. Both of these bile acids, in addition to the others, can be conjugated by the liver to taurine or glycine which will result in a lowered pKa and therefore, the compounds will remain ionized. These ionized compounds will stay in the gastrointestinal tract until reaching the ileum where they will be reabsorbed. The purpose of this conjugation is to keep the bile acids in the tract until the end to facilitate lipid digestion all the way to the ileum.

# Bile Acids

## Cholesterol

### Primary Bile Acids

Converted by 7 alpha hydroxylase

Chenodeoxycholic acid (Dihydroxy bile salt)

Cholic acid (Trihydroxy bile salt)

Converted by intestinal bacteria

### Secondary Bile Acids

Lithocolic Acid (monohydroxy bile acid) from chenodeoxychoic acid

Deoxycholic acid (dihydroxy bile acid) from cholic acid

### Tertiary Bile Acids

Urodeoxycholic acid (dihydroxy bile acid) from 7 beta hydroxylation of lithocolic acid

# Farnesol X Receptor (FXR)

- ✦ Farnesol X Receptors are activated by bile acids and PUFA. They appear to protect cells from bile acid toxicity
- ✦ FXR controls bile acid synthesis by inhibiting expression of CYP 7A hydroxylase and other bile synthetic enzymes
- ✦ FXR controls expression of the bile acid export pump (BSEP) also termed ATP binding cassette transporter B11 (ABCB11)
- ✦ FXR expression has hypotriglyceridemic effects by:
  - Inducing PPAR- $\alpha$  expression
  - Modulating lipoprotein lipase
  - Inhibition of Sterol regulatory binding element protein-1C (SREB-1c) which is mediated through the short heterodimer protein (SHP) negative effect on LXR



# Short (Small) Heterodimer Partner (SHP)

The small heterodimer partner (SHP) protein is a member of the nuclear receptor family of intracellular transcription factors and is encoded by the NR0B2 (nuclear receptor subfamily 0, group B, member 2) gene.

SHP is unusual for a nuclear receptor in that it lacks a DNA binding domain. Therefore technically it is neither a transcription factor nor nuclear receptor but nevertheless it is still classified as such due to relatively high sequence homology with other nuclear receptor family members.

The main function of SHP appears to be repression of other nuclear receptors through association to produce a non-productive heterodimer. The protein has been shown to interact with retinoid and thyroid hormone receptors, inhibiting their ligand-dependent transcriptional activation. In addition, interaction with estrogen receptors has been demonstrated, leading to inhibition of function.

Studies suggest that the protein represses nuclear hormone receptor-mediated transactivation via two separate steps: competition with coactivators and the direct effects of its transcriptional repressor function

[http://en.wikipedia.org/wiki/Small\\_heterodimer\\_partner](http://en.wikipedia.org/wiki/Small_heterodimer_partner)

# Regulation of Bile Acid Metabolism

Cholesterol is converted into oxysterols in the liver. Oxysterols activate LXR- $\alpha$ , which limits cholesterol accumulation by inducing bile-acid synthesis. In the intestine, a secondary bile acid, lithocholic acid (LCA), is formed.

Much of the bile acid secreted in the intestine returns via the enterohepatic circulation to the liver, where it inhibits de novo bile-acid synthesis.

# Regulation of Bile Acid Metabolism

At least 4 redundant pathways are involved in this feedback inhibition.

1) FXR, activated by bile acids, induces the expression of SHP. **SHP attenuates further bile-acid synthesis by inhibiting the action of LRH-1 and LXR- $\alpha$ .** LRH-1, LXR- $\alpha$  and possibly other NRs upregulate CYP7A1 and CYP8B1 expression.

2) Pregnane XR (PXR), activated by LCA, inhibits CYP7A1 expression.

3) Another pathway involved in attenuating bile-acid synthesis, involves activation of the JNK by bile acids.

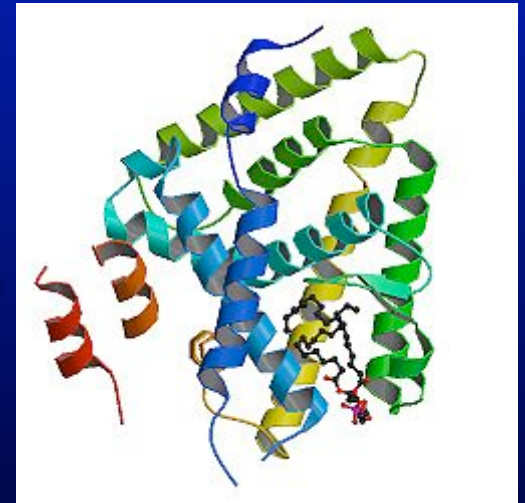
4) Finally, liver damage induced by bile-acid accumulation also inhibits bile-acid synthesis via a SHP-independent pathway that is yet to be identified.

# Regulation of Bile Acid Metabolism

**The liver receptor homolog-1 (LRH-1)** protein is a member of the nuclear receptor family of intracellular transcription factors and is encoded by the NR5A2 gene (nuclear receptor subfamily 5, group A, member 2).

