Aspectos diferenciales entre estatinas y su aproximación a la práctica clínica

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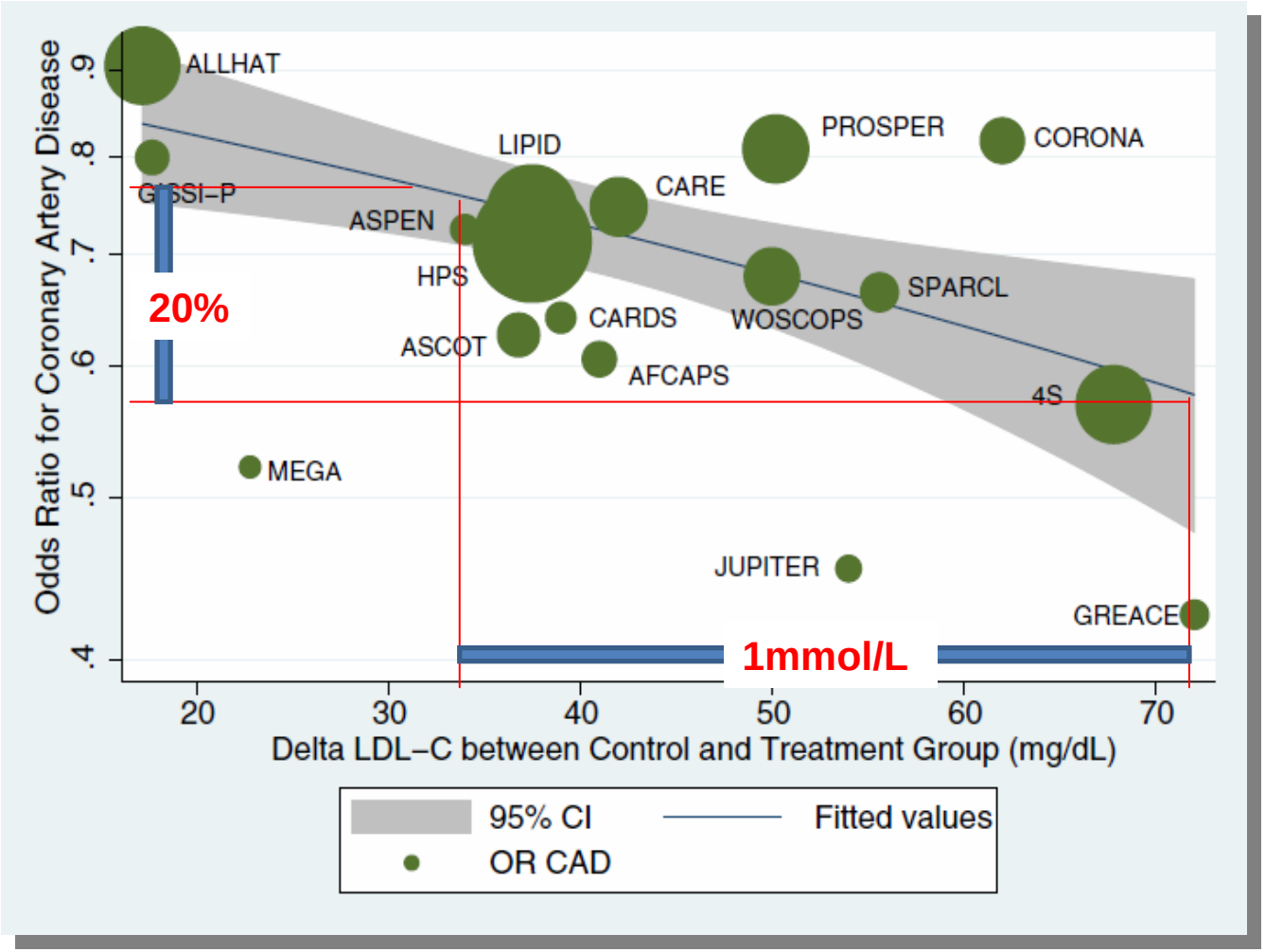
Reus


PITAVASTATI
N

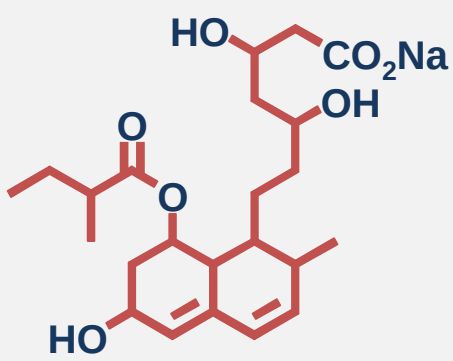
Relation of Low-Density Lipoprotein Cholesterol Reduction to Risk of Coronary Artery Disease and Death

