Statin and Liver

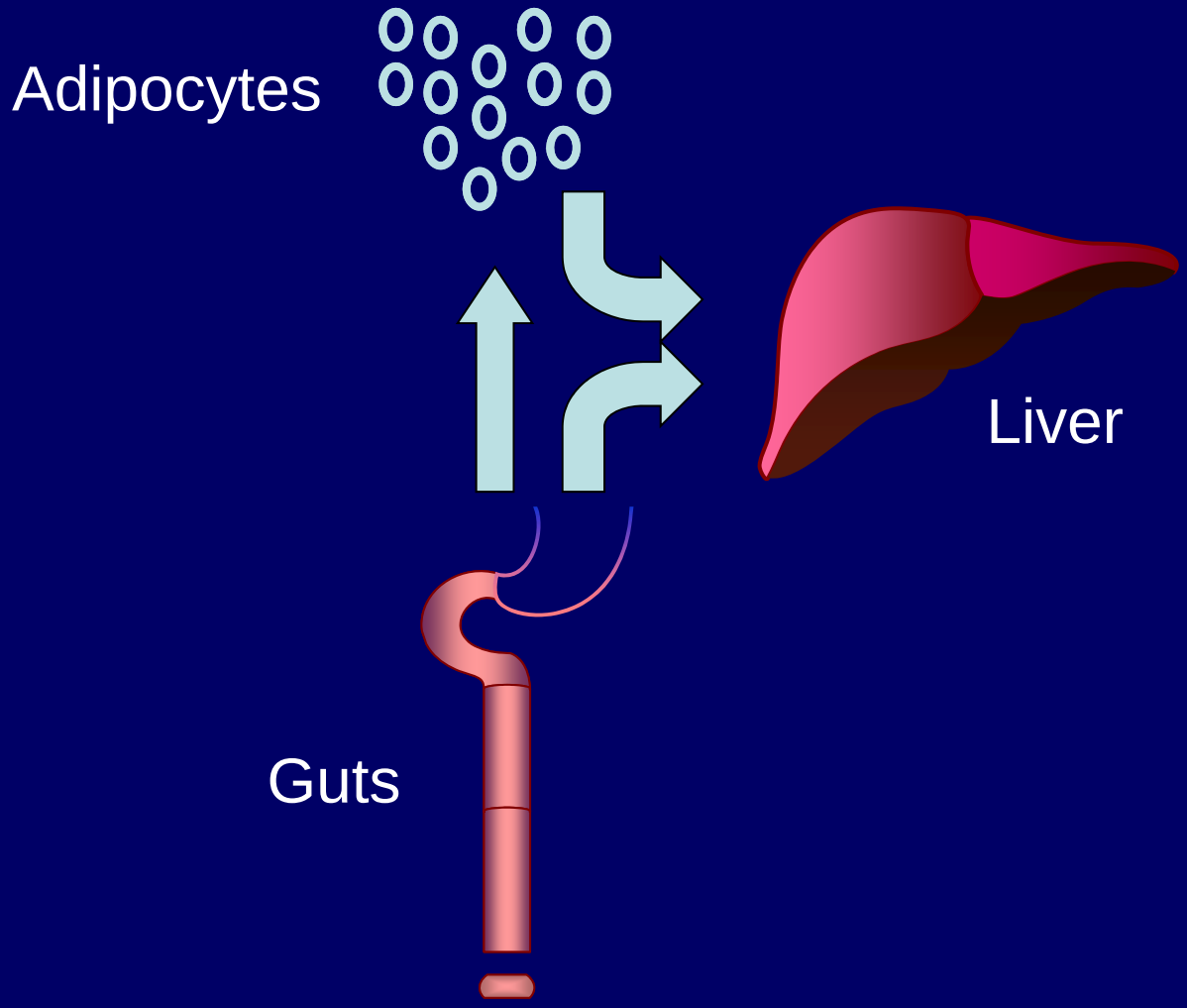
2011. 04. 15

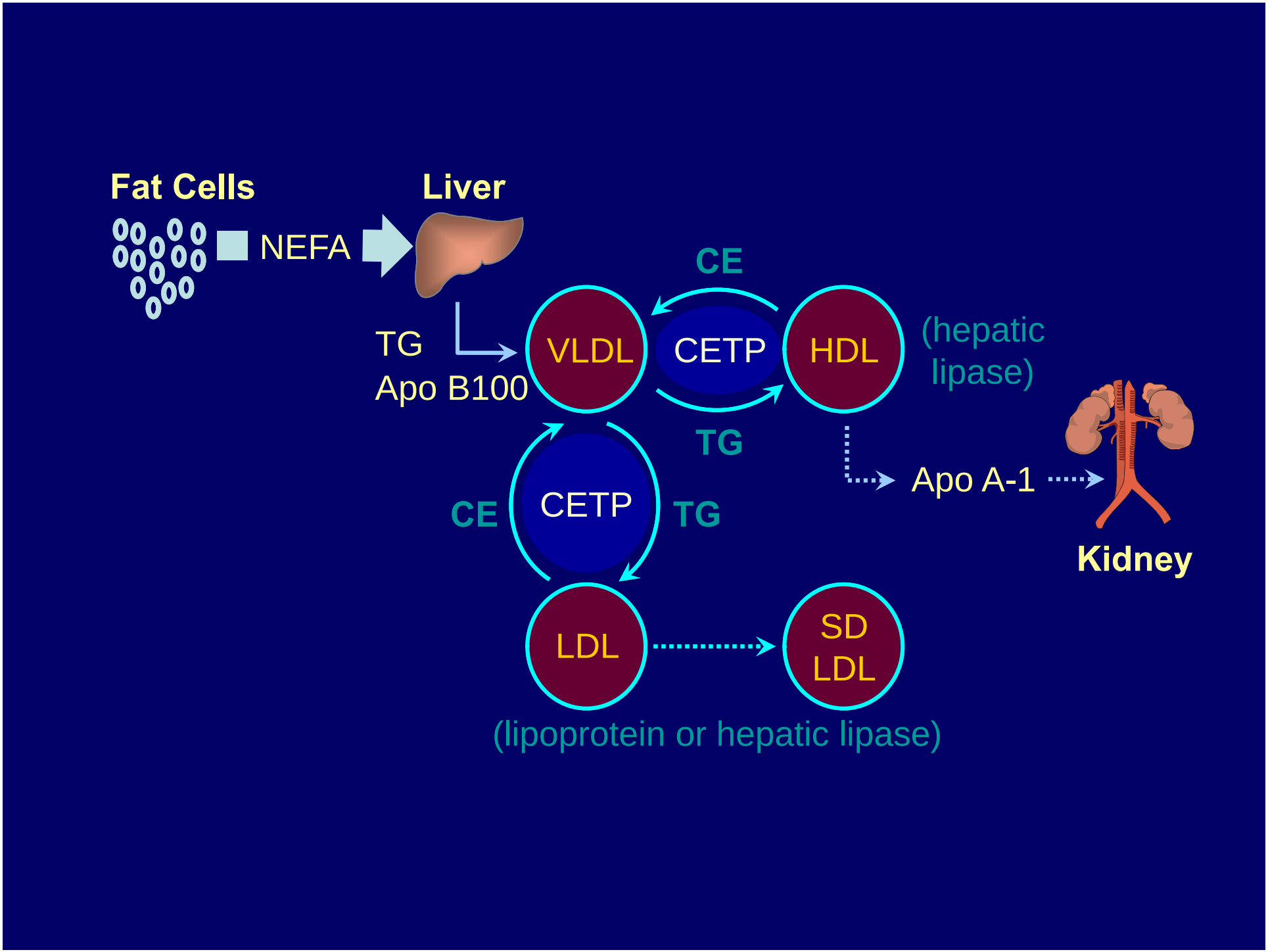
순환기 관련 학회 춘계 통합 학술 대회

서울 아산 병원

한 기 훈

Lipid Traffics




Fat Cells
NEFA
Liver
TG
Apo B100
VLDL
CE
CETP
HDL
TG
(hepatic lipase)
Apo A-1
Kidney
CE
CETP
TG
LDL
SD LDL
(lipoprotein or hepatic lipase)

Liver ; The origin of metabolism

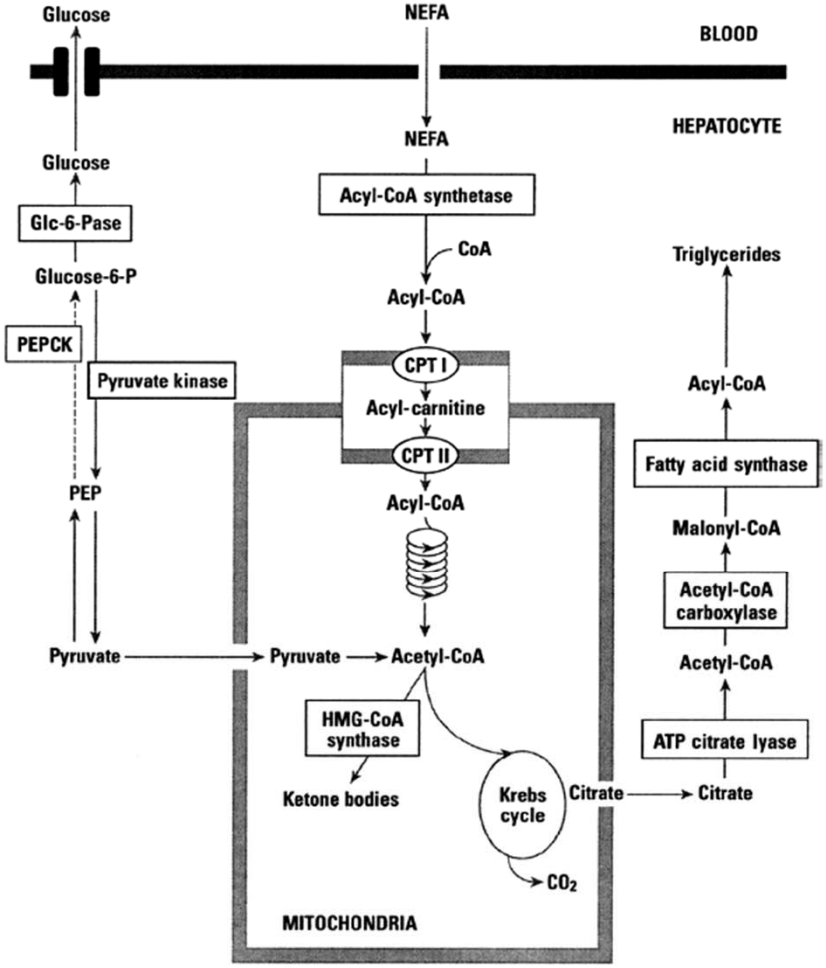


Figure 1. Substrates for triglyceride synthesis include nonesterified fatty acids (NEFAs), which undergo β-oxidation in the mitochondria to form acetyl coenzyme A (CoA), which enters the Krebs cycle and converts to citrate, a precursor of triglycerides. Alternatively, glucose is converted to pyruvate by pyruvate kinase, which is also converted in the mitochondria to acetyl-CoA and then enters the Krebs cycle to form citrate. Therefore, both glucose and NEFAs are substrates for triglyceride synthesis. ATP = adenosine triphosphate; CO_2 = carbon dioxide; CPT = carnitine palmitoyltransferase; Glc-6-P = glucose-6-phosphate; HMG = 3-hydroxy-3-methylglutaryl; Pase = phosphatase; PEP = phosphoenol pyruvate; PEPCK = phosphoenolpyruvate carboxy kinase. (Adapted from *J Nutr.*[7])