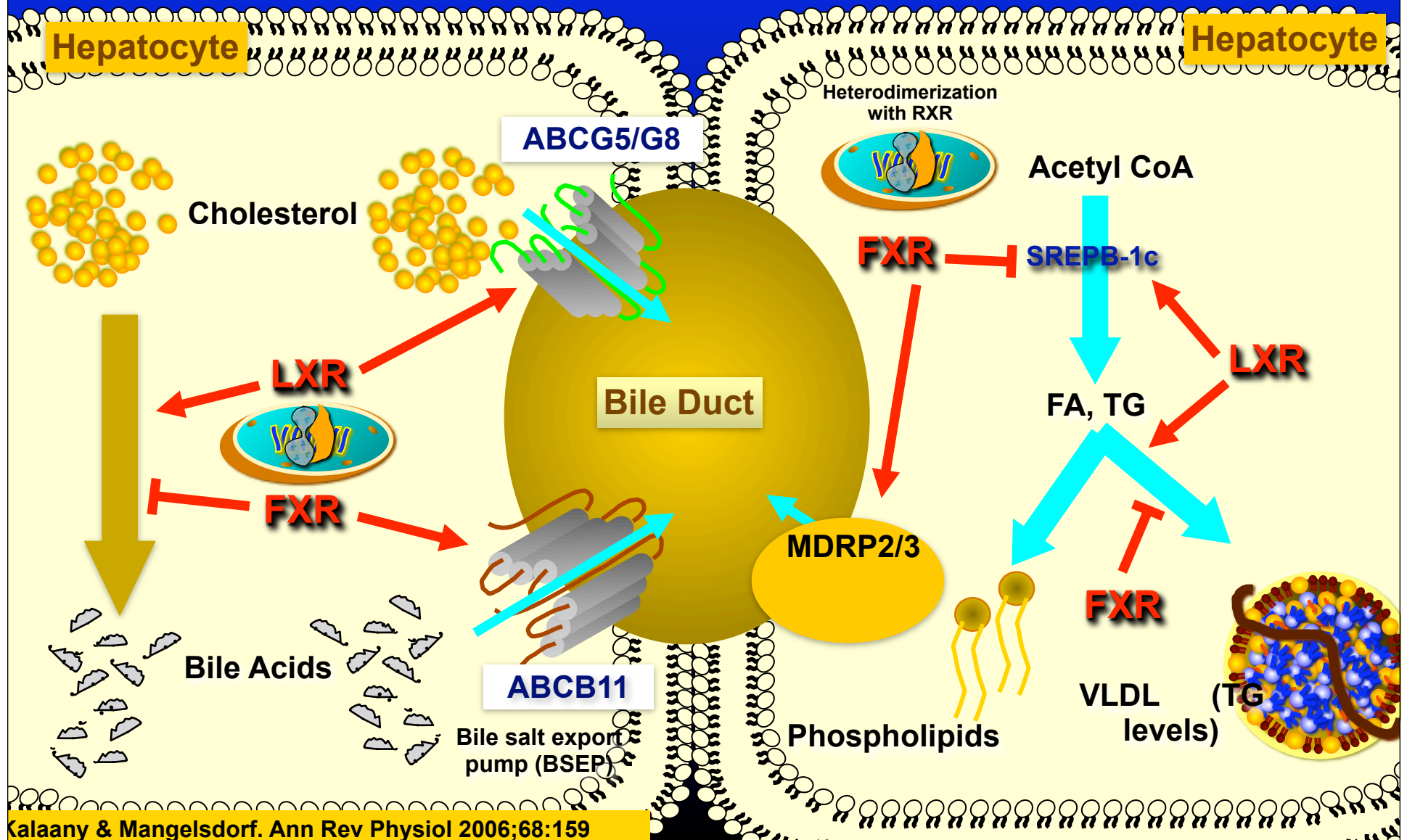
LRH-1 plays a critical role in the regulation of development, cholesterol transport, bile acid homeostasis and steroidogenesis

SHP-1 represses expression of CYP7A1 by inhibiting the activity of liver receptor homolog 1 (LRH-1)