Meta-Regression Analysis of Large-Scale Trials of Statin Therapy

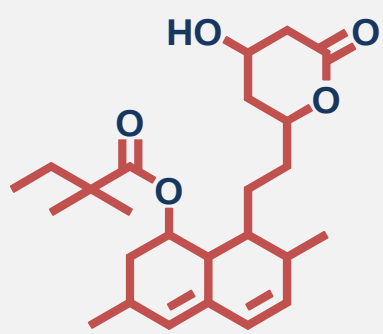


Jorge R. Kizer et al. Am J Cardiol 2010;105:1289 –1296

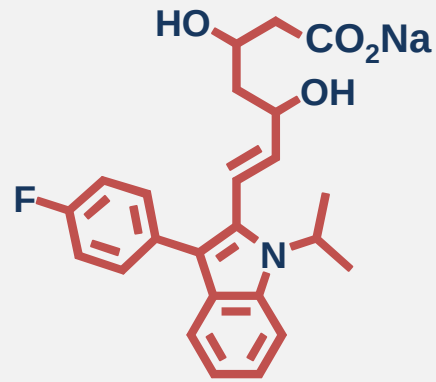
Statins vary in chemical structure



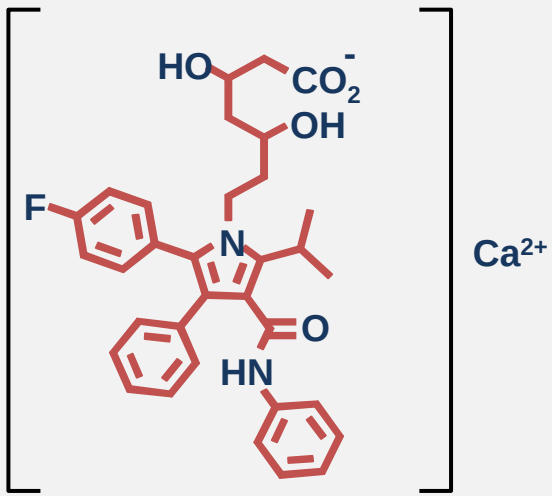
Pravastatin



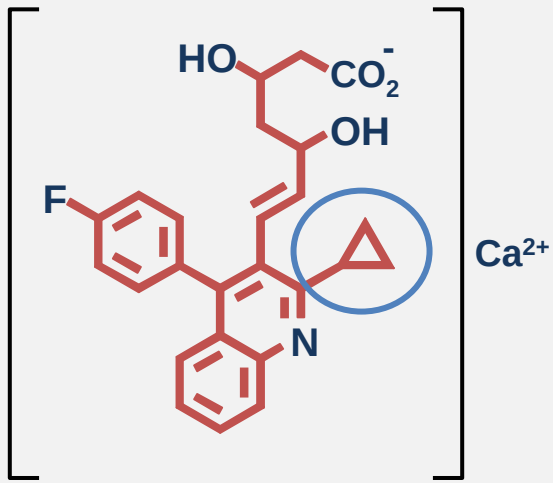
Simvastatin



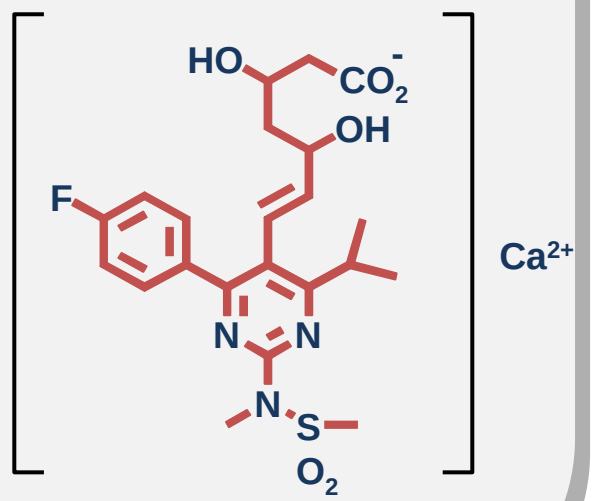
Fluvastatin



Atorvastatin

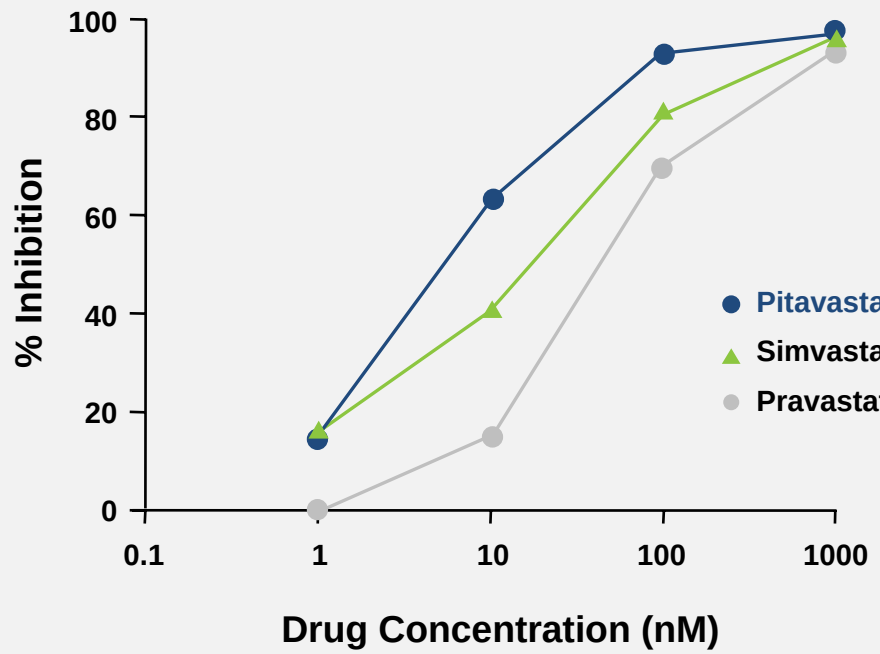


Pitavastatin



Rosuvastatin

High HMG-CoA reductase inhibition and affinity*

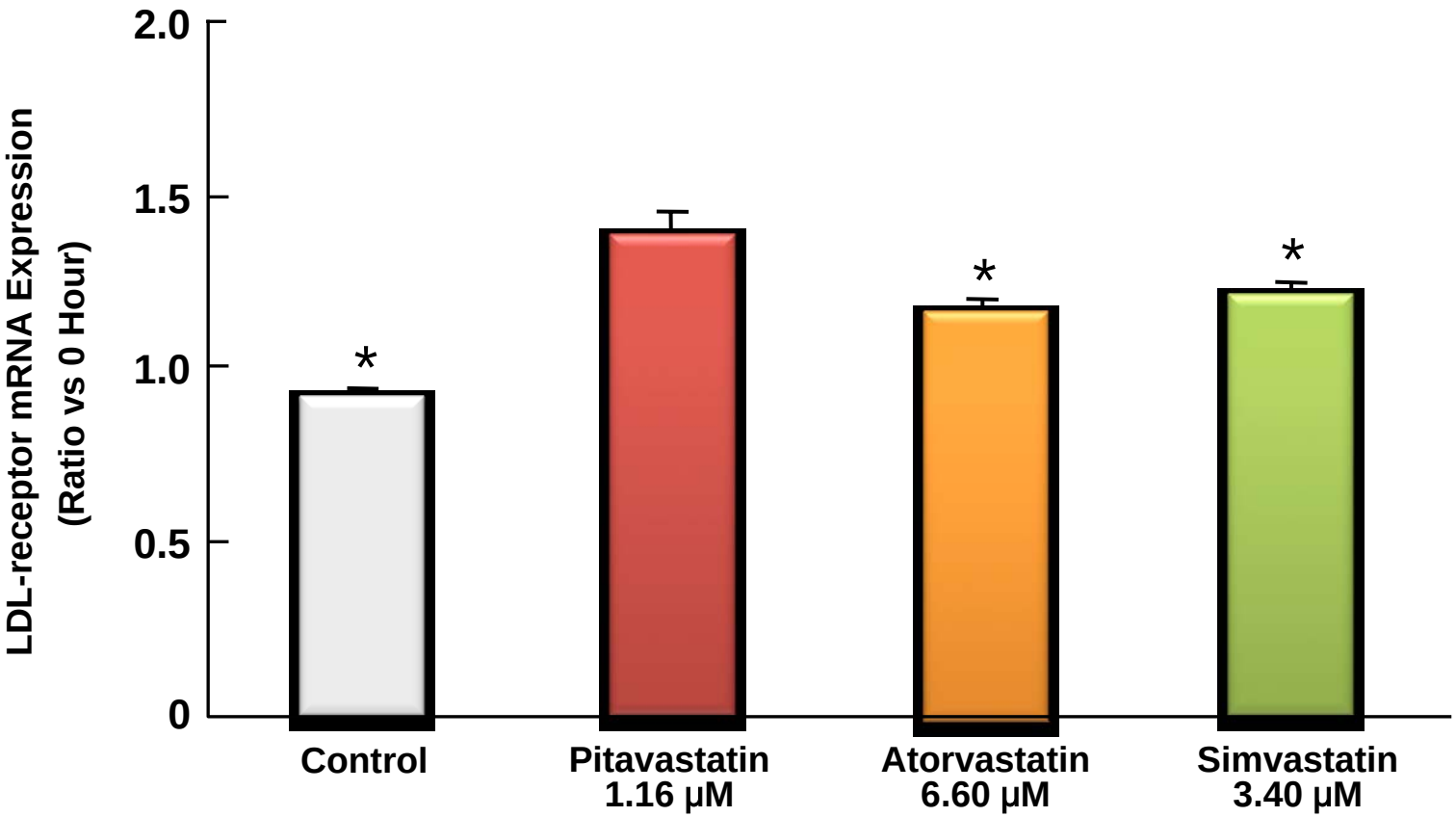


	IC_{50} (nM)	[Relative value]
Pitavastatin	6.8	[1]
Simvastatin	16	[2.4]
Pravastatin	46	[6.8]

*Rat (Wistar) liver microsomes.

Aoki. *Arzneim.-Forsch/Drug Res* 1997;47:904

Promotion of LDL-receptor mRNA expression (*in vitro*)



200 times higher than IC_{50} of cholesterol synthesis inhibitory effect

Method
Using cells derived from Hep G2, the expression of LDL-receptor mRNA was determined and compared at 12 hours after administration of each drug.

Morikawa. *J Atheroscler Thromb*. 2000;7(3):138.

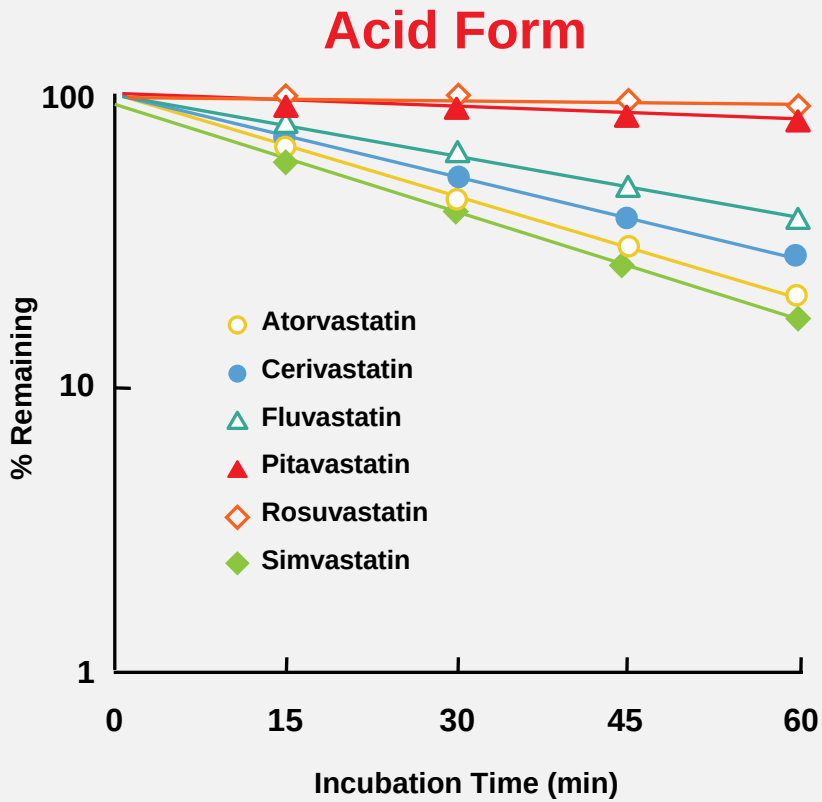
Lipophilicity, oral absorption and bioavailability

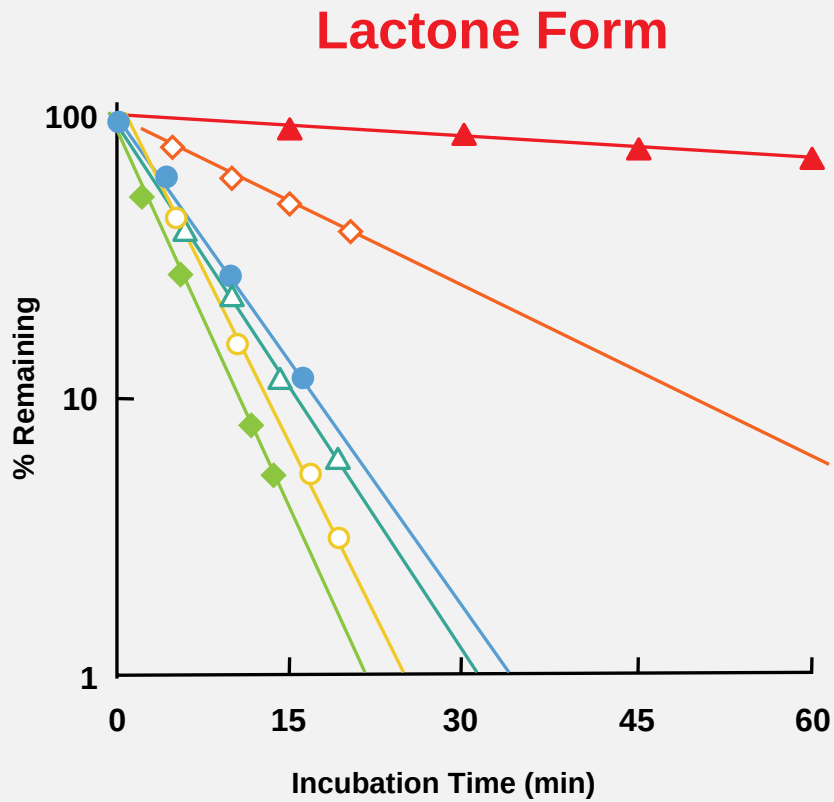
	Atorva	Fluva	Lova	Pita	Prava	Rosuva	Simva
logP (N-octanol/water partition coefficient)	1.11	1.27	1.70	1.49	-0.84	-0.33	1.60
Oral absorption (%)	30	98	31	80*	37	50*	65–85*
Absolute bioavailability (%)	12	10–35	< 5	> 60*	17	20	< 5*

*Not affected by food

Modified from Mukhtar RYL *et al*. *Intl J Clin Pract* 2005;59(2):239-252

Metabolic stability of statins in human hepatic microsomes





Metabolic stability of statins in human hepatic microsomes: (A) acid form and (B) lactone form (substrate concentration: 2.5 µM, microsomal protein concentration for acid forms: 1 mg protein/mL^{-1}, pitavastatin lactone: 1 mg protein/mL, rosuvastatin lactone: 0.5 mg protein/mL^{-1}, fluvastatin lactone and cerivastatin lactone: 0.25 mg protein/mL^{-1}, atorvastatin lactone and simvastatin: 0.1 mg protein/mL^{-1}). Data are derived from duplicate determinations.