Am J Cardiol 2006;98[suppl]:27i–33i

Liver-tropic effects on Chol. Or TG production

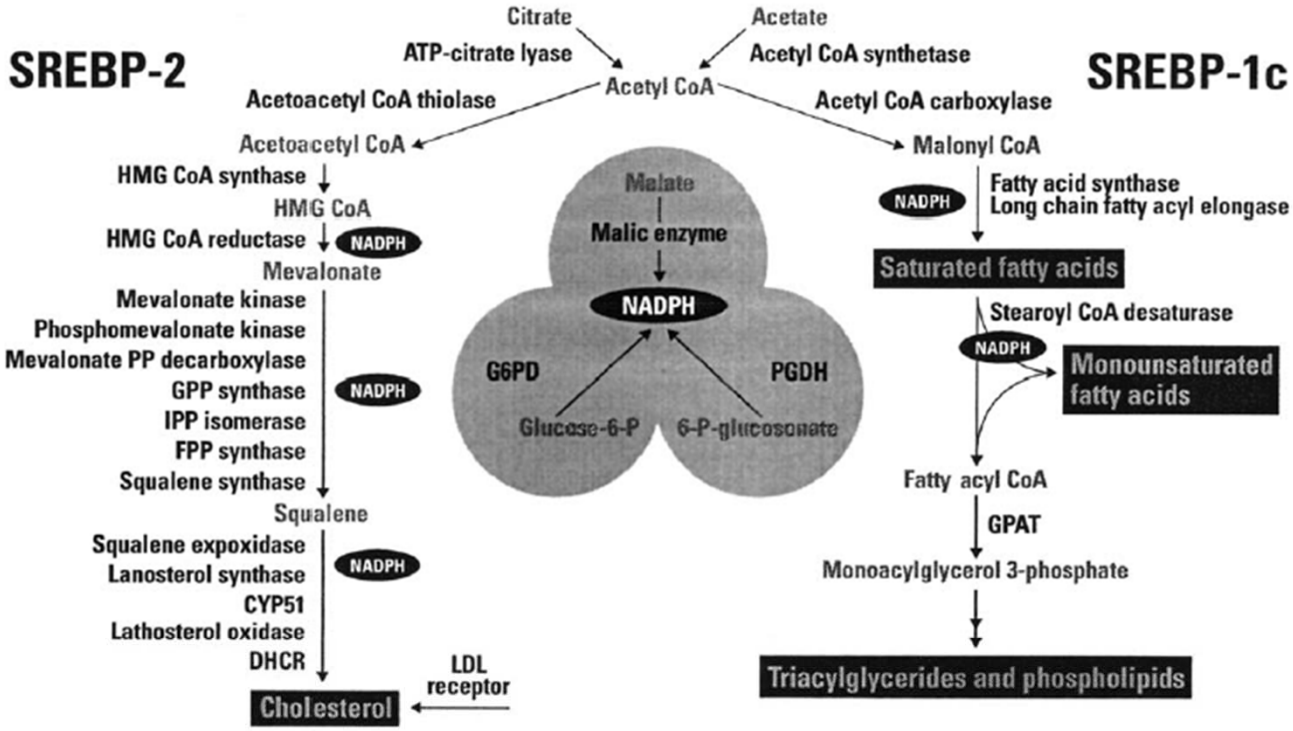
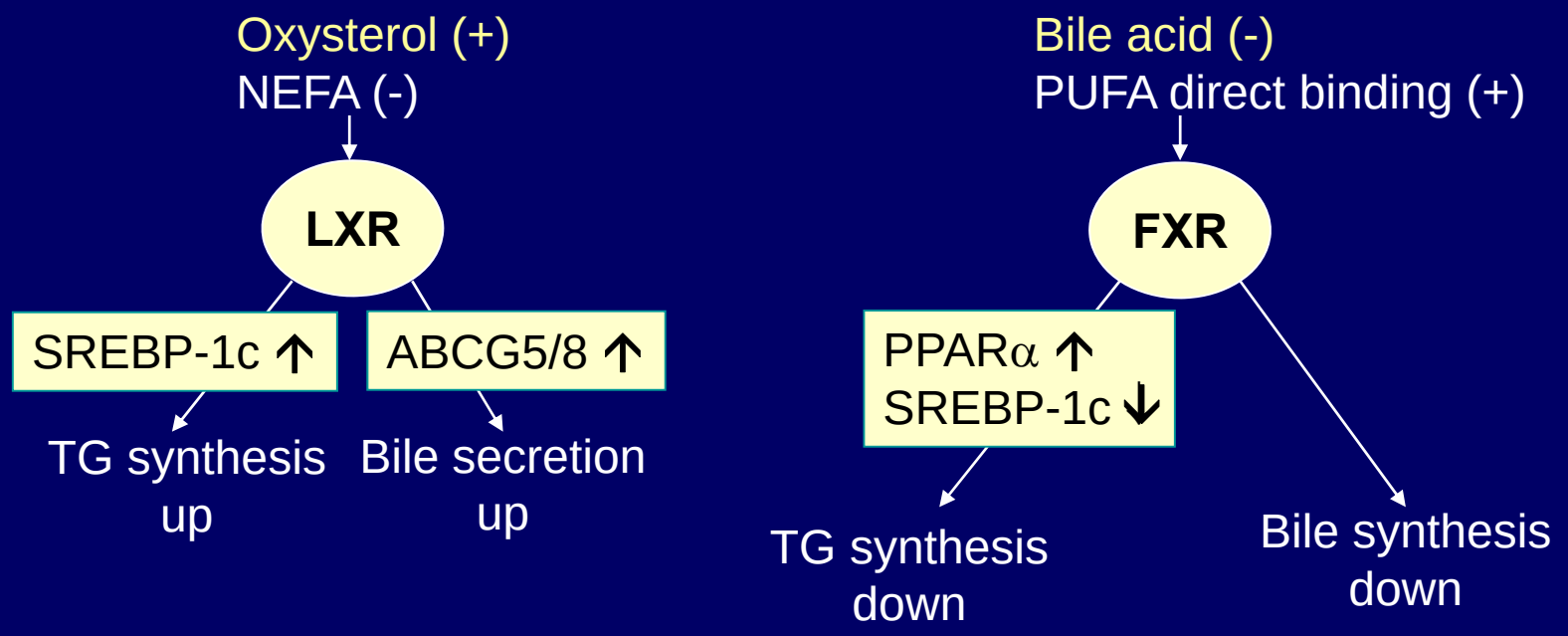


Figure 2. The liver X receptor (LXR) controls both sterol regulatory element binding protein (SREBP)–2 and SREBP-1c. SREBP-2 regulates the genes involved in cholesterol synthesis, whereas SREBP1-c stimulates the production of genes involved with the lipogenic enzymes. Inhibition of LXR would result in a decrease in both cholesterol and triglyceride synthesis. ATP = adenosine triphosphate; CoA = coenzyme A; CYP51 = cytochrome P450-51; DHCR = 7-dehydrocholesterol reductase; FPP = synthase-farnesyl diphosphate; Glucose-6-P = glucose-6 phosphate; GPAT = glycerol-3-phosphate acyltransferase; GPP = geranyl pyrophosphate; G6PD = glucose-6-phosphate dehydrogenase; HMG = 3-hydroxy-3-methylglutaryl; IPP = isopentenyl diphosphate; LDL = low-density lipoprotein; NADPH = reduced form of nicotinamide-adenine dinucleotide phosphate; PGDH = 6-phosphogluconate dehydrogenase.