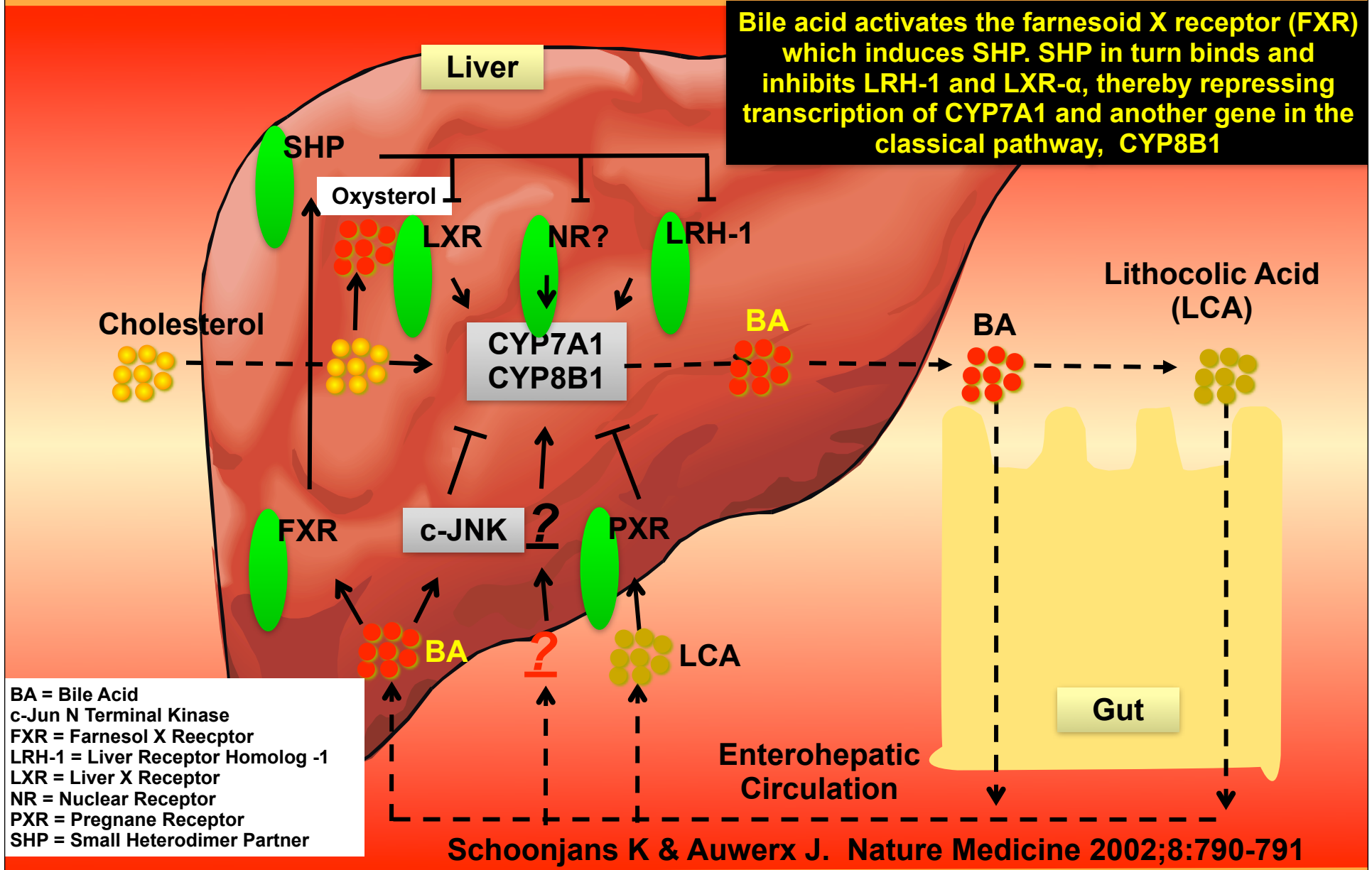




# FXR and LXR Regulation of Cholesterol, Triglycerides and Bile Acids



# Short (small) Heterodimer Partner (SHP)



# Bile Acid Sequestrants: Resins

- ✦ Bile acids are amphipathic polar derivatives of cholesterol necessary for absorption sterols, fats and fat soluble vitamins
- ✦ Resins were among the first drugs to demonstrate CV event reduction
- ✦ The available resins are cholestyramine and colestipol
  - These have frequent GI side effects and impair absorption of many drugs



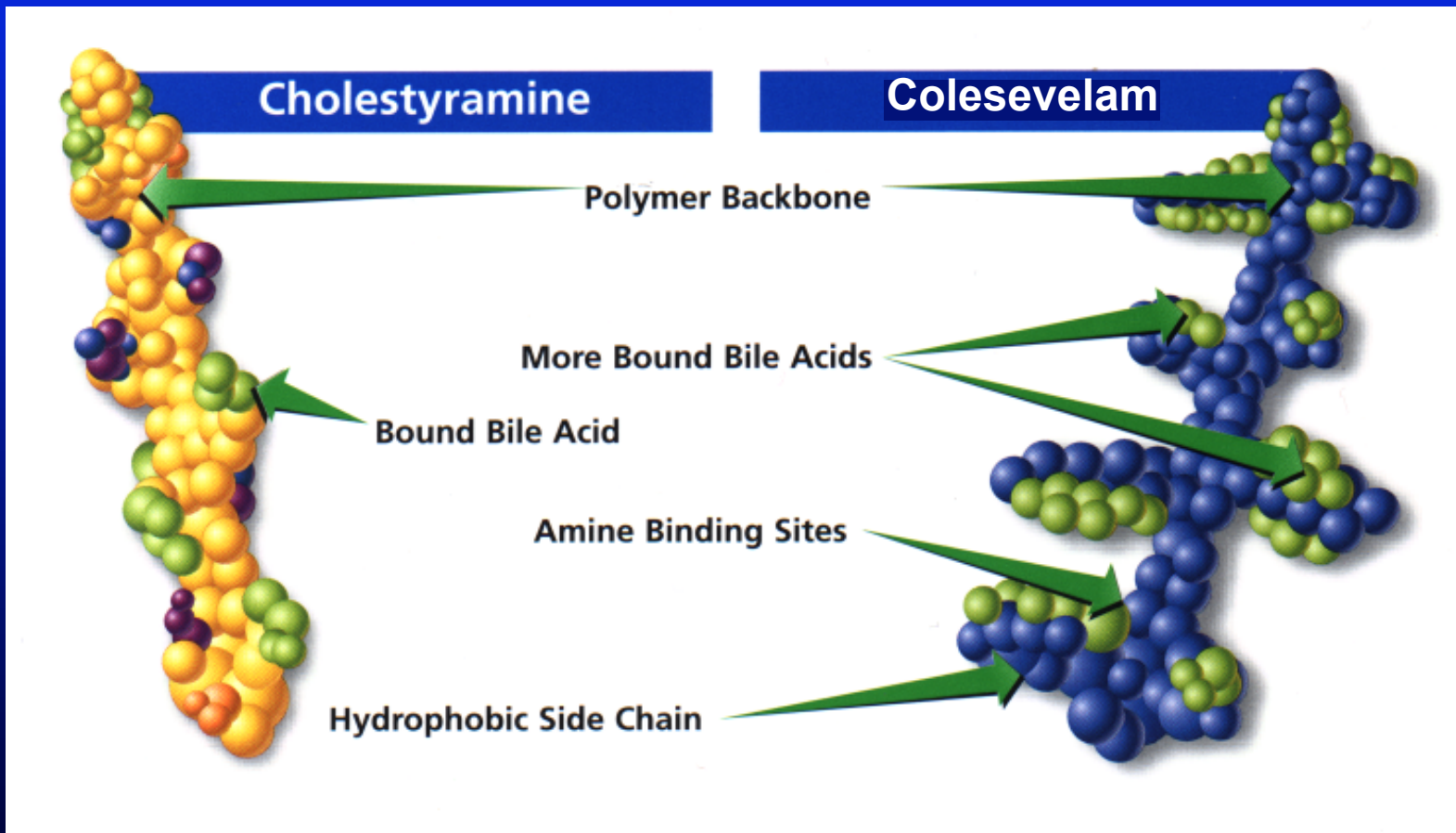
# Bile Acid Sequestrants: Polymers

- ✦ Colesevalam is a hydrophilic, water insoluble **polymer** that is not hydrolyzed by digestive enzymes and is not absorbed from the GI tract into the systemic circulation
- ✦ It has a unique biochemical polymer structure
  - Because of this structure there is better GI tolerability and less potential drug interactions
- ✦ No metabolism in the intestine is required
- ✦ No requirement for liver function testing
  - No impact of liver enzymes in patients on statins