Fujino. *Xenobiotica* 2004;34(11/12):961

Parent and lactone forms of statins and CYP isoform involvement

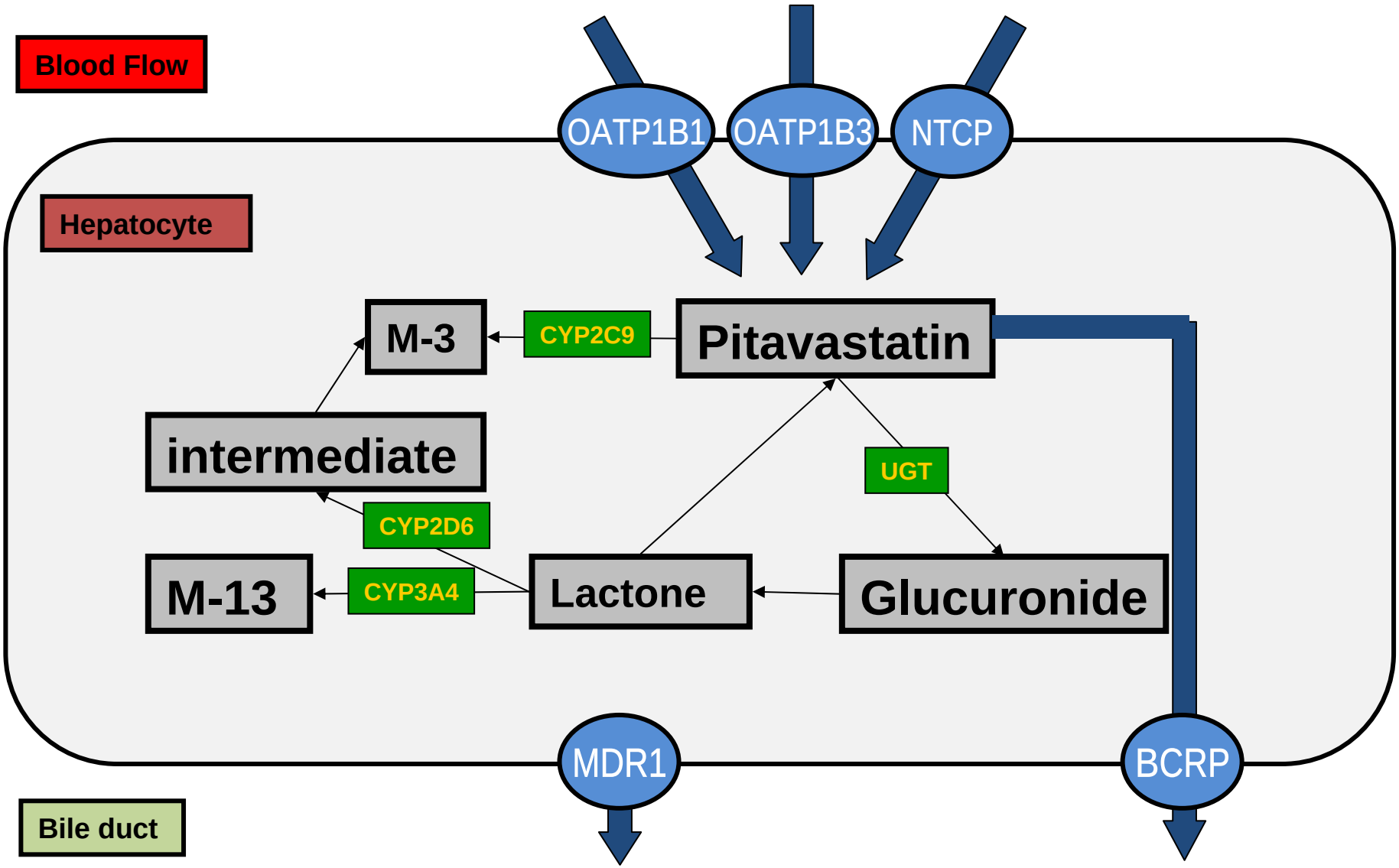
	Metabolic Clearance* (Cl_{int}) (µL min^{-1} mg^{-1} protein)			CYP Enzymes	
Statin	**Acid Form**	**Lactone Form**	**CL_{int} Ratio (lactone/acid)**	**Acid Form**	**Lactone Form**
Atorvastatin	26	1892	73	CYP3A4	CYP3A4
Simvastatin	28	1959	70	CYP3A4	CYP3A4
Cerivastatin	21	622	30	CYP2C8	CYP3A4
				CYP3A4	
Fluvastatin	33	226	7	CYP2C9	CYP3A4
				CYP3A4†	
Rosuvastatin	1.1	70.7	64	CYP2C9	CYP3A4
				CYP7C19	CYP2C9†
					CYP2D6†
Pitavastatin	2.5	5.4	2	CYP2C9	CYP3A4
				CYP2C8	CYP2D6†

*Substrate concentration: 2.5 µM.

†Minor involvement.

Fujino. *Xenobiotica* 2004;34(11/12):961

Distribution and metabolism of pitavastatin



Hirano M, et al. *J Pharmacol Exp Ther* 2004;311:139-146

Hepatic OATP Involved in Statin Uptake

Human Hepatic OATP				
Statin	**OATP1B1**	**OATP1B3**	**OATP1A2**	**OATP2B1**
Simvastatin	✔	-	-	-
Lovastatin	*	-	-	-
Atorvastatin	✔	-	-	-
Fluvastatin	✔	✔	-	✔
Cerivastatin	✔	-	-	-
Pitavastatin	✔	✔	-	✔
Pravastatin	✔	✔	-	✔
Rosuvastatin	✔	✔	✔	✔

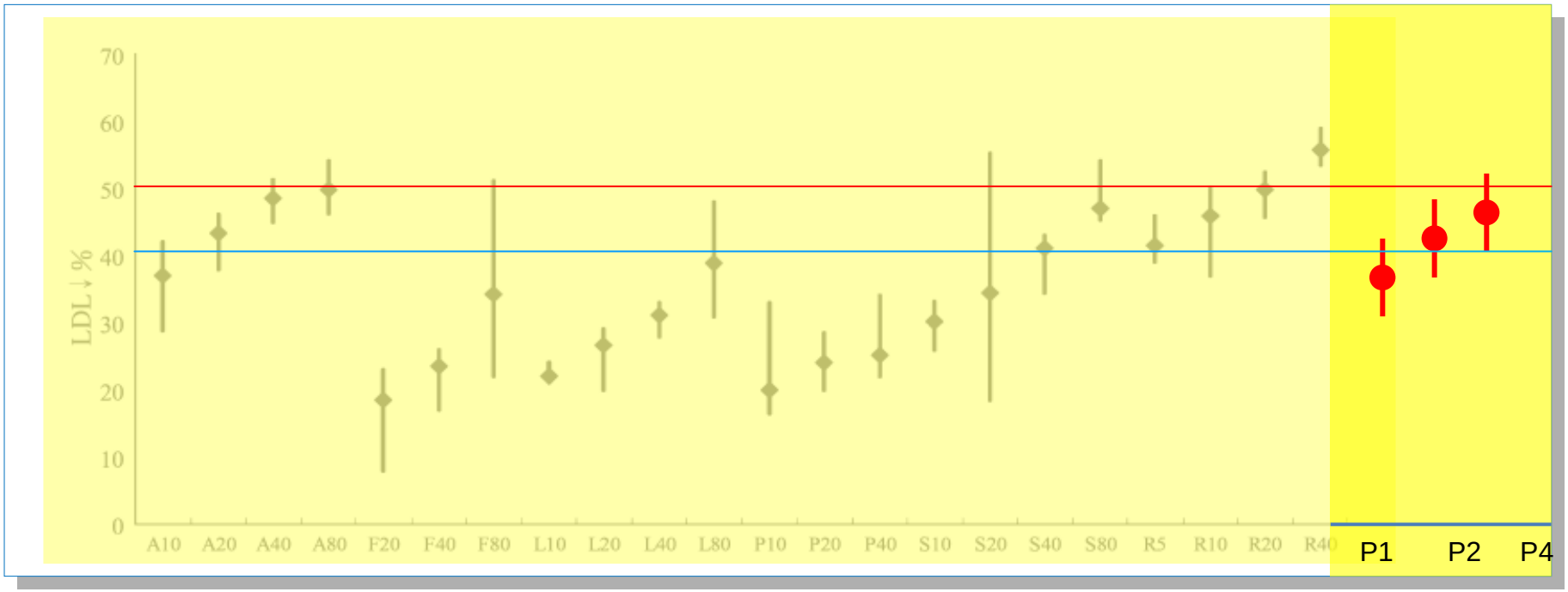
✓ Data in publications, **–** No data available, † Author's own data, ***** Inhibits OATP1B1-mediated transport of a model substrate.