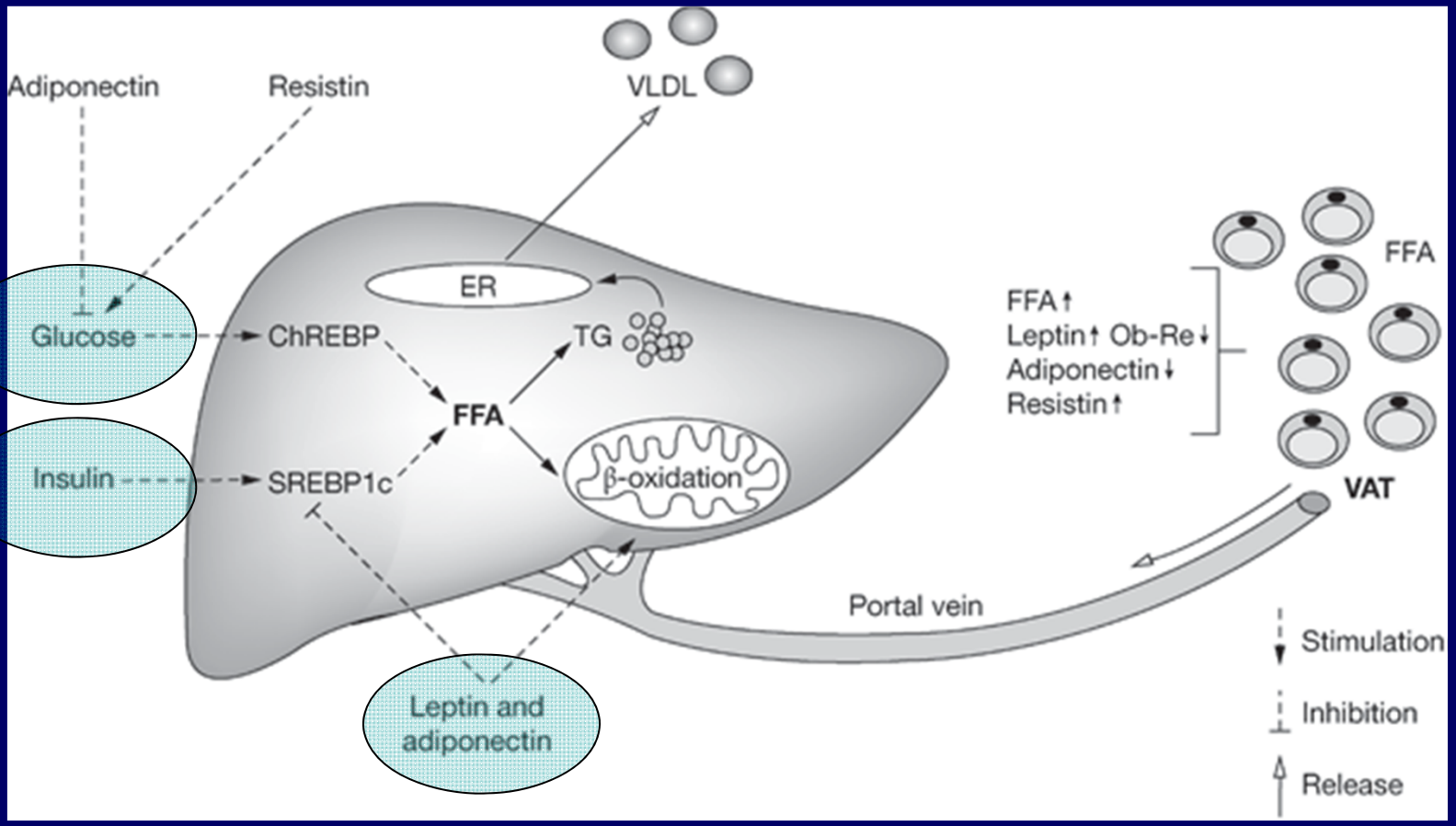
Am J Cardiol 2006;98[suppl]:27i–33i

Liver-tropic effects on TG or Bile



Am J Cardiol 2006;98[suppl]:27i–33i

Visceral adipose FFA and fatty liver disease

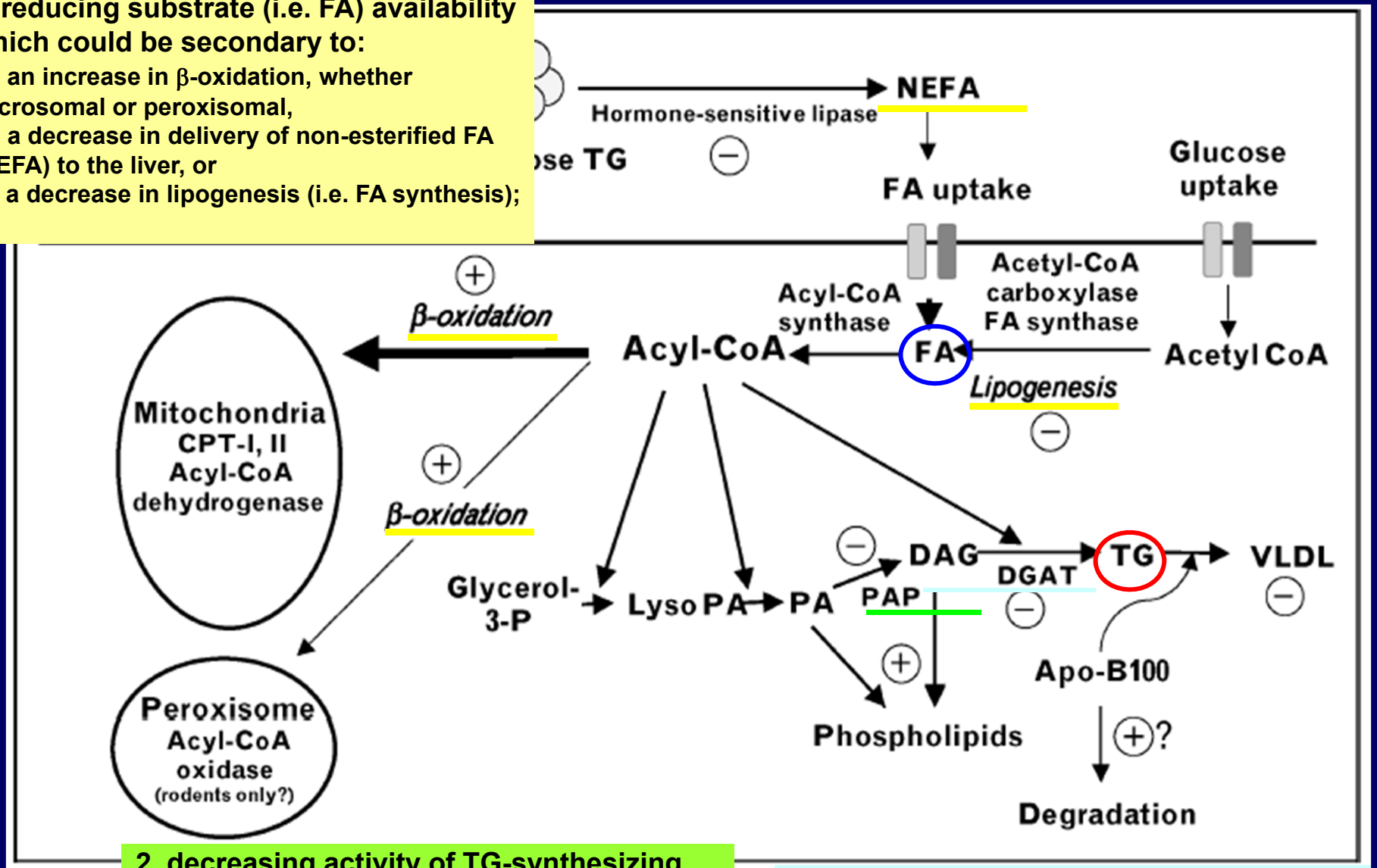


Schäffler A *et al*. (2005) Mechanisms of Disease: adipocytokines and visceral adipose tissue—emerging role in nonalcoholic fatty liver disease *Nat Clin Pract Gastroenterol Hepatol* **2:** 273–280
doi:10.1038/ncpgasthep0186

nature CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY

Potential TG-Lowering Strategies

1. reducing substrate (i.e. FA) availability which could be secondary to:
(a) an increase in β-oxidation, whether microsomal or peroxisomal,
(b) a decrease in delivery of non-esterified FA (NEFA) to the liver, or
(c) a decrease in lipogenesis (i.e. FA synthesis);

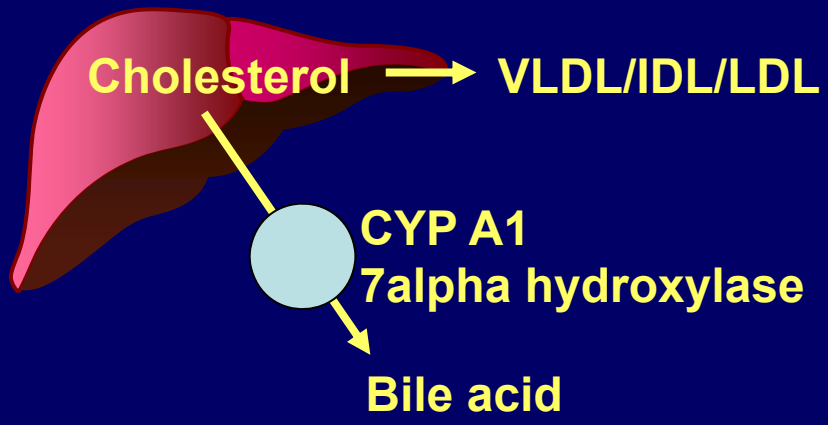


2. decreasing activity of TG-synthesizing enzymes, such as diacylgylcerol acyltranferase (DGAT) or phosphatidic acid phosphohydrolase (PAP);

3. increasing phospholipid synthesis [which could drain diacylglycerol (DAG) away from DGAT].

Gall stone formation

- Cholelithiasis ;
  cholesterol supersaturation,
  accelerated nucleation, &
  gallbladder dysmotility



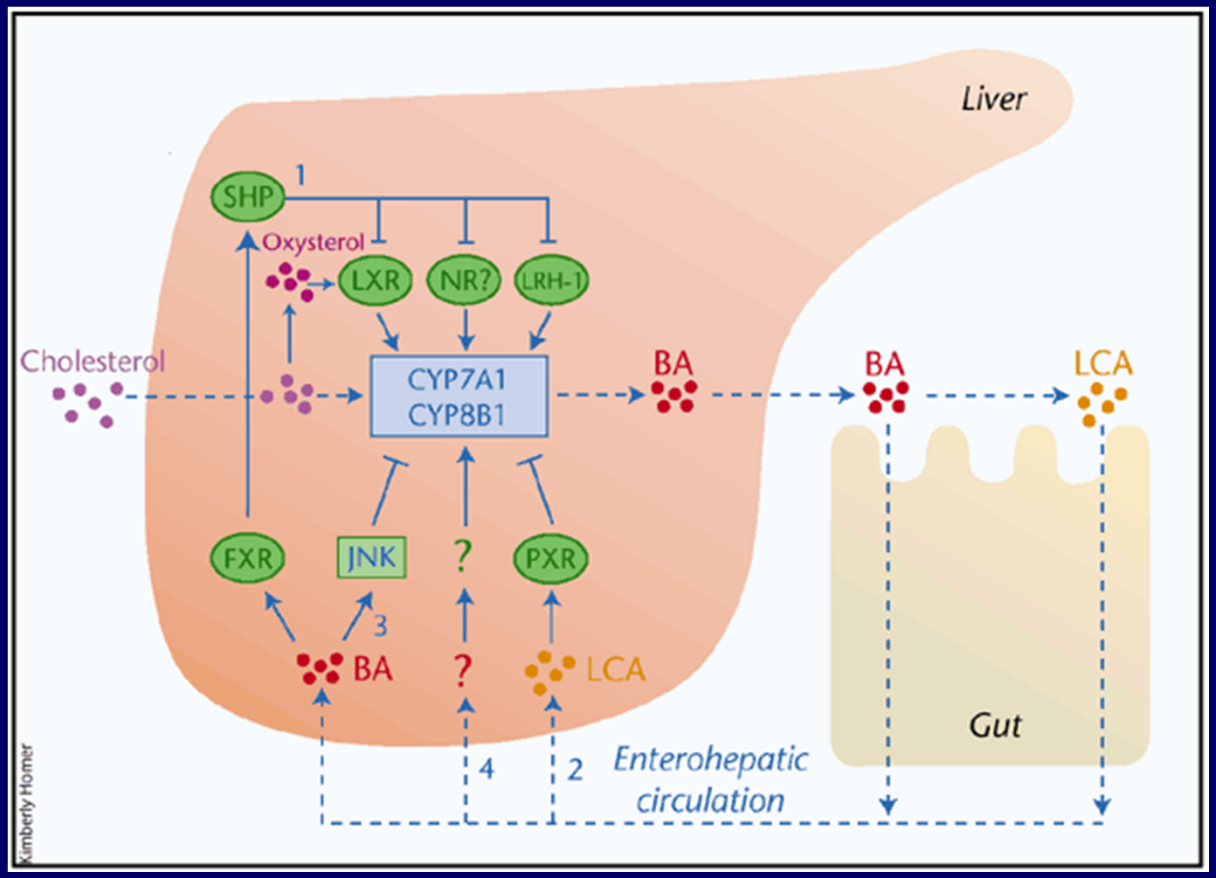


Figure 1. Regulation of bile-acid metabolism and enterohepatic circulation.
Cholesterol is converted into oxysterols in the liver. Oxysterols activate LXR-alpha , which limits cholesterol accumulation by inducing bile-acid synthesis. In the intestine, a secondary bile acid, lithocholic acid (LCA), is 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. Studies in SHP-deficient mice suggest that at least 4 redundant pathways are involved in this feedback inhibition (indicated by a number). 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) 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.