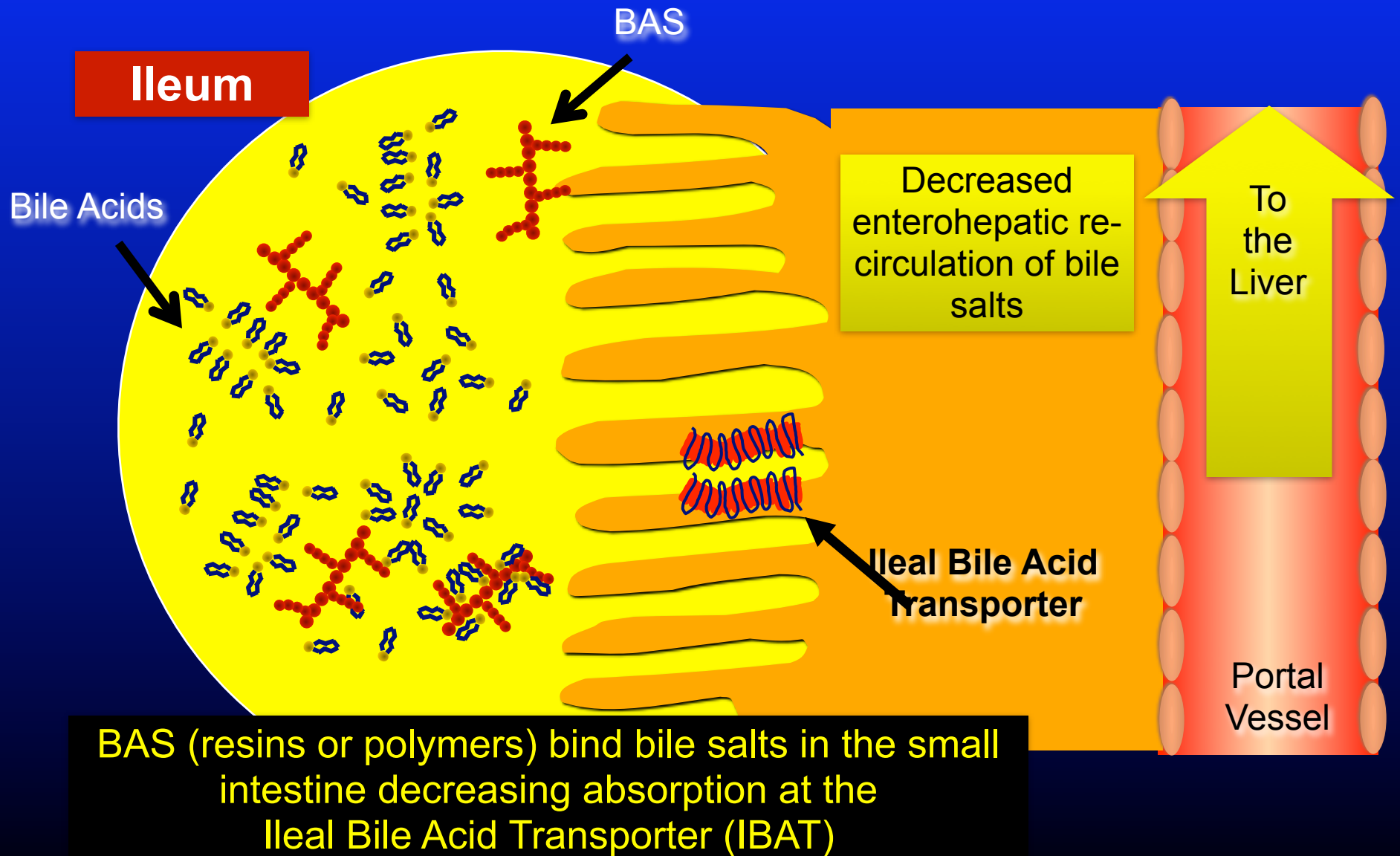
**Sankyo Pharma WelChol prescribing information**