Adapted from Poirier. *Curr Opin Drug Discov Devel* 2007


Eficaz reducción LDL
Efecto sobre perfil lipídico
Efectos clínicos
Valor añadido
Seguridad y tolerancia

LDL Lowering Potency

A systematic review and meta-analysis on the therapeutic equivalence of statins. LDL

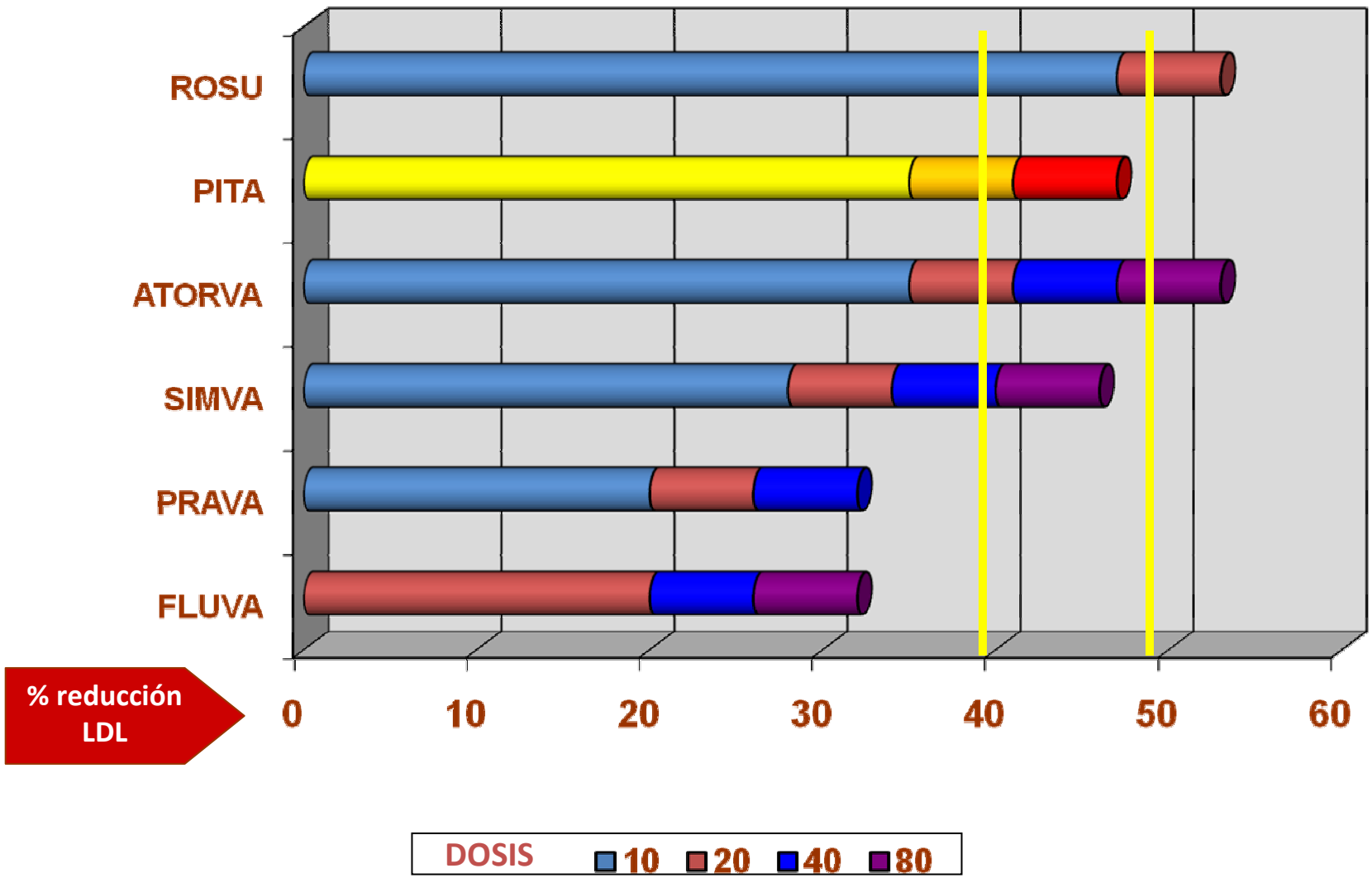


ATOR **FLUVA** **LOVA** **PRAVA** **SIMVA** **ROSU** **P ITA**

Journal of Clinical Pharmacy and Therapeutics (2010) 35, 139–151

Int J Clin Pract, February 2005, 59, 2, 239–252

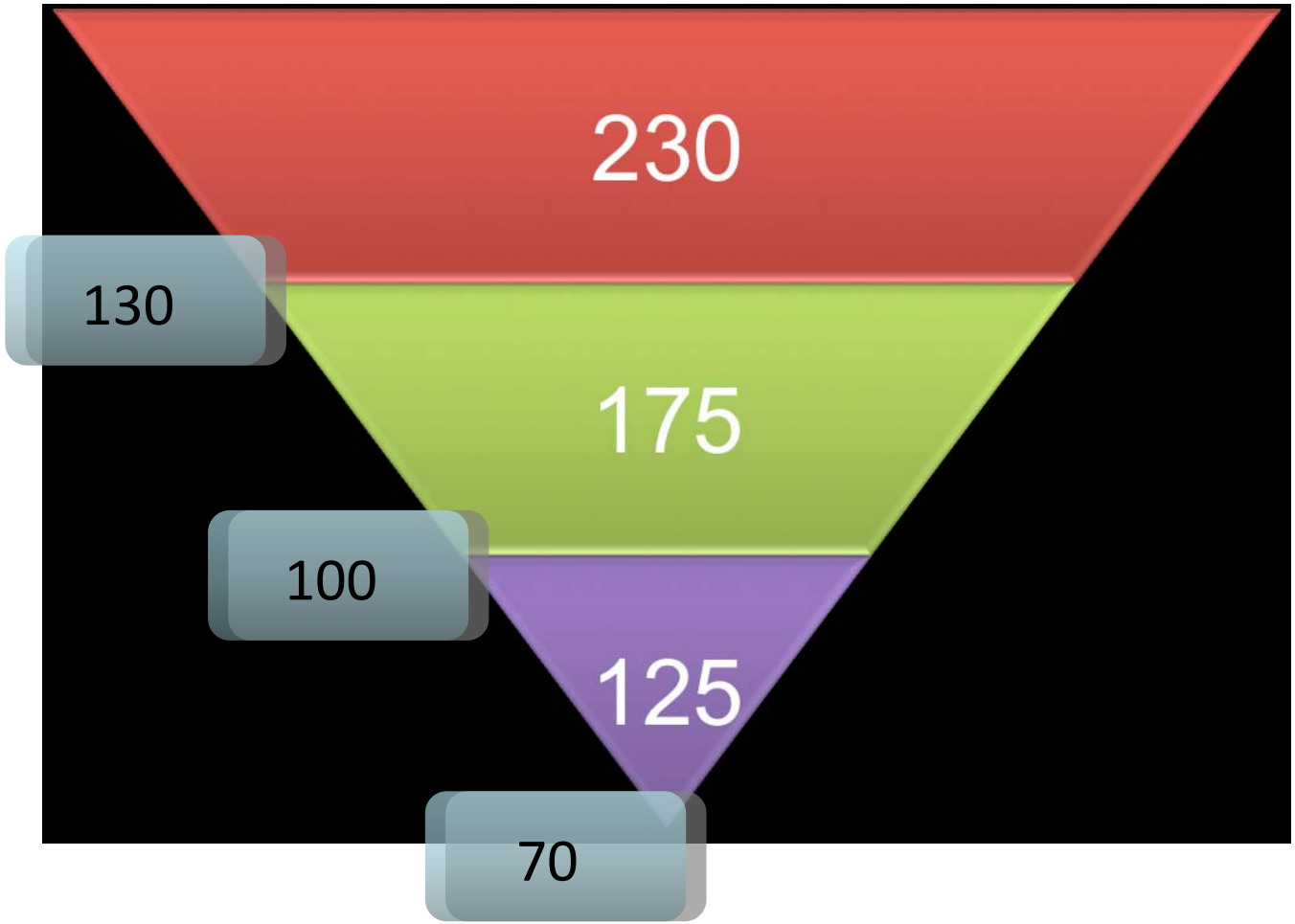
LDL Lowering Potency



Reckless J.P.D et al. Int J Clin Pract, 2005, 59, 2, 239–252
McKenney JM et al. Curr Med Opin 2003; 19: 689–98
Schaefer EJ et al. Am J Cardiol 2004; 93: 31–9.