Kimberly Homer

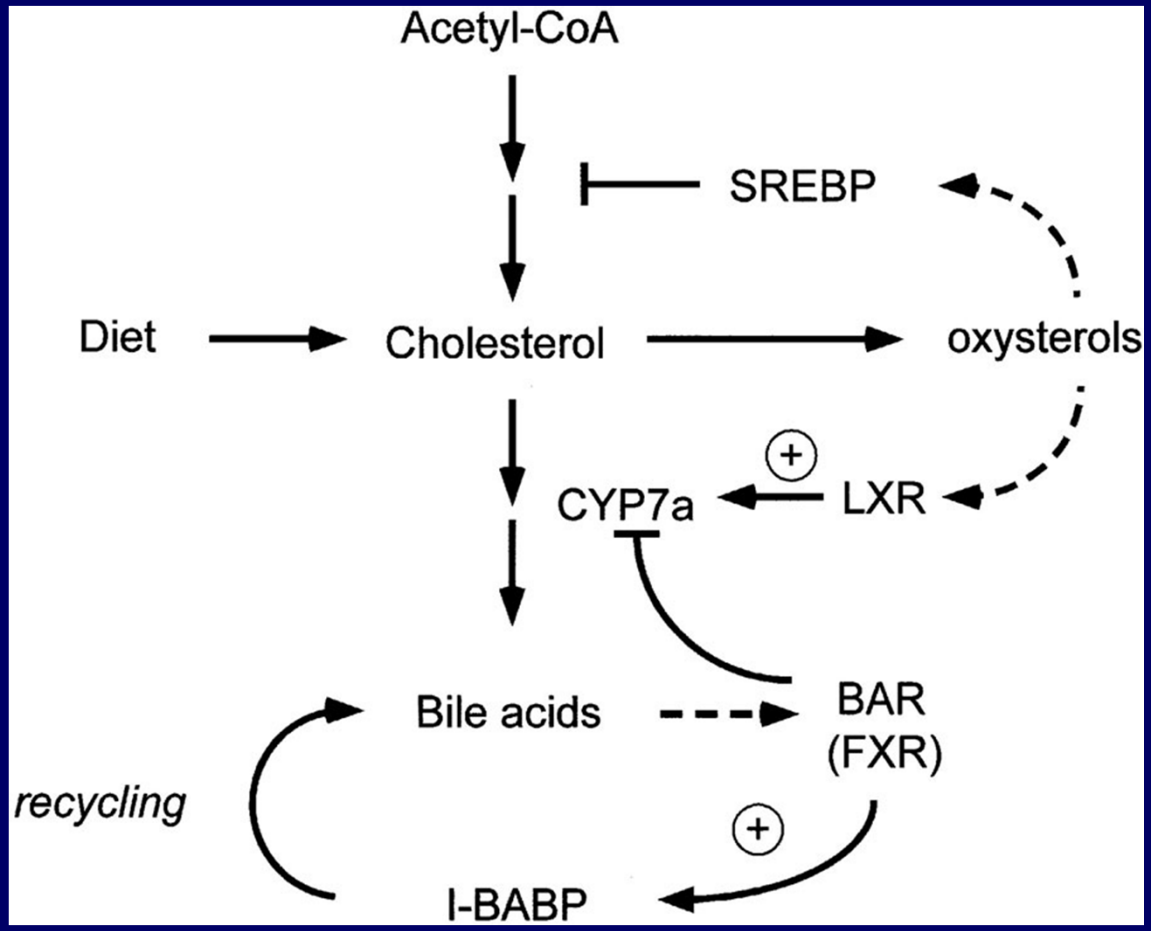
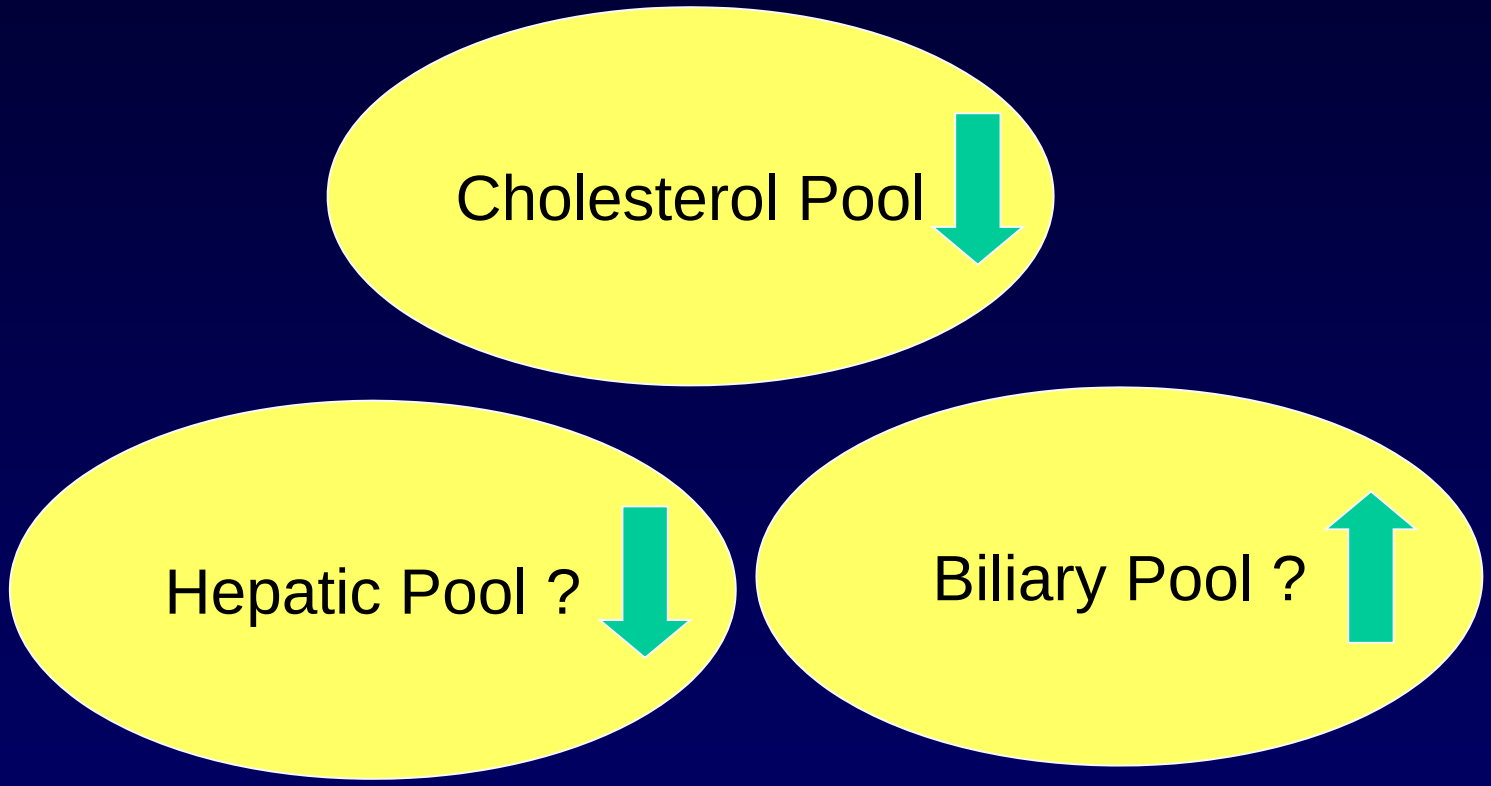


Figure 2 Role of LXR and BAR in the regulation of bile acid synthesis. Synthesis of bile acids is regulated at the level of the rate-limiting step catalysed by cholesterol 7alpha hydroxylase. To prevent excessive build-up of free cholesterol in the liver, cholesterol stimulates its own conversion to bile acids by activating the nuclear receptor LXR, which increases transcription of the Cyp7alpha gene. This so-called feedforward mechanism requires conversion of cholesterol to oxysterols, which are the ligands for LXR. Overproduction of bile acids is prevented by binding to their nuclear receptor BAR (bile acid receptors or FXR), which subsequently downregulates the expression of the Cyp7 gene. In order to stimulate recycling, the bile acids–BAR complex also stimulates recycling of bile acids by inducing transcription of I-BABP (intestinal bile acids binding protein), a protein that is responsible for re-uptake of bile acids in the intestine.
Nature vol 18 n 22

Ideal conditions to avoid fatty liver and cholelithiasis



Lipid Modifying Drugs and Gall Stone

- Statins ; decrease (decreasing cholesterol saturation index)
- Niacin ; neutral
- Resin ; neutral
- Fibrates ; increase (inhibition of CYP A1)
- Fish oils ; may decrease
- Ezetimibe ; ? NPC1L1 in human
  Intestine >>> Liver ?

Pitavastatin and liver

- Life Sci. 1999;65(14):1493-502.

Effect of NK-104, a new synthetic HMG-CoA reductase inhibitor, on triglyceride secretion and fatty acid oxidation in rat liver.

Yamamoto K et al, Saga Medical University, Japan.

Isolated rat liver was perfused with NK-104 in the presence of exogenous [1-(14)C]oleic acid substrate.

NK-104 caused a significant decrease in the secretion rate of triglyceride by the perfused liver without affecting uptake of exogenous [1-(14)C]oleic acid.

NK-104 significantly decreased hepatic triglyceride concentration. The altered triglyceride secretion was accompanied by a concomitant decreased incorporation of exogenous [1-(14)C]oleate into triglyceride.

The conversion of exogenous [1-(14)C]oleic acid substrate indicated an inverse relationship between the pathways of oxidation and esterification. No effect of NK-104 on hepatic secretion of cholesterol was observed. These results suggest that NK-104 exerts its hypotriglyceridemic action, primarily by diverting the exogenous free fatty acid to the pathways of oxidation at the expense of esterification.

- Biochem Biophys Res Commun. 2002;290(1):131-9.

Fibrate and statin synergistically increase the transcriptional activities of PPARalpha/RXRalpha and decrease the transactivation of NFkappaB.

Inoue I et al, Saitama Medical School, Japan.

Although pitavastatin was not a ligand for nuclear receptors in the CARLA, it induced transcriptional activation of PPARalpha/RXRalpha, PPARdelta/RXRalpha, and PPARgamma2/RXRalpha.

Pitavastatin synergistically and dose-dependently increased the transcriptional activation of PPARalpha/RXRalpha induced by bezafibrate.

Concomitant administration of pitavastatin and bezafibrate decreased the NFkappaB and the activation of NFkappaB by mitogen-activated protein kinase kinase kinase (MEKK) also decreased the transactivation of PPARalpha/RXRalpha.

- Diabetes Care. 2005 Nov;28(11):2728-32.

Effect of pitavastatin on urinary liver-type fatty acid-binding protein levels in patients with early diabetic nephropathy.

Nakamura T et al, Shinmatsudo Central General Hospital, Chiba, Tokyo, Japan.

Pitavastatin (1mg/day) decreased I-FABP serum levels

Can pitavastatin reverse fatty liver ?

Egawa T et al, Pitavastatin ameliorates severe hepatic steatosis in aromatase-deficient (Ar-/-) mice. Lipids. 2003 May;38(5):519-23.

- Northern blot analysis of Ar-/- mice liver revealed a significant restoration of mRNA expression of essential enzymes involved in FA beta-oxidation such as very long fatty acyl-CoA synthetase in peroxisome, peroxisomal fatty acyl-CoA oxidase, and medium-chain acyl-CoA dehydrogenase.
- Severe hepatic steatosis observed in Ar-/- mice substantially regressed.
- Consistent findings were obtained in the in vitro assays of FA beta-oxidation activity.

Pitavastatin can reverse fatty liver in humans !
; PITCH trial, KOREA

PITCH

PITavastatin versus atorvastatin for patients with hyperCholesterolemia and mild to moderate Hepatic damage

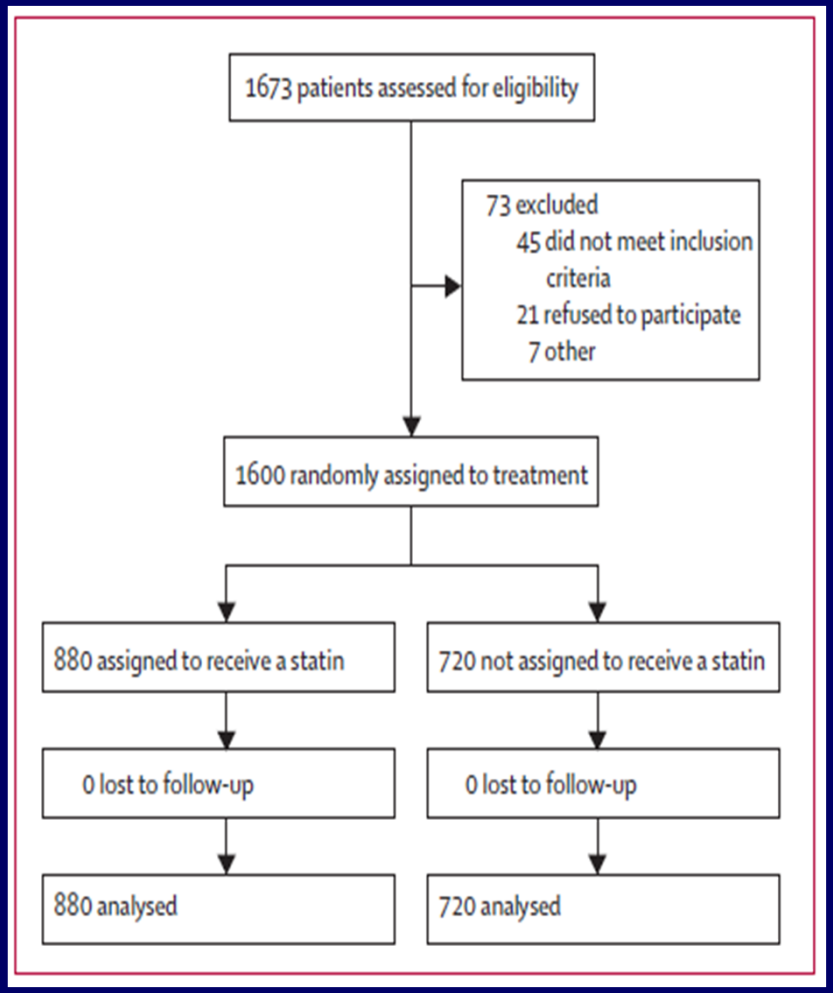
Background

The effect of statins on the liver

- Statin treatment = hepatic adverse events ?
- Transient elevation of serum aminotransferase levels
  - most common
  - asymptomatic
  - often occurs in the first 12 weeks of therapy
- But statin is relatively contra-indicated in patients with hepatic dysfunction.

GREACE study

Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests: a post-hoc analysis



	Patients with abnormal liver tests (n=437)	Patients with normal liver tests (n=1163)
Aspirin and other antiplatelet agents	393 (90%)	1035 (89%)
β blockers	363 (83%)	1000 (86%)
ACE inhibitors or AT1 antagonists	127 (29%)	302 (26%)
Nitrates	61 (14%)	174 (15%)
Calcium-channel blockers	118 (27%)	302 (26%)
Diuretics	52 (12%)	140 (12%)
Statin treatment (for >6 months during study)	227 (52%)	651 (56%)
Median statin dose (mg/day [range])		
Atorvastatin	25 (10–80)	23 (10–80)
Simvastatin	22 (10–40)	20 (10–40)
Pravastatin	29 (20–40)	31 (20–40)
Fluvastatin	40 (40–40)	40 (40–40)

Data are number (%) unless otherwise stated. Characteristics were well balanced between groups. ACE=angiotensin converting enzyme. AT1=angiotensin II type 1 receptor.