**Bays H & Stein E. Expert Opin Pharmacol 2003;4:pp 1906-1907**

# Bile Acid Sequestrants: Mechanism of Action



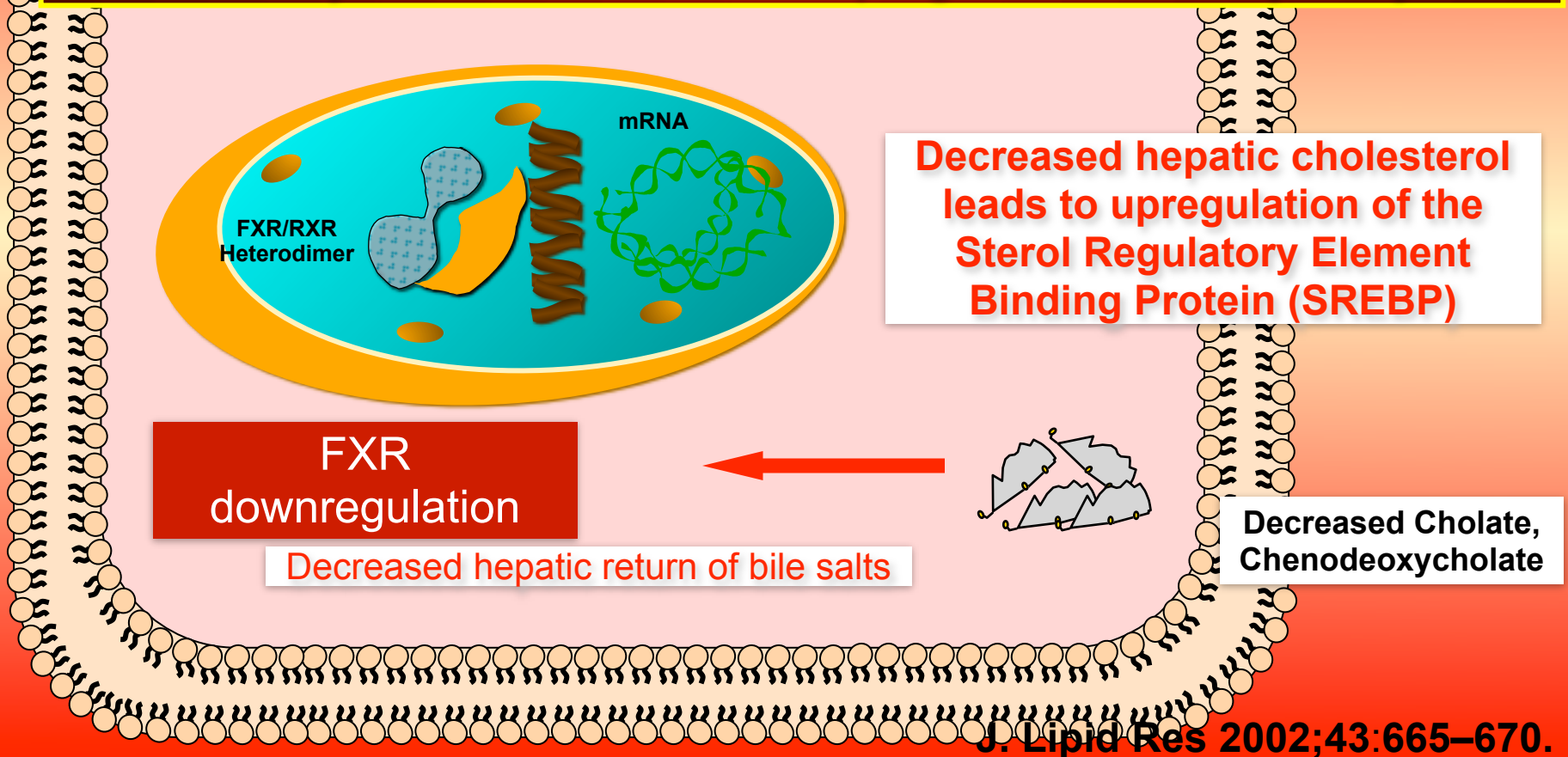
# Bile Acid Sequestrants: Mechanism of Action



# Bile Acid Sequestrants: Mechanism of Action

Farnesoid X Activated receptors (FXRs) prevent bile acid toxicity and modulate (upregulate) cholesterol 7 $\alpha$ -hydroxylase activity and increase bile acid synthesis from cholesterol

Upon hepatocyte cholate depletion, FXRs are down-regulated and bile acid synthesis increases via upregulation of 7 $\alpha$  hydroxylase





# Bile Acid Sequestrants: MOA

In addition to SREBP upregulation, the decreased FXR mediated down-regulation of short heterodimer protein (SHP) levels also upregulate Liver X receptors