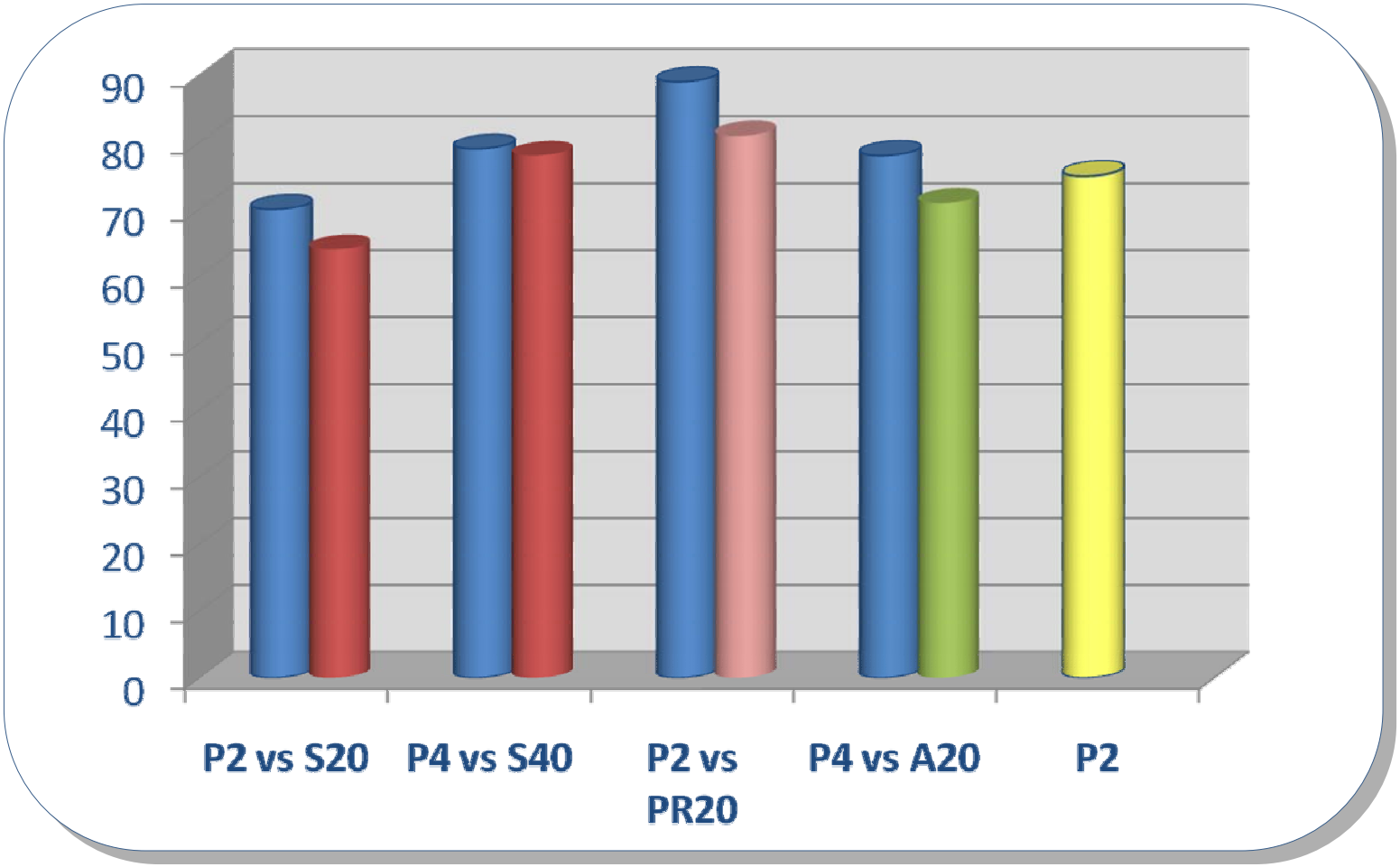
LDL Lowering Potency

PITAVASTATIN will put on target patients with the following Initial LDL concentrations



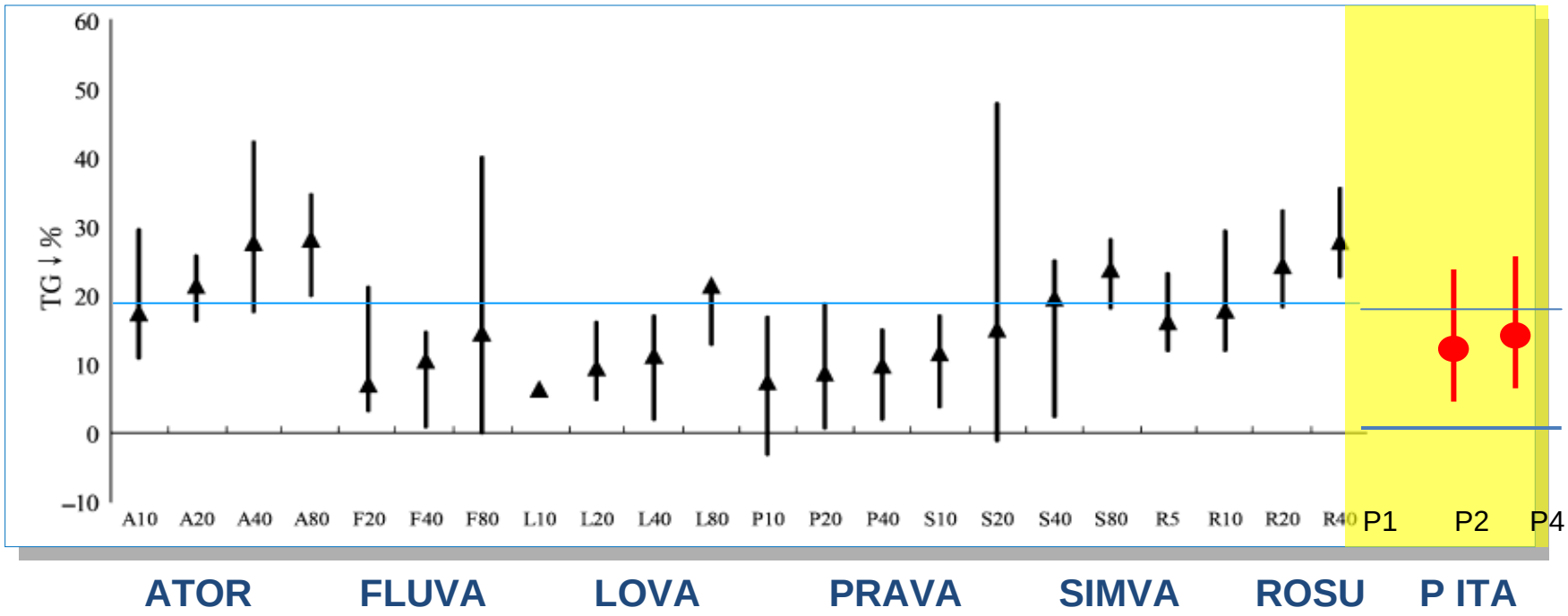
LDL Lowering Potency

Three out of Four patients on PITAVASTIN achieve LDL targets regardless of age, gender or clinical setting



1. Ose L, *et al. Curr Med Res Opin*. 2009;25(11):2755-64
2. Stender S, *et al. Atherosclerosis* Supplements 2009;10(2):P770
3. Graham I, *et al. Atherosclerosis* 2007;194:1-45

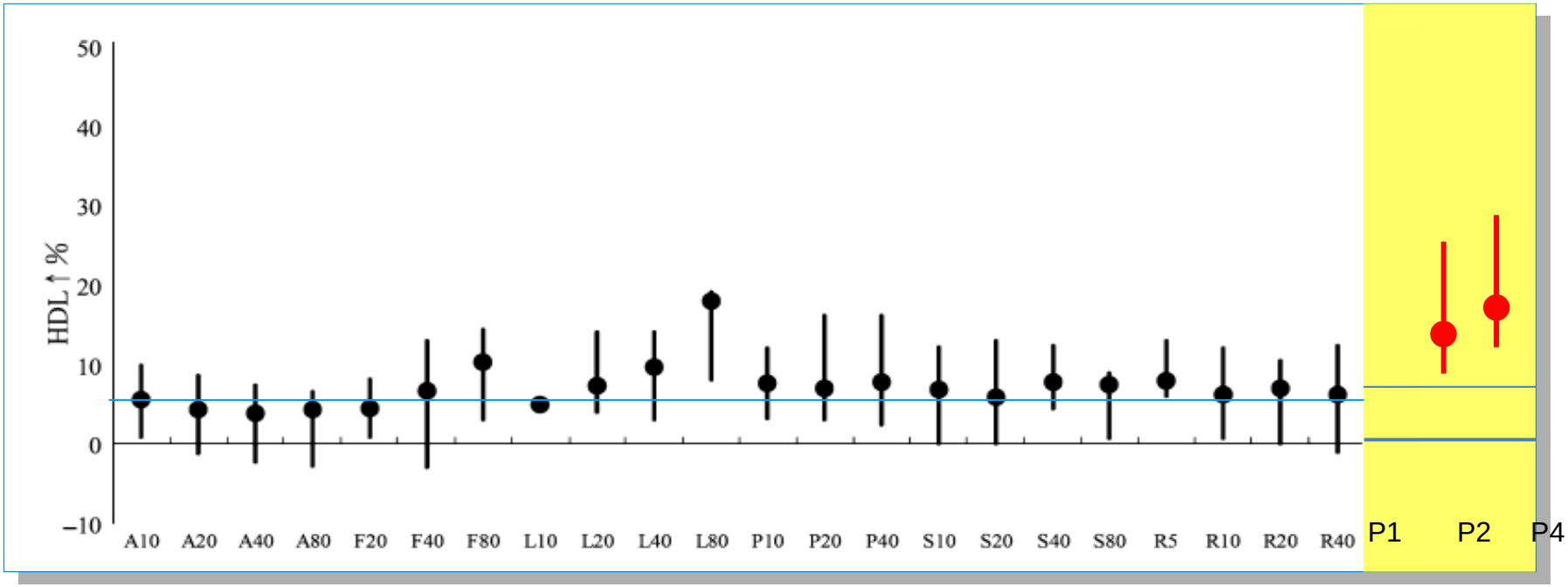
A systematic review and meta-analysis on the therapeutic equivalence of statins. TG