Table 2: **Drug treatment in all GREACE patients according to liver function tests during the 3 years of study**

Lancet 2010;376:1916–22

GREACE study

Changes in characteristics of participants with abnormal liver function tests

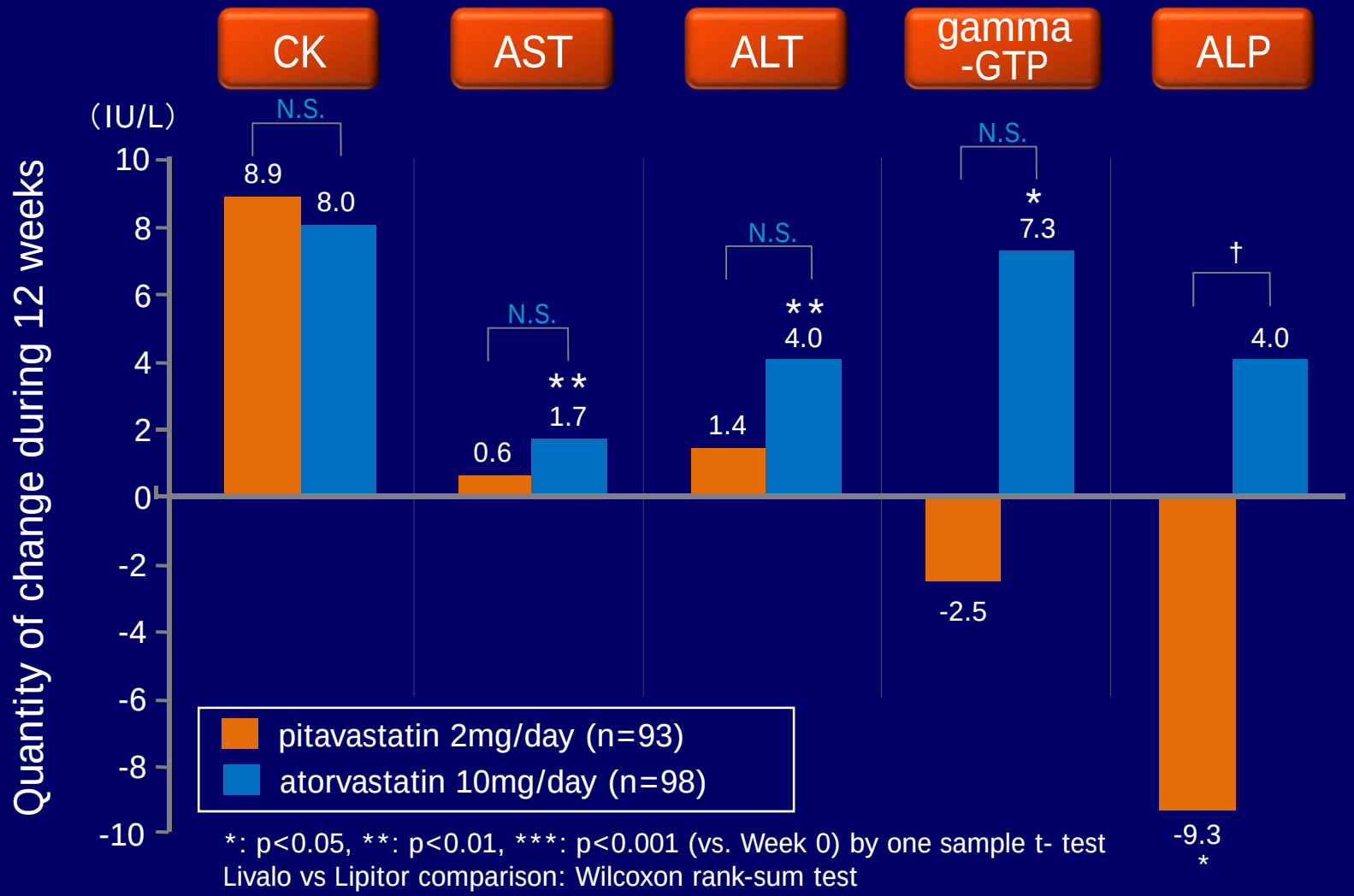
	Participants on statins				Participants not on statins			
	Baseline (n=227)	End of study (n=227)	Percentage change	p value	Baseline (n=210)	End of study (n=210)	Percentage change	p value
Total cholesterol (mmol/L)	6·36 (0·70)	4·16 (0·21)*	−35%	<0·0001	6·41 (0·75)	6·21 (0·83)	−3%	0·8
LDL cholesterol (mmol/L)	4·37 (0·47)	2·46 (0·16)*	−44%	<0·0001	4·45 (0·72)	4·24 (0·83)	−5%	0·8
HDL cholesterol (mmol/L)	0·96 (0·18)	1·03 (0·18)*	8%	0·02	0·98 (0·26)	0·96 (0·23)	3%	0·9
Triglycerides (mmol/L)	2·20 (0·63)	1·49 (0·26)*	−32%	<0·0001	2·13 (0·58)	1·98 (0·62)	−7%	0·8
Alanine aminotransferase (IU/L)	57 (8)	37 (6)*	−35%	<0·0001	56 (9)	63 (7)	12%	0·003
Aspartate aminotransferase (IU/L)	49 (7)	26 (4)*	−47%	<0·0001	49 (7)	55 (8)	12%	0·01
γ-glutamyl transpeptidase (IU/L)	70 (10)	38 (6)*	−46%	<0·0001	68 (10)	79 (12)	16%	0·001
EGFR (mL/min per 1·73 m²)	59 (17)	70 (10)*	19%	<0·0001	68 (19)	64 (18)	−6%	0·8
Cardiovascular events	..	22 (9·7%)	..	..	..	63 (30·0%)	..	..
Cardiovascular events per 100 patient-years	..	3·2	..	..	..	10·0	..	..

Data are mean (SD) or n (%) unless otherwise stated. EGFR=estimated glomerular filtration rate. ..=not applicable. *p<0·05 versus end of study in participants with abnormal liver function tests who were not on statins.

Lancet 2010;376:1916–22

CHIBA Study

Change in CK and hepatic parameters



*: p<0.05, **: p<0.01, ***: p<0.001 (vs. Week 0) by one sample t- test
Livalo vs Lipitor comparison: Wilcoxon rank-sum test

Patients: Hypercholesterolemia (including FH)
Method: Livalo® 2mg/day, atorvastatin 10mg/day for 12weeks

Yokote K et.al Atherosclerosis 2008 201(2):345-352

Background

Non-Alcoholic Fatty Liver Disease (NAFLD)

- Recently, NAFLD is highly prevalent even in Korea, which has the potential to progress to cryptogenic cirrhosis and hepatocellular carcinoma.
- It is not only regarded as a hepatic component of the metabolic syndrome but also as an independent risk factor and a marker for increase in cardiovascular disease.

Korean J Med 2010;79:481-489

Objective

To evaluate and compare the influence of Pitavastatin with Atorvastatin in hypercholesterolemia patients, who have mild to moderate hepatic damage.

Subjects

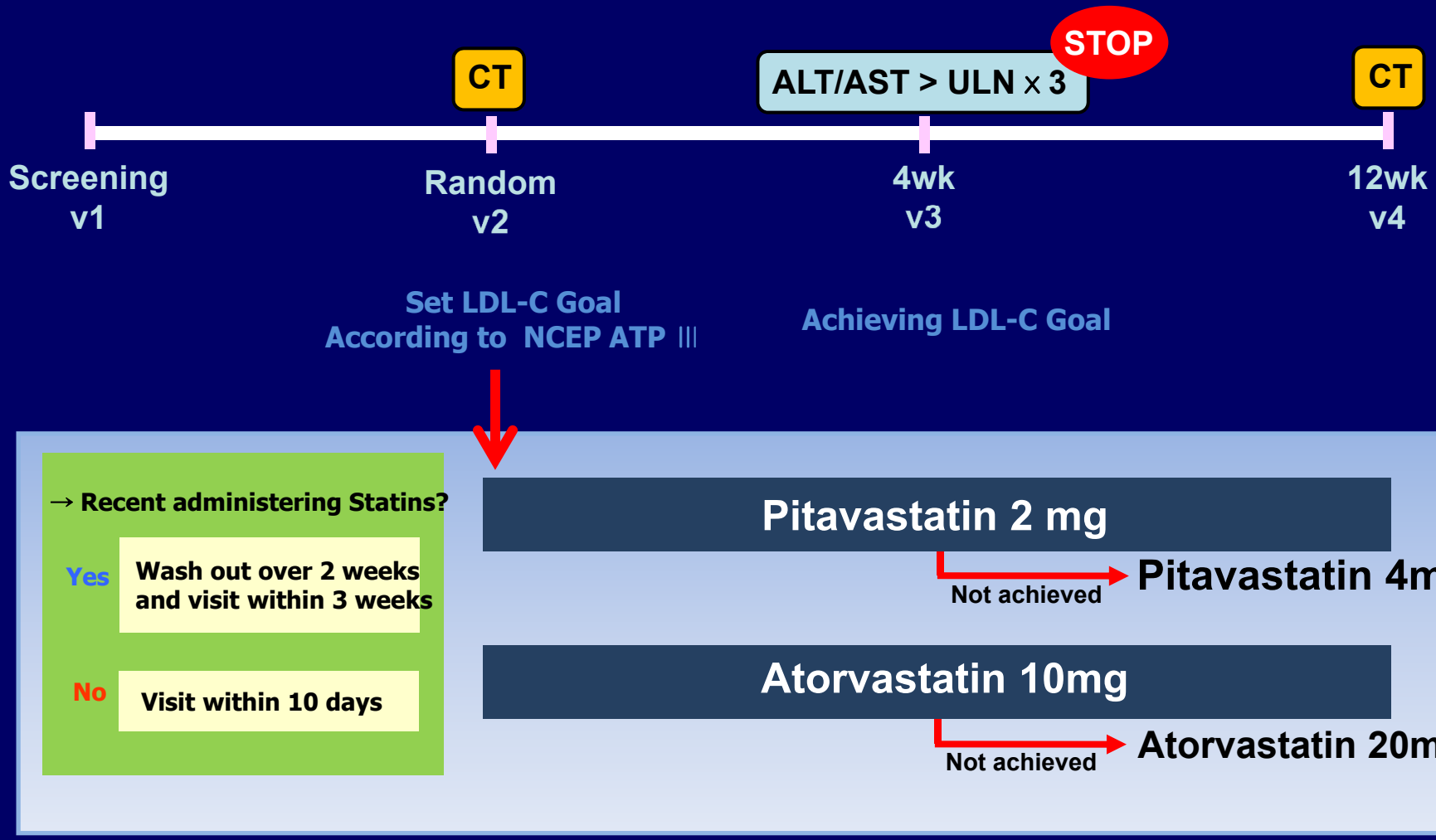
Hypercholesterolemia patients,
who have mild to moderate hepatic damage

Inclusion criteria

- Patients who have taken statin over 2 months, or patients whose fasting LDL-C (Friedewald LDL-C) is over 130mg/dL
- Patients with a ALT value greater than 1.25 times and 2.5 times lower than upper limit of normal

Study design

12-week, multi-center, prospective, randomized, open labeled, active drug-controlled, dose titration study