**LDL receptor production upregulated (SREBP)**

**HMG CoA reductase upregulated (SREBP 2c)**

**TG & VLDL production increased (SREBP 1c)**

LXR/RXR  
Heterodimer

↓ oxysterols

Cholesterol

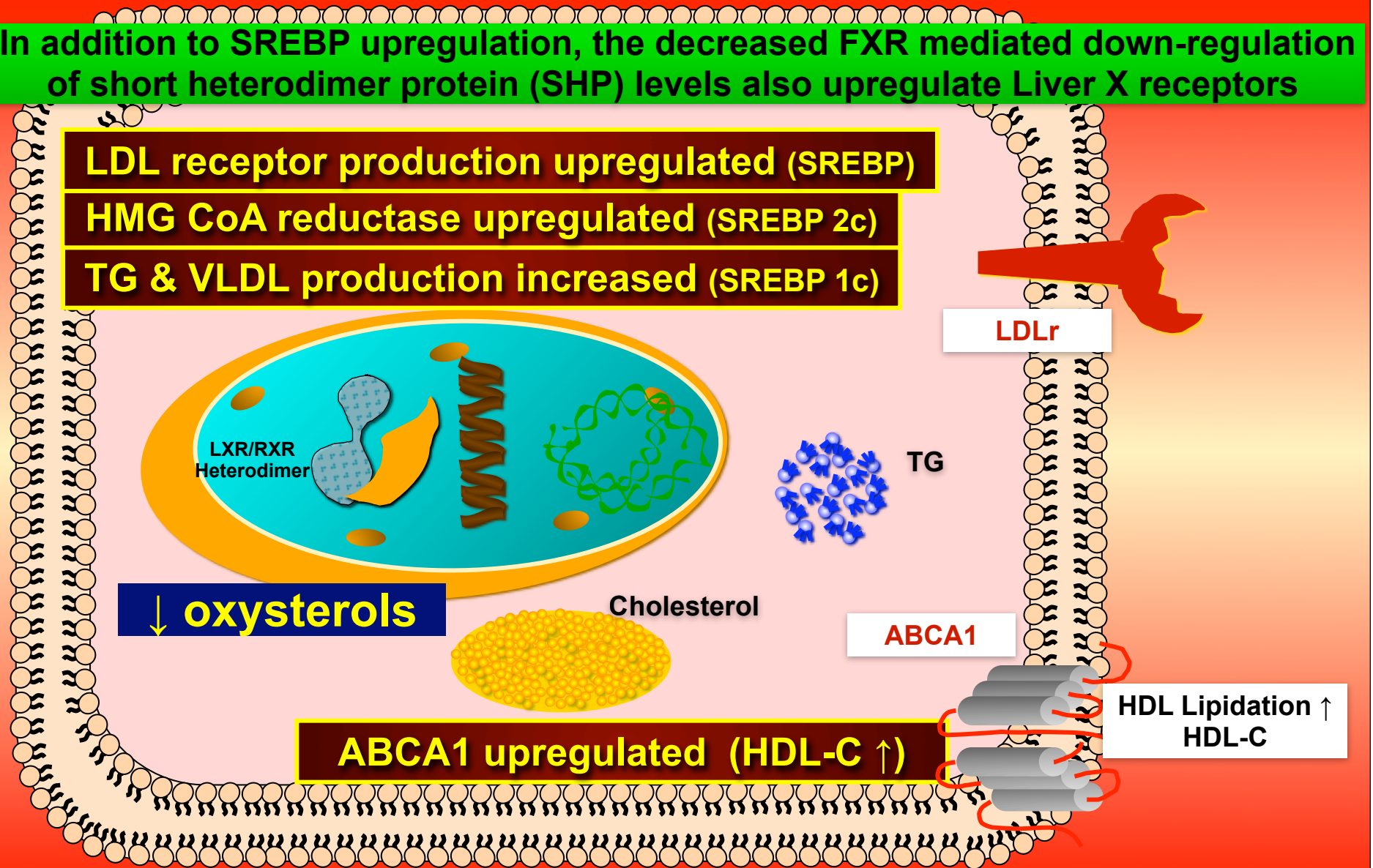
TG

ABCA1

**ABCA1 upregulated (HDL-C ↑)**

LDLr

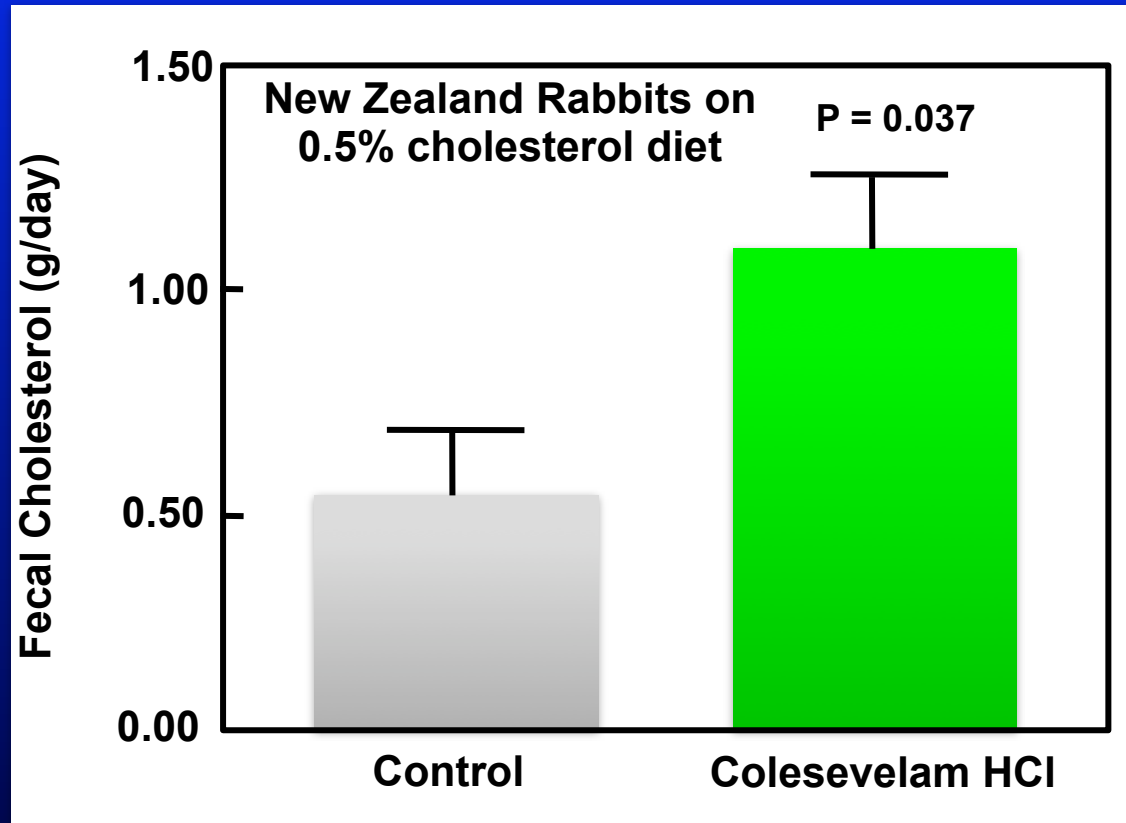
HDL Lipidation ↑  
HDL-C



# Bile Acid Sequestrants: Resins

- ✦ The hepatic gene expression data support the hypothesis that inhibition of bile acid reabsorption enhances the expression of genes involved with reverse cholesterol transport.
- ✦ There were significant increases in the gene expression for apo A-I, LCAT, and CETP in the colestevlam HCl-treated animals compared with controls, probably mediated by an enhanced expression of LXR.
- ✦ LXR agonists have been documented to enhance expression of apo A-I, CETP, and ABCA1 and ABCG1, which are involved in promoting cellular efflux of cholesterol from the periphery, which is carried by HDL particles to the liver for conversion into bile salts.