Journal of Clinical Pharmacy and Therapeutics (2010) 35, 139–151

Int J Clin Pract, February 2005, 59, 2, 239–252

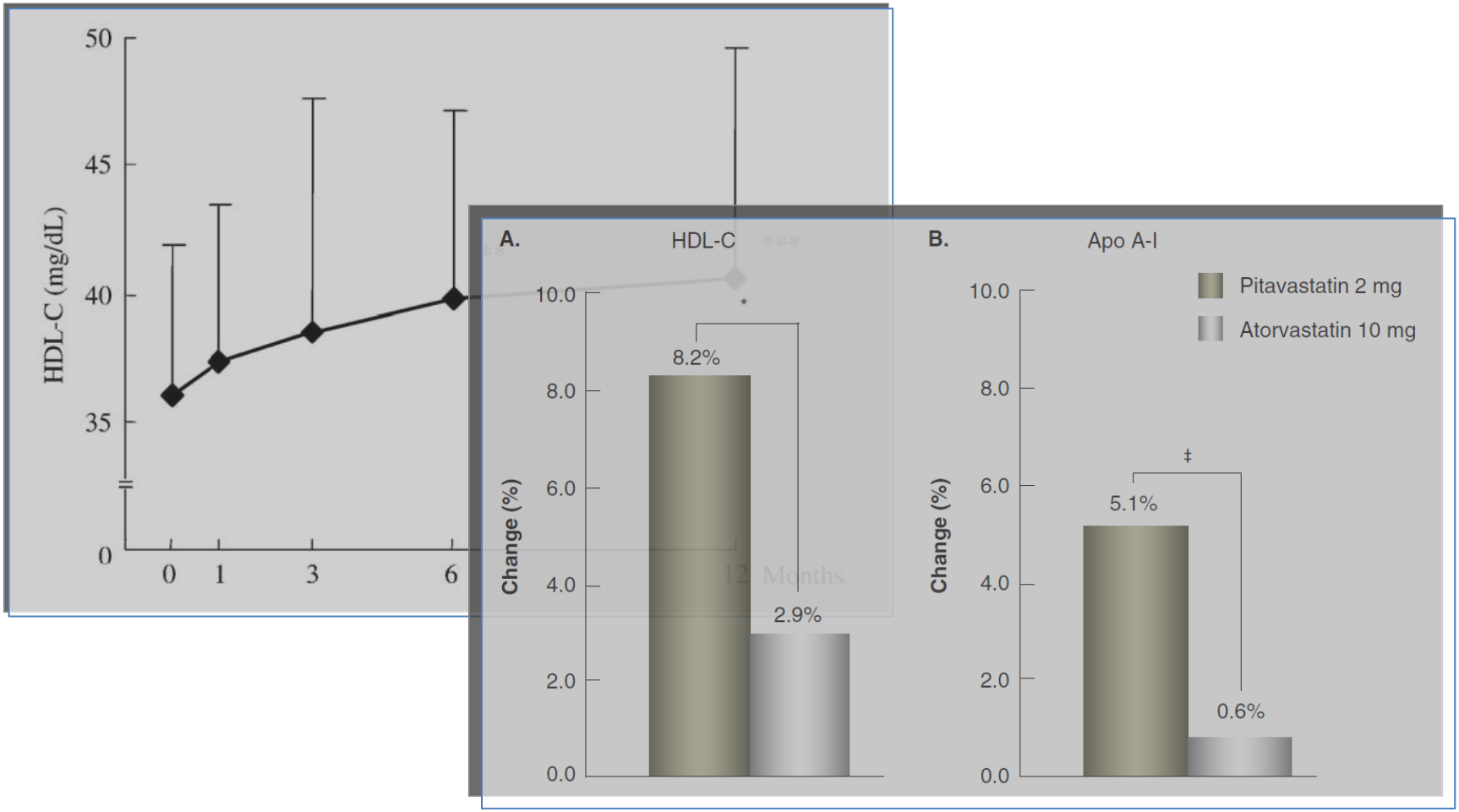
A systematic review and meta-analysis on the therapeutic equivalence of statins. HDL



Journal of Clinical Pharmacy and Therapeutics (2010) 35, 139–151

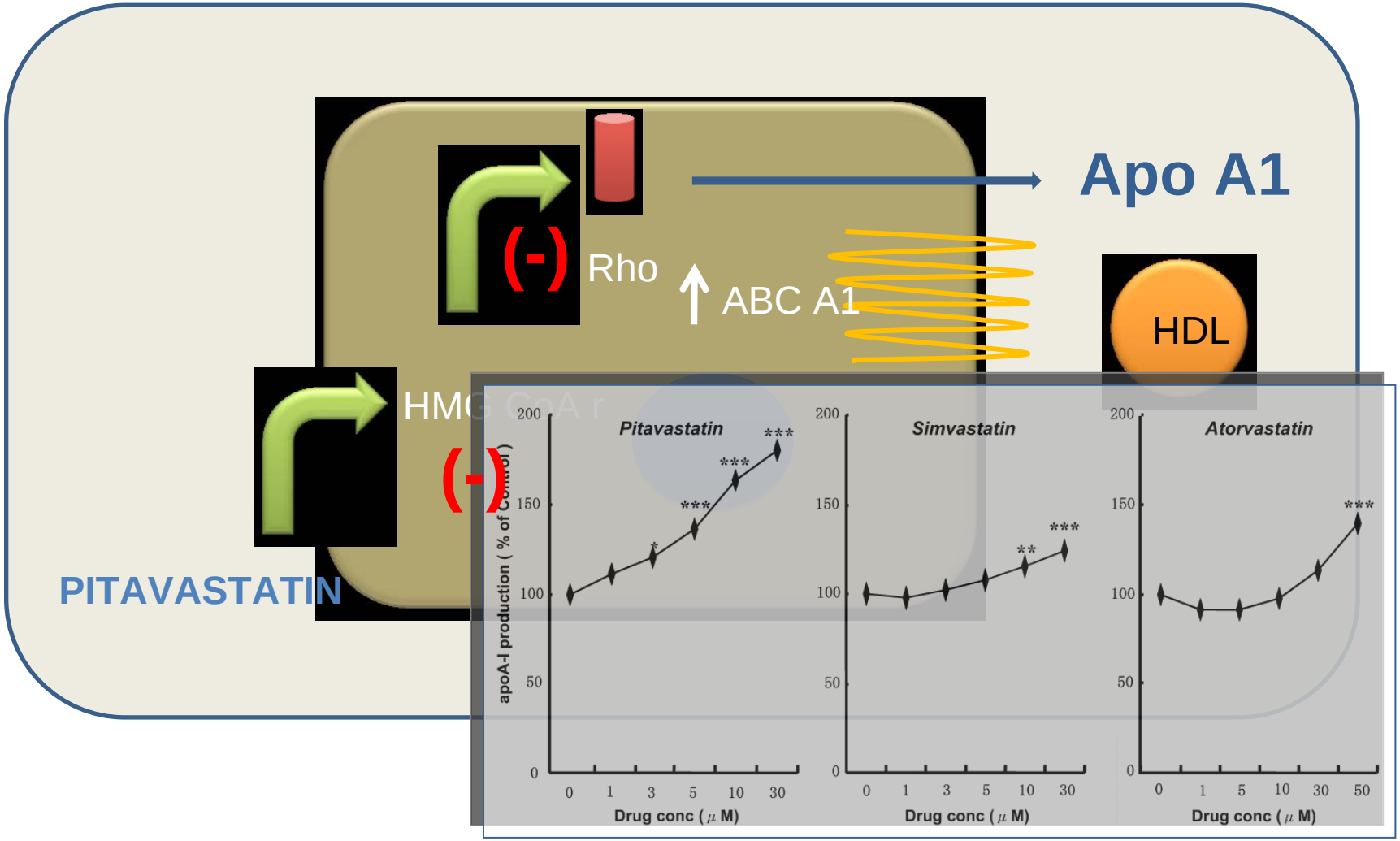
Int J Clin Pract, February 2005, 59, 2, 239–252

HDL-C and apolipoprotein A-I are persistently elevated during long-term treatment with PITAVASTATIN



Fukutomi T, et al, Int J Cardiol (2009),doi:10.1016/j.ijcard.2008.11.1
Tamio T et al. Expert Opin. Pharmacother. 2010 11:817-828
Sasaki J et al . Clin Ther 2008;30:1089-101

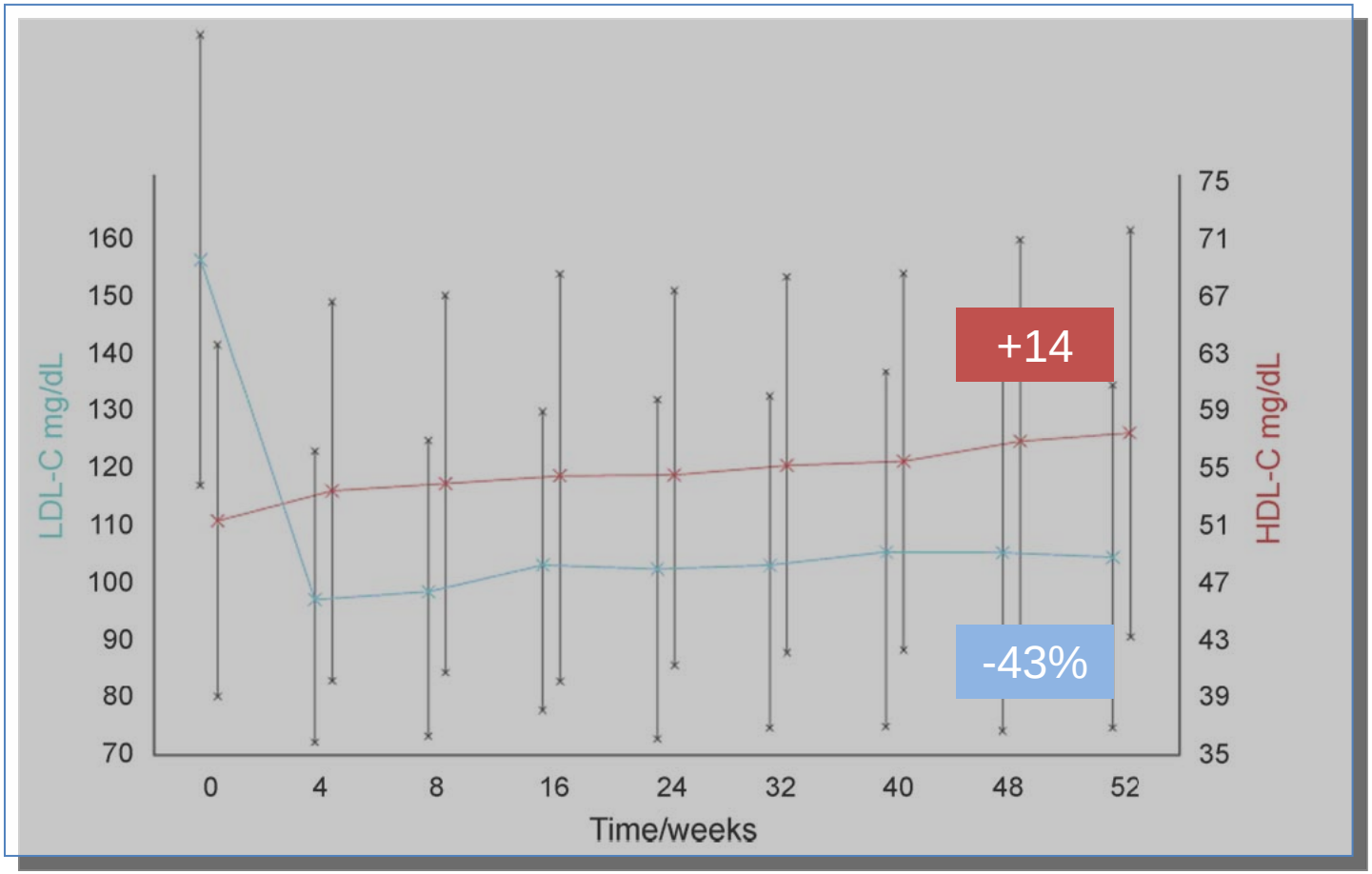
Pitavastatin enhance apo A-I production in HepG2 cell



pitavastatin (3μM) > simvastatin (10μM) > atorvastatin (50μM)