Efficacy endpoints

Primary endpoints

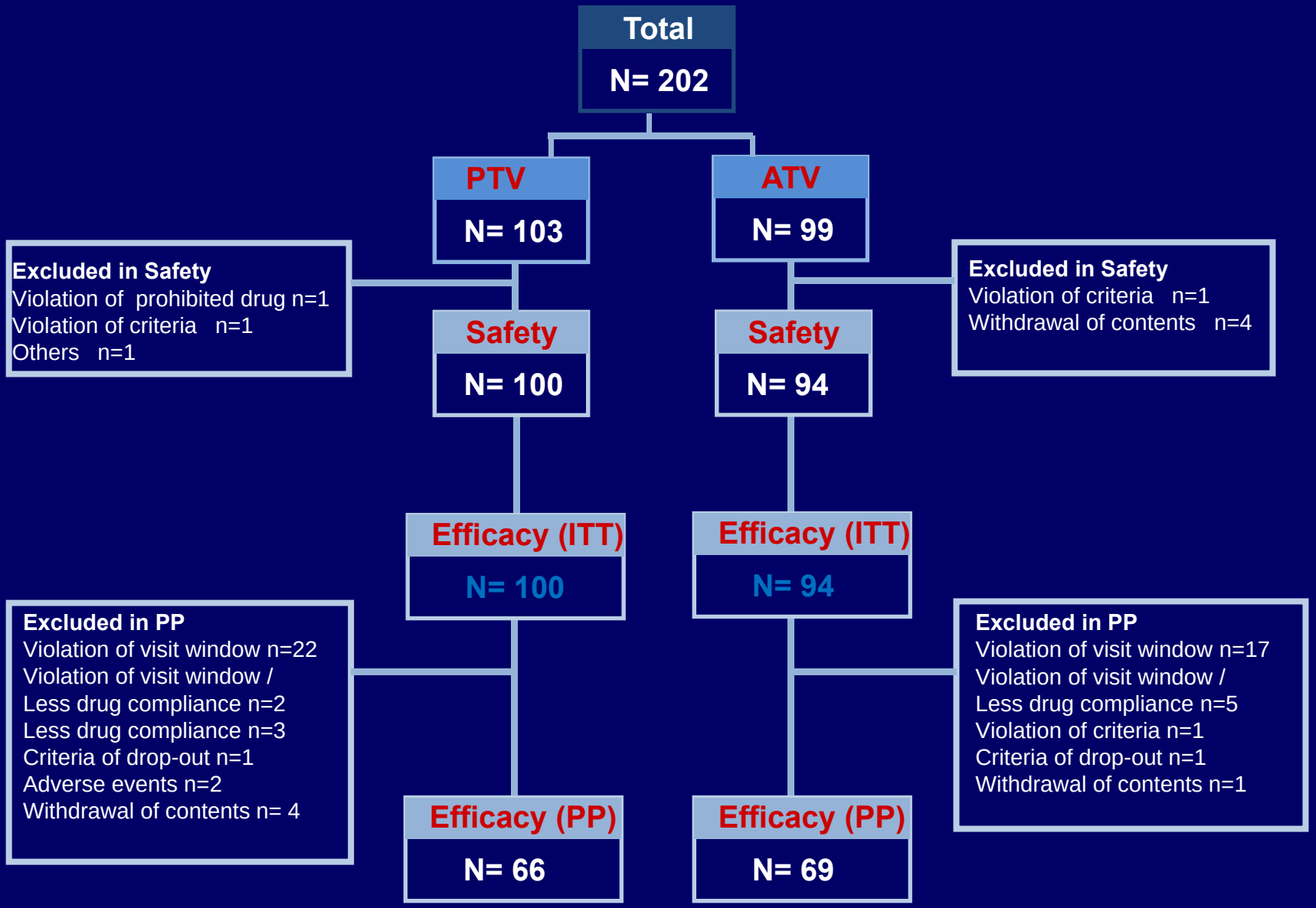
- **The ratio of patients with a greater ALT value than CTCAE* grade 2 at 12weeks**

Secondary endpoints

- **The change of ALT values at 12weeks**
- **The change of AST values at 12weeks**
- **The changes of LDL-C, TC, TG, HDL-C at 12weeks**
- **The change of the amount of fat in the liver for patients with fatty livers**

* CTCAE: Common Terminology Criteria of Adverse Event

Subjects' disposition



Baseline characteristics (1)

Category	Pitavastatin (n=100)	ATV (n=94)	p-value
Sex: N (%)			
Male	67(67.00)	64(68.09)	0.8719
Female	33(33.00)	30(31.91)	
Age: years Mean(SD)	55.3(9.8)	54.9(8.5)	0.7758
Height: cm	165.7(8.2)	166.0(8.1)	0.7999
Weight: Kg	74.1(13.0)	75.0(11.7)	0.6097
BMI: kg/m^2	26.8(3.3)	27.1(2.9)	0.5655
Waist circumference: cm	91.8(10.1)	92.1(7.7)	0.8142
Life style: N(%)			
Regular	50(50.00)	58(62.37)	0.2236
Generally regular	31(31.00)	22(23.66)	
Irregular	19(19.00)	13(13.98)	
Exercise: N(%)			
≥3 times/week	31(31.00)	29(31.18)	0.9971
<3 times/week	33(33.00)	31(33.33)	
barely not	36(36.00)	33(35.48)	
Smoking: N(%)			
Recent smoker	20(20.00)	25(26.60)	0.3561
Non-smoker	51(51.00)	49(52.13)	
Quit smoking	29(29.00)	20(21.28)	
Drinking: N(%)			
Drinking	53(53.00)	58(61.70)	0.2208
Non-drinking	47(47.00)	36(38.30)	

Baseline characteristics (2)

Category	Pitavastatin (n=100)	ATV (n=94)	p-value
Diabetes: N (%)			
Yes	29(29.29)	24(25.53)	0.5585
No	70(70.71)	70(74.47)	
Hypertension: N (%)			
Yes	69(69.70)	64(68.82)	0.8949
No	30(30.30)	29(31.18)	
Metabolic syndrome: N (%)			
Yes	68(68.00)	74(78.72)	0.0919
No	32(32.00)	20(21.28)	
History of statins within 2 months: N (%)			
Yes	68(68.00)	59(62.77)	0.4435
No	32(32.00)	35(37.23)	
List of statins: case			
Atorvastatin	26	17	
Fluvastatin	1	5	
Pitavastatin	4	4	
Rosuvastatin	16	16	
Simvastatin	20	22	
Unknown	2	0	
Total	69	64	

Primary endpoint

Proportion of subjects over CTCAE grade II in ALT value at 12weeks

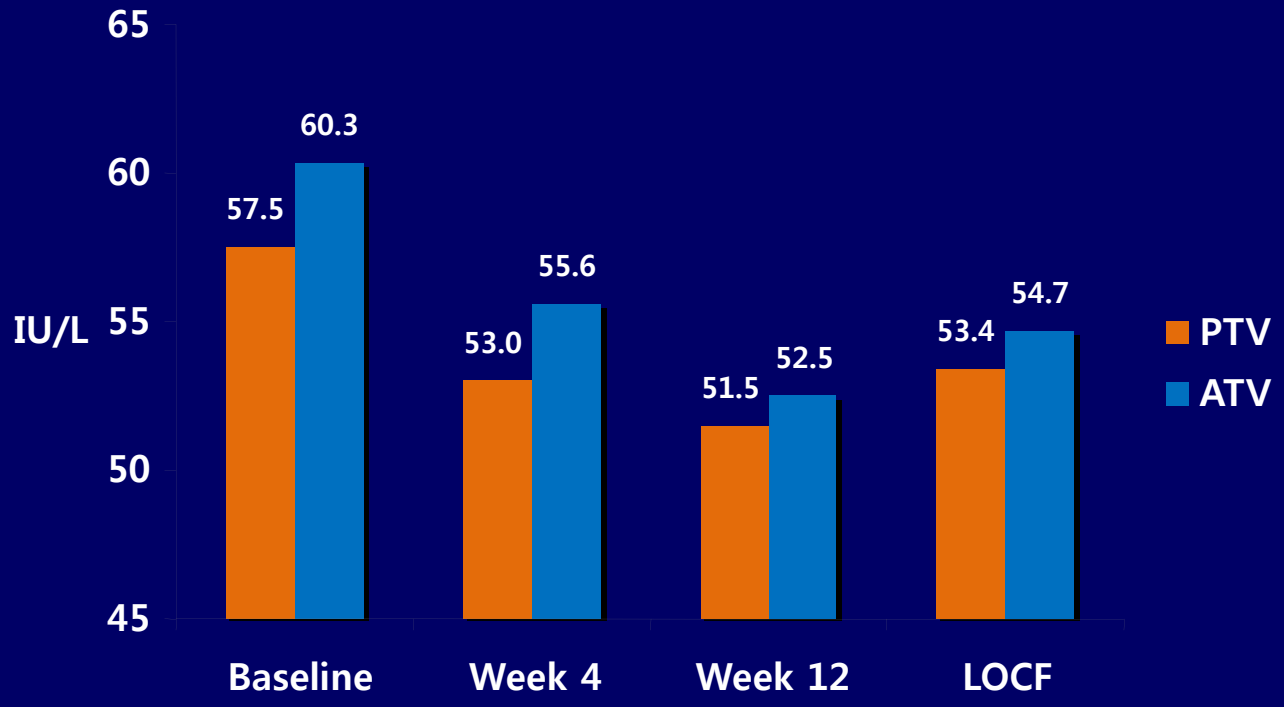
	Pitavastatin	ATV	*p*-value
Yes	7(7.00)	6(6.38)	
No	93(93.00)	88(93.62)	0.8636
Total	100	94	

There is no significant difference within two groups and 93% of subjects in pitavastatin group had not shown increase over CTCAE Grade II in ALT value.

Possible to administer Pitavastatin safely in patients with mild to moderate hepatic damage.

Secondary endpoint (1)

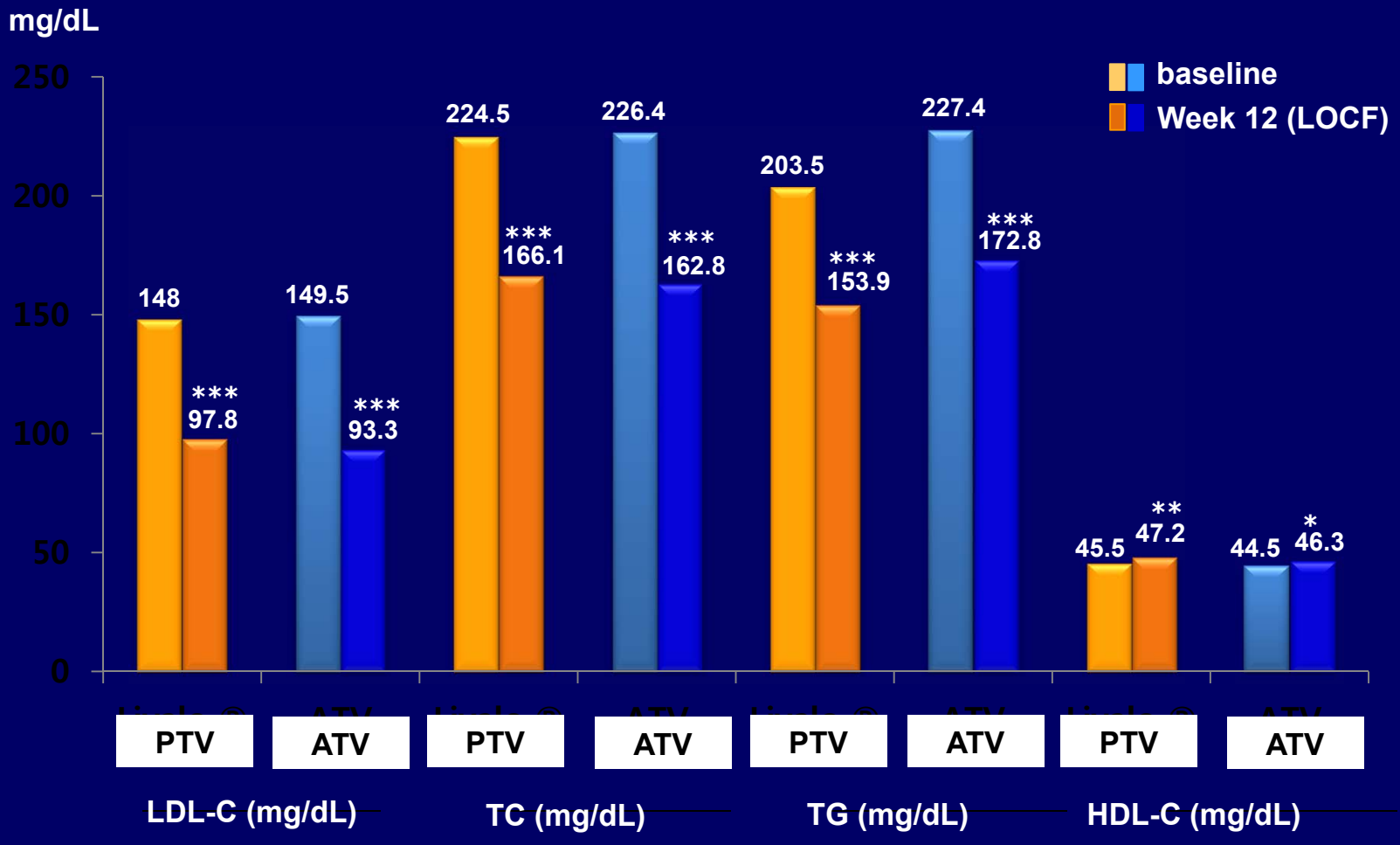
Change of ALT value at 12weeks



Data are presented as mean±S.D. Pitavastatin (*n*=100) ; ATV (*n*=94)
p=0.7108 vs. atorvastatin
LOCF=Last Observation Carried Forward