# Colesevelam & Stool Cholesterol Excretion



Fecal cholesterol concentrations were higher in the colesevelam HCl group than in controls (1.09 g/day vs. 0.53 g/day, respectively;  $P=0.037$ )

Increased stool sterols suggests RCT

Hepatic gene expression for LXR and the expression of genes regulated by LXR, including SRB1, apo A1, LCAT, CETP, CYP7A1, and the LDL receptor, were all significantly higher in the colesevelam HCl group than in controls



# Bile Acid Sequestrants: FXR, SHP

- ✦ FXR activation normally induces expression of small heterodimer partner (SHP), which in turn, inhibits LXR activity, as well as CYP7A1.
- ✦ Repressed FXR activity, through the binding of bile acids with BAS, would be expected to decrease SHP, and release the inhibition of LXR.
- ✦ Thus, this indirect effect of FXR repression would be a relative increase in hepatic LXR activity, which downregulates enzymes that may contribute to hepatic insulin resistance and glucose intolerance.
- ✦ Increased LXR activity may also suppress hepatic gluconeogenesis, improve hepatic glucose utilization, and increase hepatic glucose uptake.

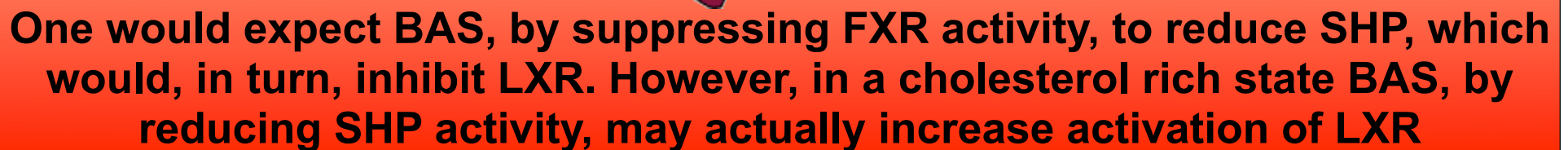
# Impact of FXR on Lipid Metabolism

- ✦ FXR activation by bile acids induces the expression of SREBP-1c in mice and PPAR $\alpha$  in humans which modulate TG metabolism
- ✦ FXR represses apo-A-I expression and therefore HDL-C levels, but also enhances the remodeling of HDL particles by induction of PLTP and CETP expression

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**Davidson M et al. The Journal of Applied Research . 2006;6:4-13**



# Mechanisms by Which BAS May Lower Glucose Levels

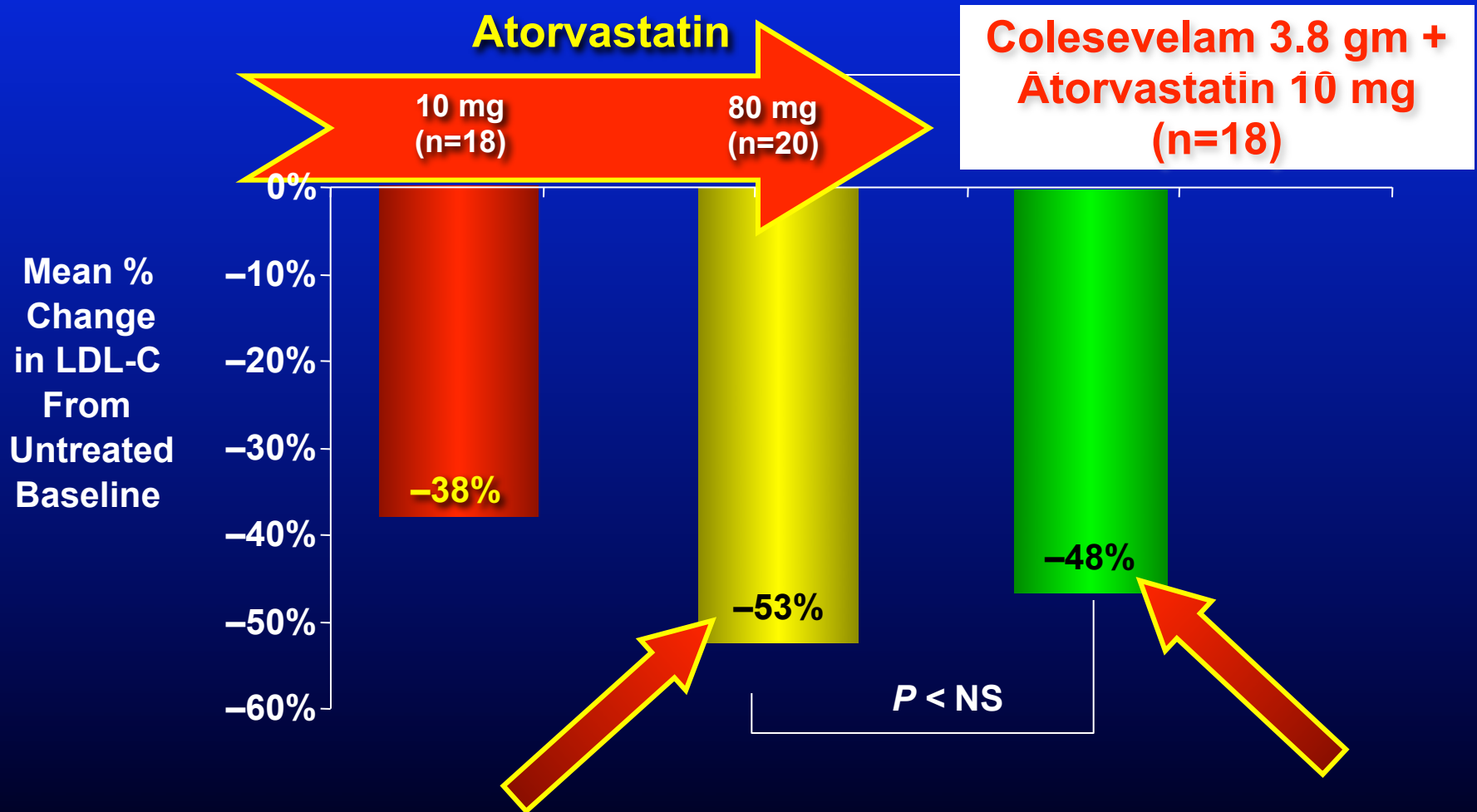
- ✦ BAS may alter luminal bile acid composition and affect intestinal glucose absorption
- ✦ BAS increase the intestinal release of the incretin cholecystokinin, which results in an increase in pancreatic insulin secretion
- ✦ BAS decrease the enterohepatic bile acid pool, decrease FXR activity, and reduce the inhibition of LXR activity
- ✦ The ensuing increased LXR activity may
  - Downregulate enzymes causally related to hepatic insulin resistance and glucose intolerance
  - Suppress hepatic gluconeogenesis
  - Improve hepatic glucose utilization and glucose uptake
- ✦ BAS bind bile acids, which may increase HNF4 $\alpha$ , an important transcription factor that promotes pancreatic insulin secretion