Maejima T *et al Biochem. Biophys. Res. Commun. 324, 835–839 (2004).*

Long-term treatment with pitavastatin is effective and well tolerated by patients with primary hypercholesterolemia or combined dyslipidemia



Atherosclerosis 210 (2010) 202–208

PITAVASTATIN improves lipid profile globally

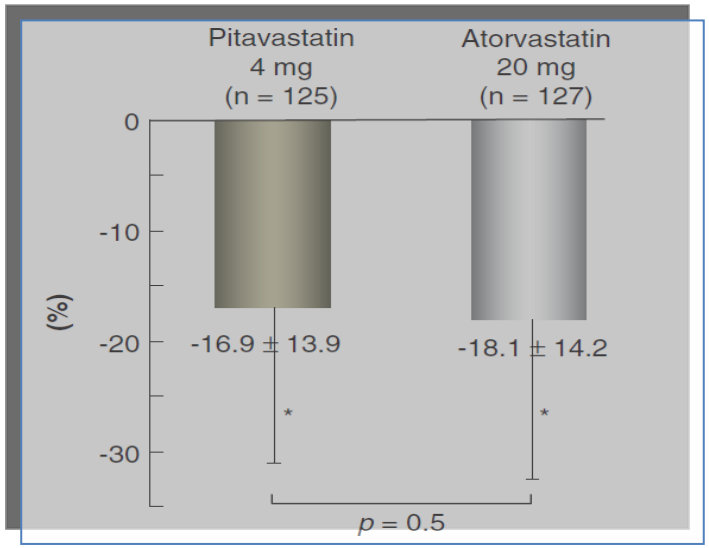
1353 patients – 52 weeks follow-up

Leiv Ose et al Atherosclerosis 2010

* Takafumi Hiro et al J Am Coll Cardiol 2009;54:293–302

Clinical outcomes

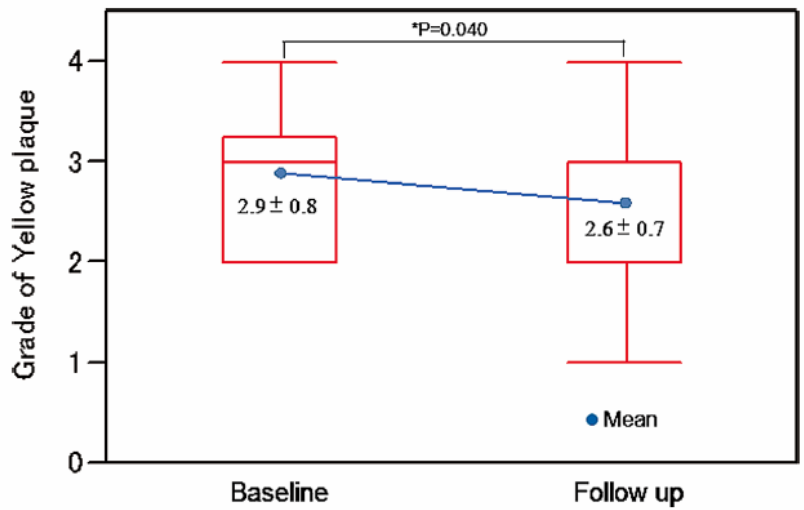
No clinical outcome data yet



On going: LIVES extension study

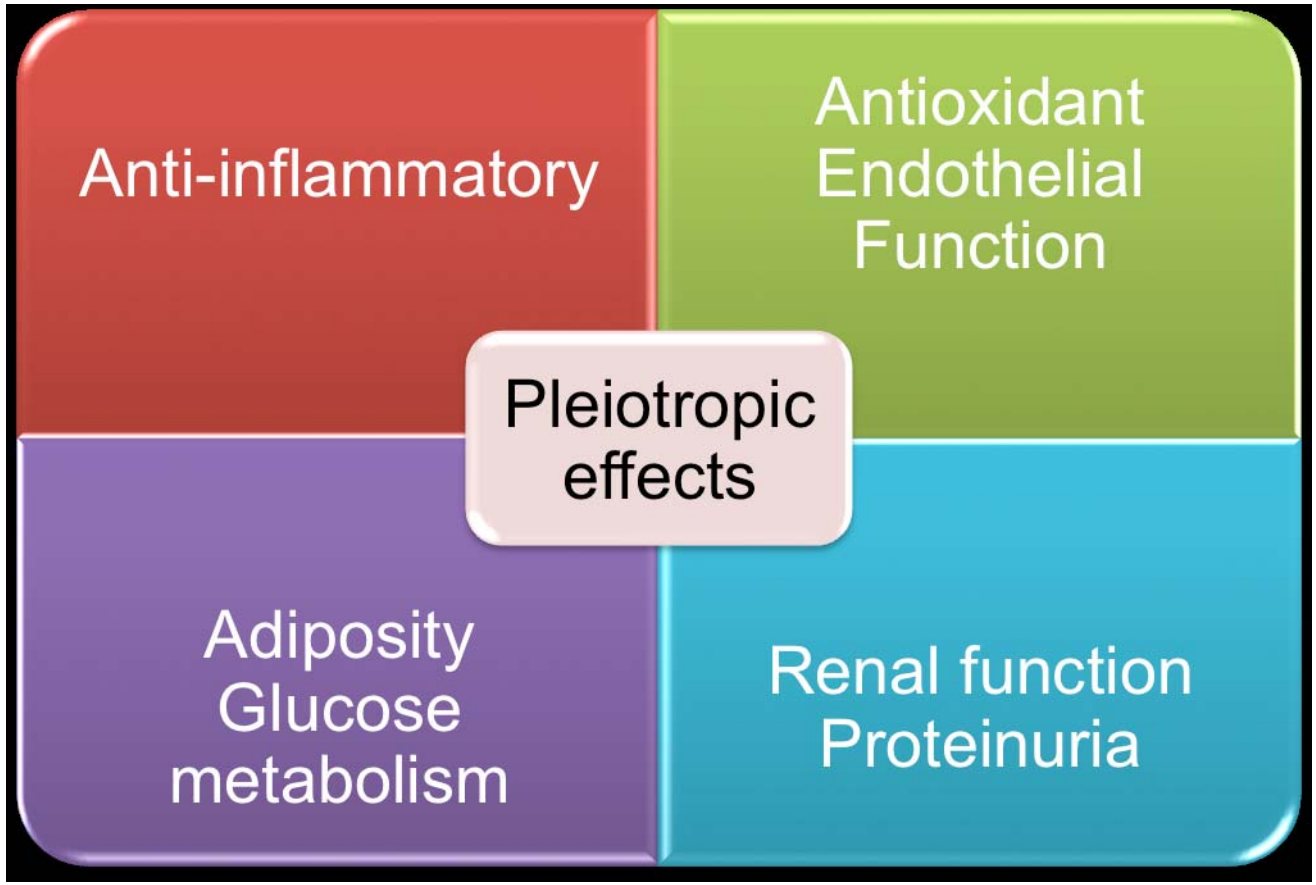
Changes in plaque volume in JAPAN-ACS study

Comparison of yellow grade at baseline and week 52 in the TOGETHAR trial

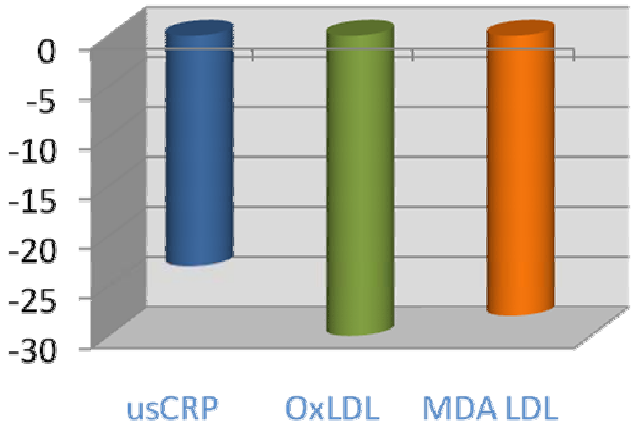


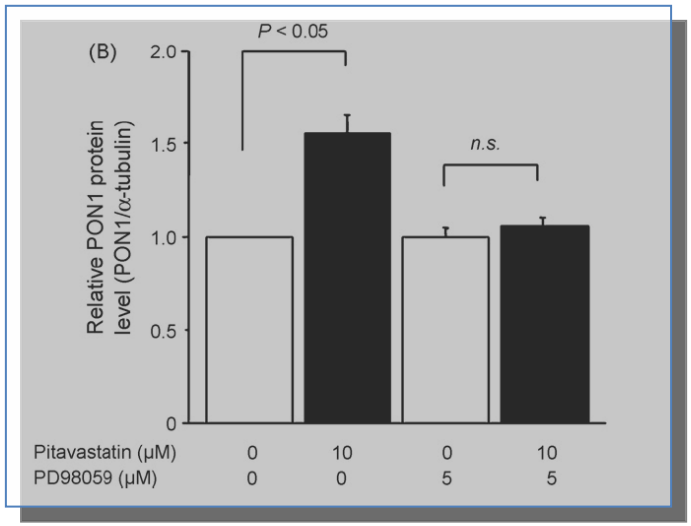
Takafumi Hiro et al J Am Coll Cardiol 2009;54:293–302
Tamio T et al. Expert Opin. Pharmacother. 2010 11:817-828
Kodama J et al . Circ J . 2010