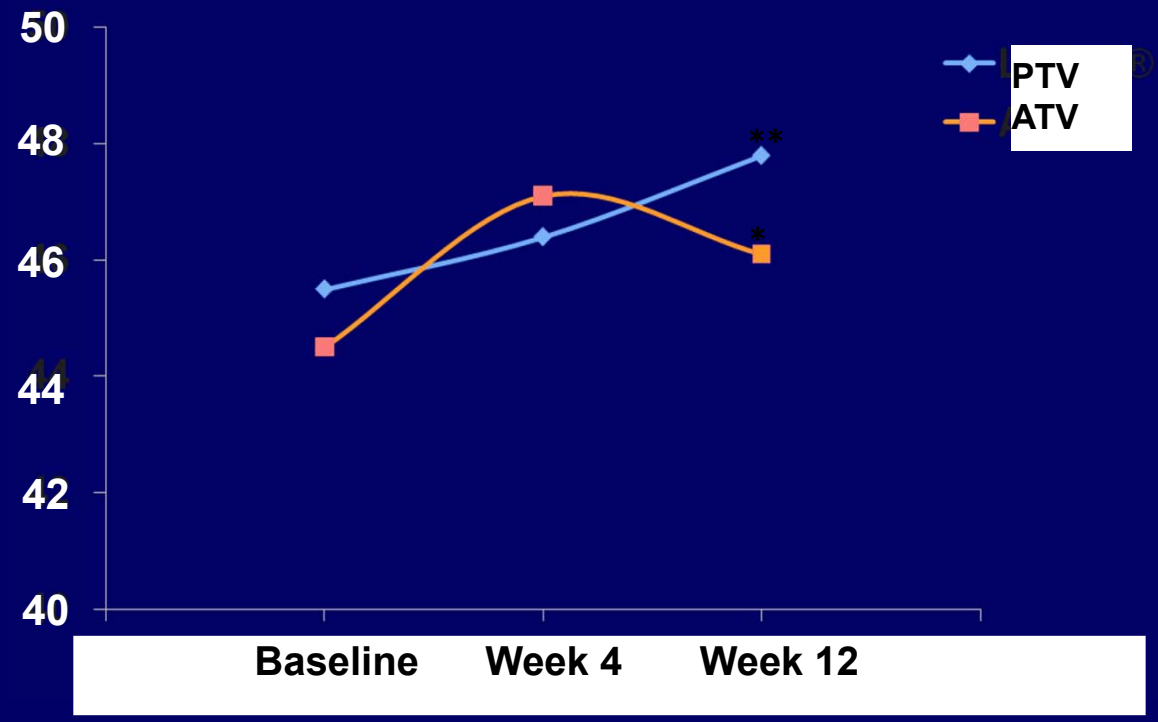
Secondary endpoint (3)

Change of lipid profile at 12weeks



* p=0.0188 vs. baseline, **p=0.0181 vs. baseline, *** p<0.001 vs. baseline

Change of HDL-C at 12weeks



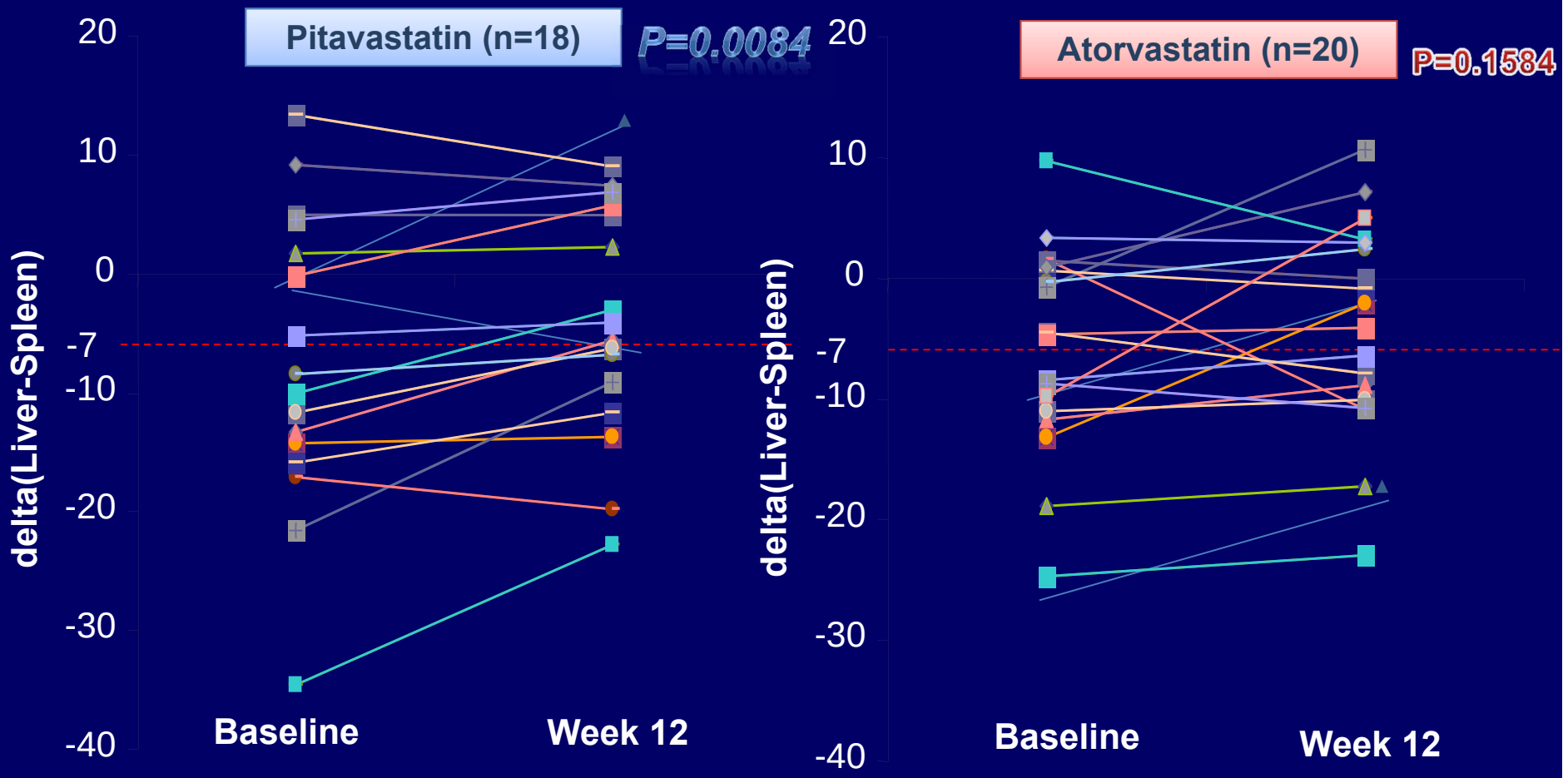
All groups showed significant increase in HDL-C levels.

Pitavastatin groups showed trend of continuous increase HDL-C by time.

*** p=0.0188 vs. baseline, **p=0.0181 vs. baseline**

*change1=4weeks-Baseline, change2=12weeks-Baseline, change3=LOCF-Baseline

Change of liver fat measured by CT at 12weeks



	Baseline	Week 12	Mean of change [a]	PTV vs. ATV change	
Pitavastatin	-6.7±12	-3.4±9.6	3.3±4.7	-1.2(-4.9,2.5) [b]	P-Value
Atorvastatin	-7.1±10.1	-5.0±9.2	2.1±6.4		0.5152

Data are presented as mean±S.D. Pitavastatin (*n*=20) ; ATV (*n*=18) *p=0.0084

a) Mean of change=Week 12-Baseline b) Mean and confidence interval for the change(PTV-ATC)

Subgroup analysis-CT subjects

Change of liver fat measured by CT (Δ≤-7)

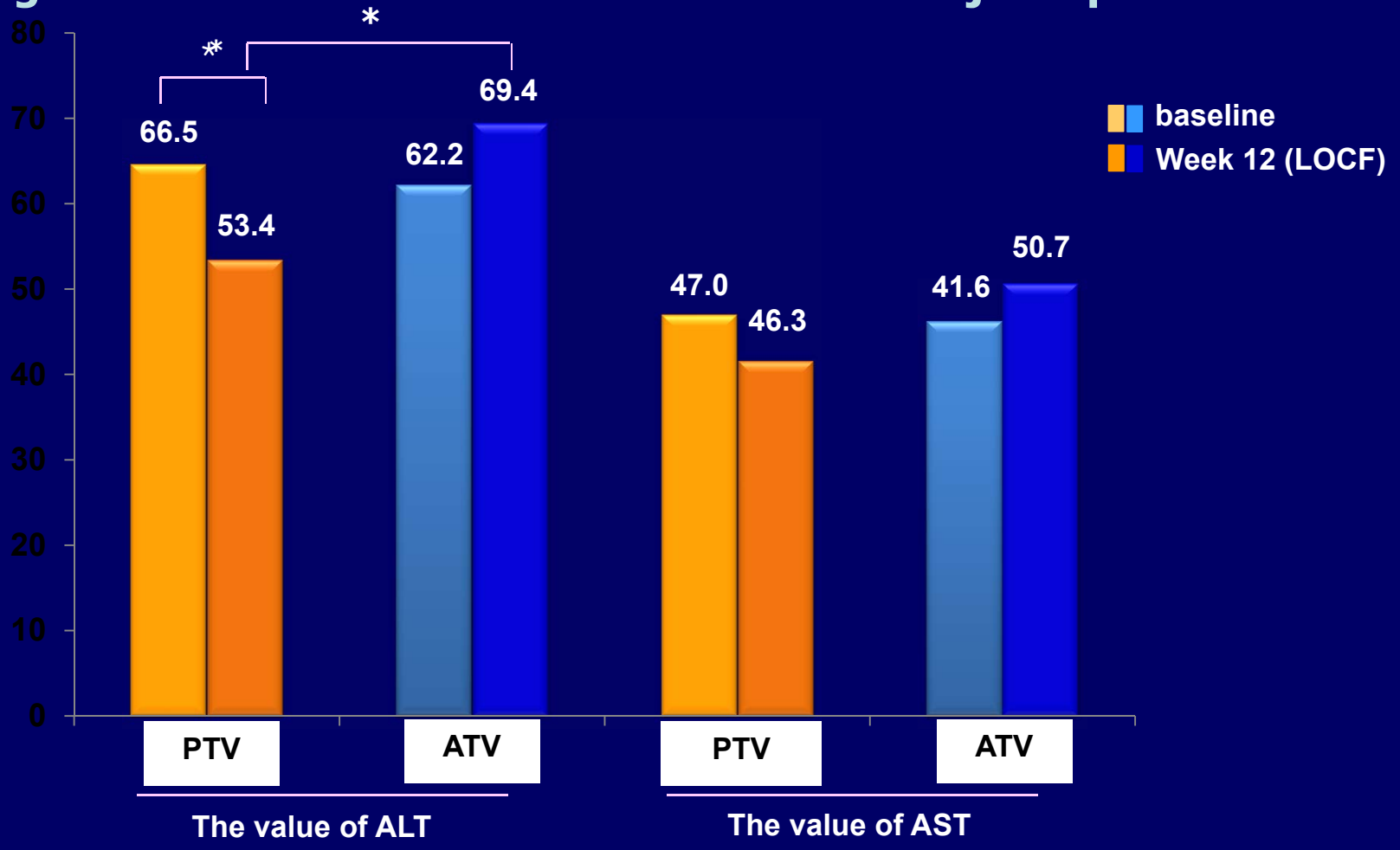
	Baseline	Week 12	Mean of change	PTV vs. ATV change
Pitavastatin	-16.3±7.9	-11±6.7	5.3±5.1	P-Value
Atorvastatin	-15.0±7.7	-10.3±8.7	4.7±5.3	0.8002