**FXR = farnesoid X receptor; LXR = liver X receptor; HNF4 $\alpha$  = hepatocyte nuclear factor 4 alpha. .**

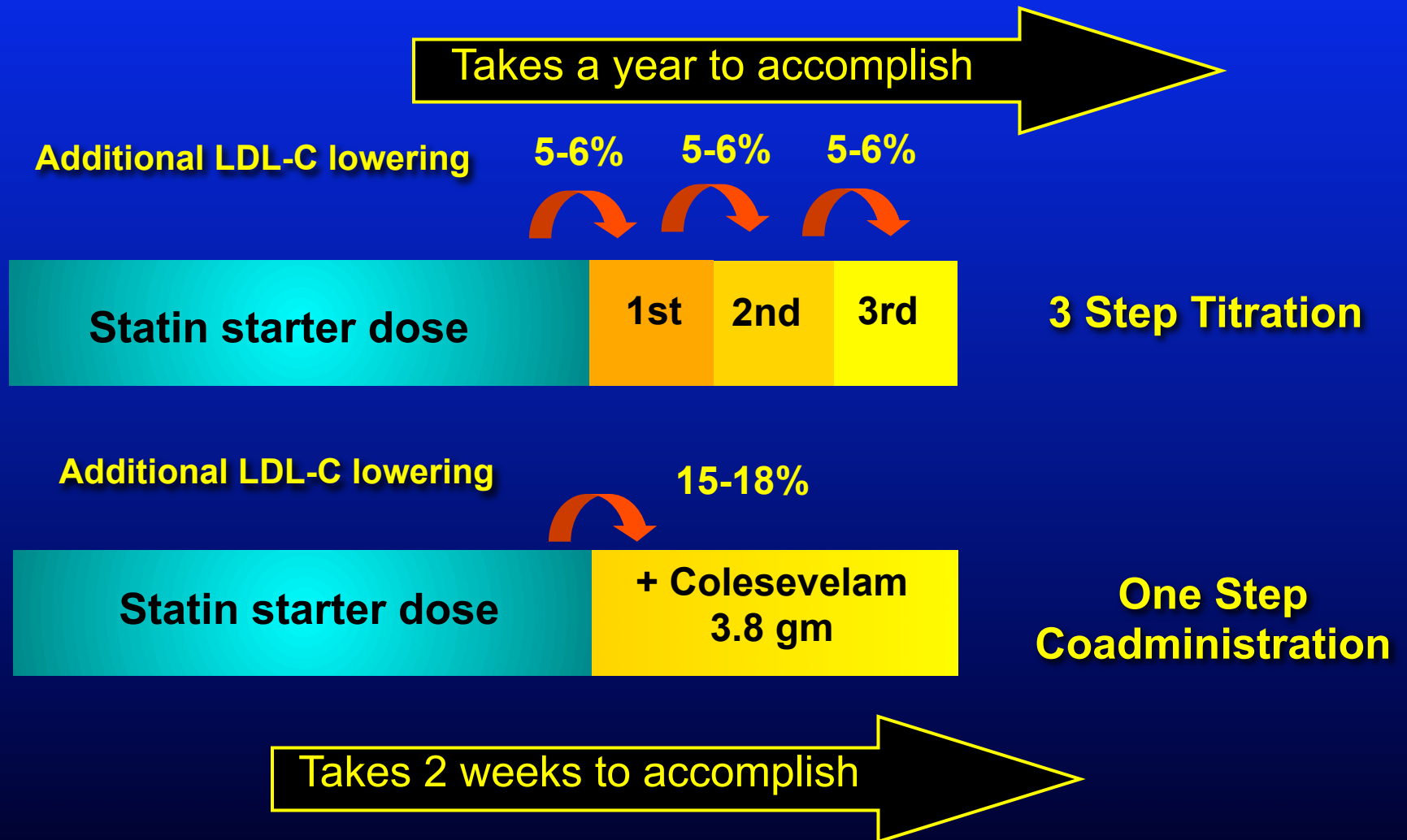
**Bays HE, Cohen DE. 2007. Submitted for publication.**



# Colesevelam + Atorvastatin vs Atorvastatin



# Colesevelam/Statin: LDL-C Lowering



Adapted from Bays et al. Expert Opin Pharmacother. 2003;4:779-790