Change of liver fat measured by CT (Δ>-7)

	Baseline	Week 12	Mean of change	PTV vs. ATV change
Pitavastatin	2.9±5.7	4.2±4.4	1.3±3.5	P-Value
Atorvastatin	0.7±4.1	0.2±6.6	-0.5±6.6	0.4731

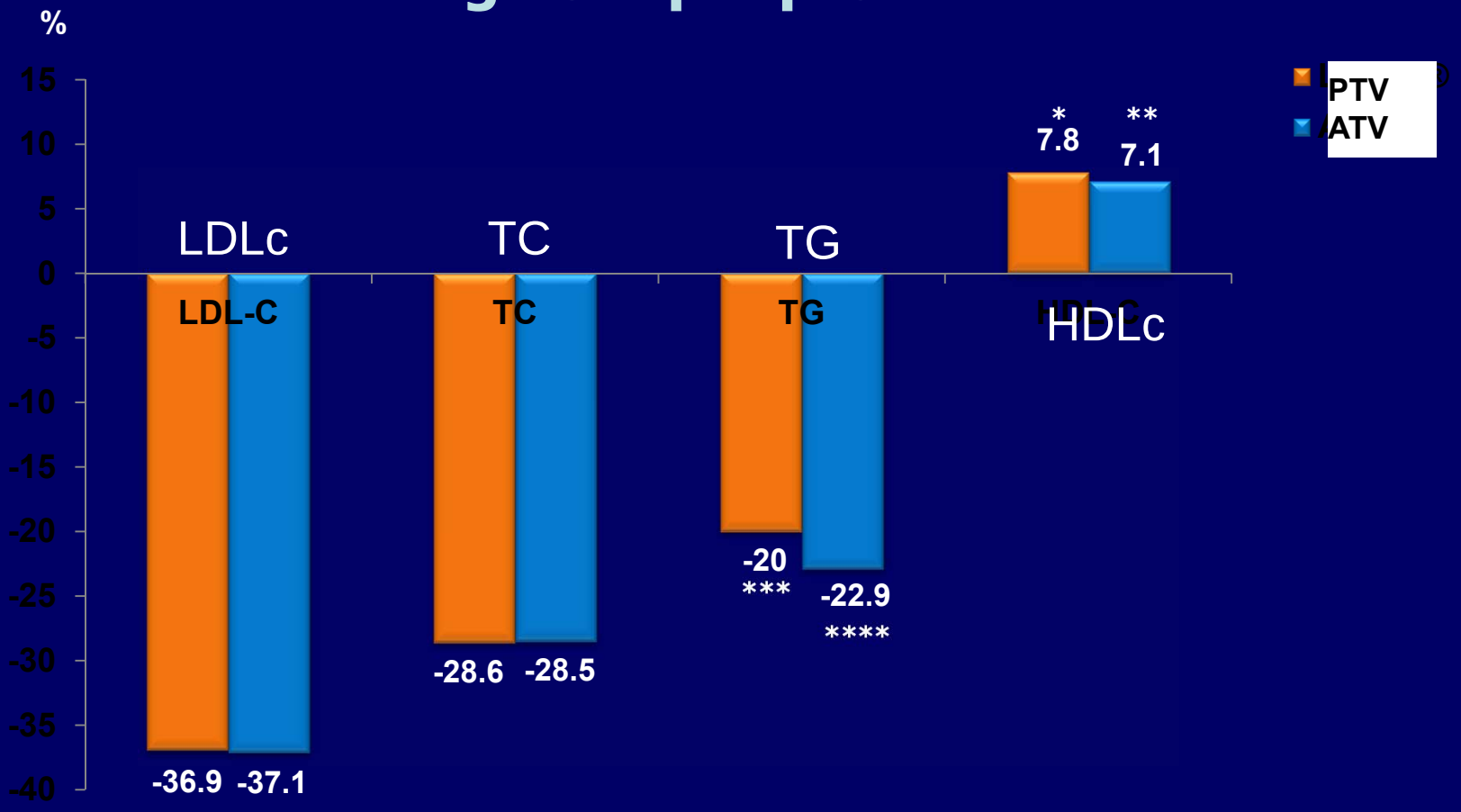
Subgroup analysis-CT subjects

Change of ALT and AST after treatment with subjects performed CT



There was significant difference within PTV and ATV groups in ALT levels after treatment with the subjects performed CT.

Subgroup analysis-CT subjects



* p=0.0326 vs. baseline, **p=0.0262 vs. baseline, ***p=0.013vs. baseline , ****p=0.0011vs. baseline, ζ p<0.001

Subgroup analysis-CT subjects

Change of weight

	Baseline	Week 12
Pitavastatin	73.6	74.5
ATV	78.9	78.7

Change of waist circumference

	Baseline	Week 12
Pitavastatin	94.0	93.1
ATV	95.0	95.1

Safety evaluation

	Adverse events*			Adverse Drug Reactions**		
	Pitavastatin	ATV	Total	Pitavastatin	ATV	Total
Number of patients experienced AEs N(%)	28(28.00)	25(26.60)	53(27.32)	12(12.00)	6(6.38)	18(9.28)
Cases N(%)	29(29.00)	27(28.72)	56(28.87)	13(13.00)	6(6.38)	19(9.79)

* : p=0.9969, ** : p=0.3221

There was no significant difference between two groups in incidence rate of adverse events .

Safety evaluation

System Organ class/ Preferred term	Adverse Events			Adverse Drug Reactions		
	PTV	ATV	Total	PTV	ATV	Total
Liver & Biliary System Disorder	**3 (3.00)**	**2 (2.13)**	**5 (2.58)**	**1 (1.00)**	**1 (1.06)**	**2 (2.06)**
Bilirubinaemia	0	1	1	0	0	0
Hepatic enzyme increased	0	1	1	0	1	1
Cholecystitis	1	0	1	0	0	0
SGPT increased	2	0	2	1	0	1
Musculo-Skeletal System Disorder	**1 (1.00)**	**1 (1.06)**	**2 (1.03)**	**0 (0.00)**	**1 (1.06)**	**1 (0.52)**
Musculoskeletal pain	1	0	1	0	0	0
Myalgia	0	1	1	0	1	1
Metabolic & Nutritional Disorder	**3 (3.00)**	**6 (6.38)**	**9 (4.64)**	**1 (1.00)**	**3 (3.19)**	**4 (2.06)**
BUN increased	0	1	1	0	0	0
CK increased	1	2	3	1	2	3
Diabetes Melitus	1	1	2	0	0	0
Oedema	0	1	1	0	0	0
Hyperglycaemia	0	1	1	0	1	1
Hypertriglyceridaemia	1	0	1	0	0	0

Conclusion

This study is first randomized controlled trial to compare the effect of statins on hepatic function in patients with mild to moderate hepatic damage

Conventional doses of both pitavastatin (2-4 mg/day) and atorvastatin (10-20 mg/day) can be considered as a therapeutic option for alleviating non-viral and non-alcoholic hepatic steatosis with high safety.

Relationship between the dose of statin and the incidence of persistent elevation of ALT >3 Times ULN

	Placebo %	10mg %	20mg %	40mg %	80mg %
Lovastatin[1]	0.1		0.1	0.9	2.3
Simvastatin[1]			0.7	0.9	2.1
Pravastatin[1]	1.3			1.4	
Fluvastatin[1]	0.28		0.2	1.5	2.7
Atorvastatin[1]		**0.2**	**0.2**	**0.6**	**2.3**
Rosuvastatin[1]		0	0	0.1	

	Placebo %	1mg %	2mg %	4mg %	
Pitavastatin[2]	**0**	**0**	**0**	**0.5**	

1. Hepatology 2005;41(4):690-695 2. FDA, label information

Summary ; Pitavastatin and liver

- 30 % LDL reduction
- Preserved HDL elevation
- Not a diabetic statin
- Decrease TG production and secretion
- Increase beta-oxydation
- Decrease the elevated ALT
- Reduce fatty liver
- Safe in case of mild-moderate ALT elevation

Pitava-statin
Liver-statin

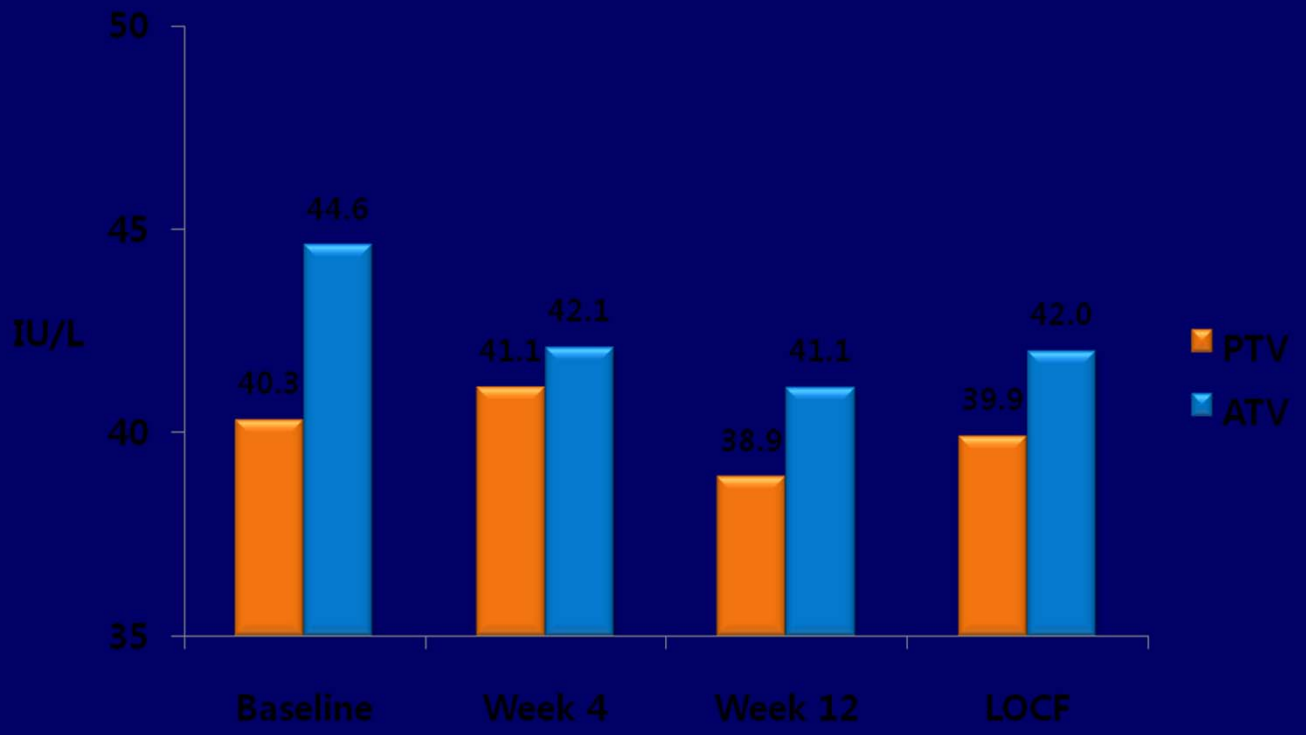
LIVALO

for the LIVer And LOw LDL


PITA vastatin

Secondary endpoint (2)

Change of AST value at 12weeks



Data are presented as mean±S.D. Pitavastatin (*n*=100) ; ATV (*n*=94)

p=0.3936 vs. atorvastatin

LOCF=Last Observation Carried Forward