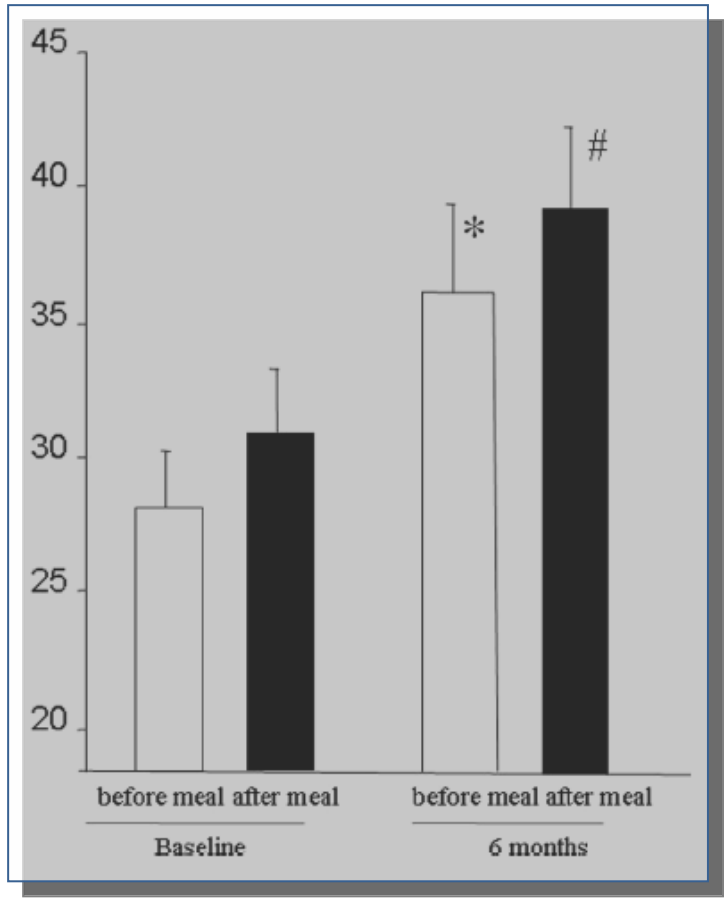
Added value


Anti-inflammatory
Antioxidant
Endothelial
Function
Pleiotropic
effects
Adiposity
Glucose
metabolism
Renal function
Proteinuria

Added value







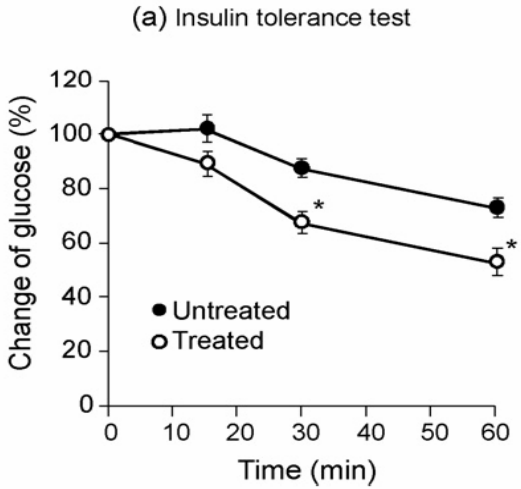
Effects of Pitavastatin on Fasting and Postprandial Endothelial Function (FMD) in CAD patients

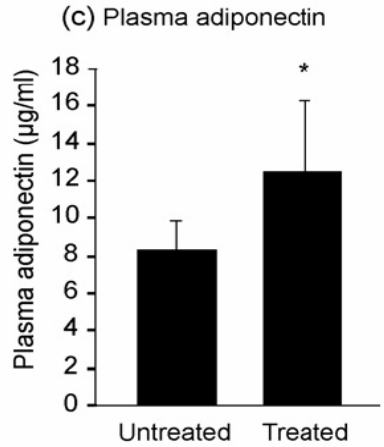
Motomura T et al. J Ather Throm 2009, 16
Arii K et al. Atherosclerosis 202 (2009) 439–445

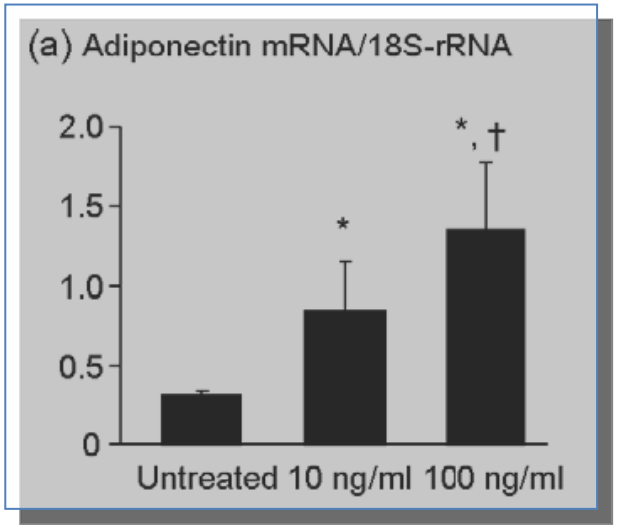
Leiv Ose et al. Atherosclerosis 210 (2010) 202–208
Kenshiro Arao et al. Circ J 2009; 73: 1523 – 1530

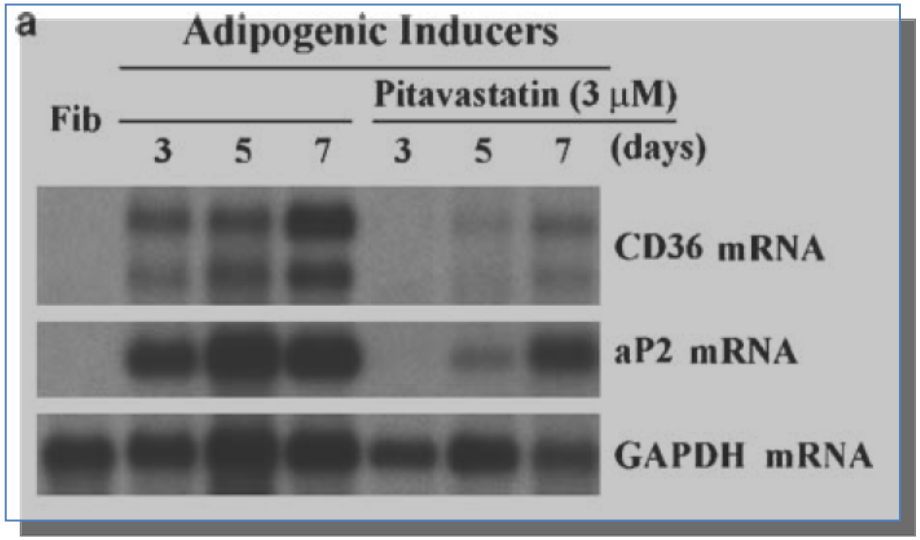
Added value

Beneficial direct adipotropic actions of PITAVASTATINA. Cell and animal models



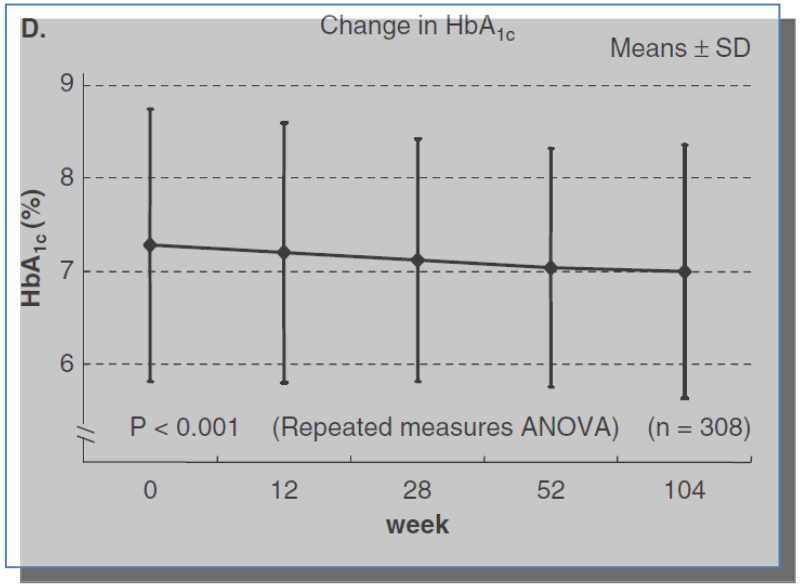






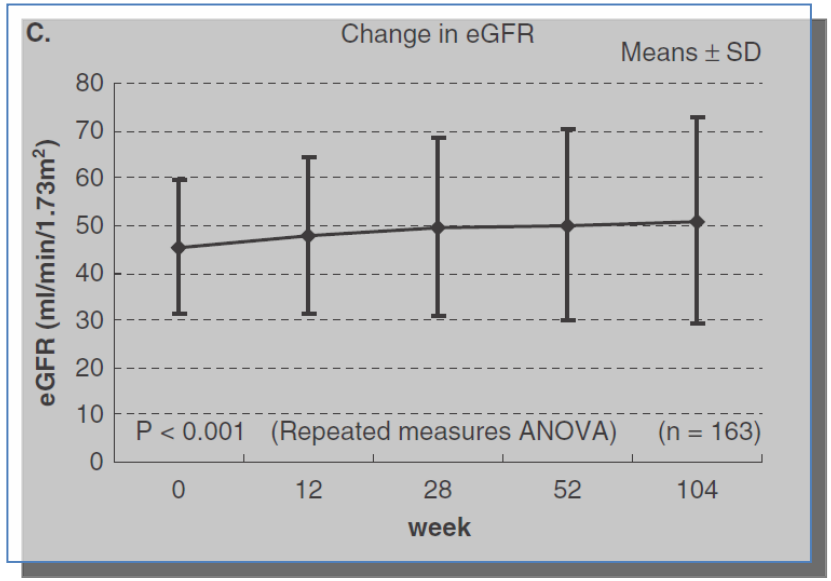
Yasuhiro Ishihara et al. Atherosclerosis 2010 ; AC Nicholson et al. British Journal of Pharmacology (2007) 151, 807–815;

Added value



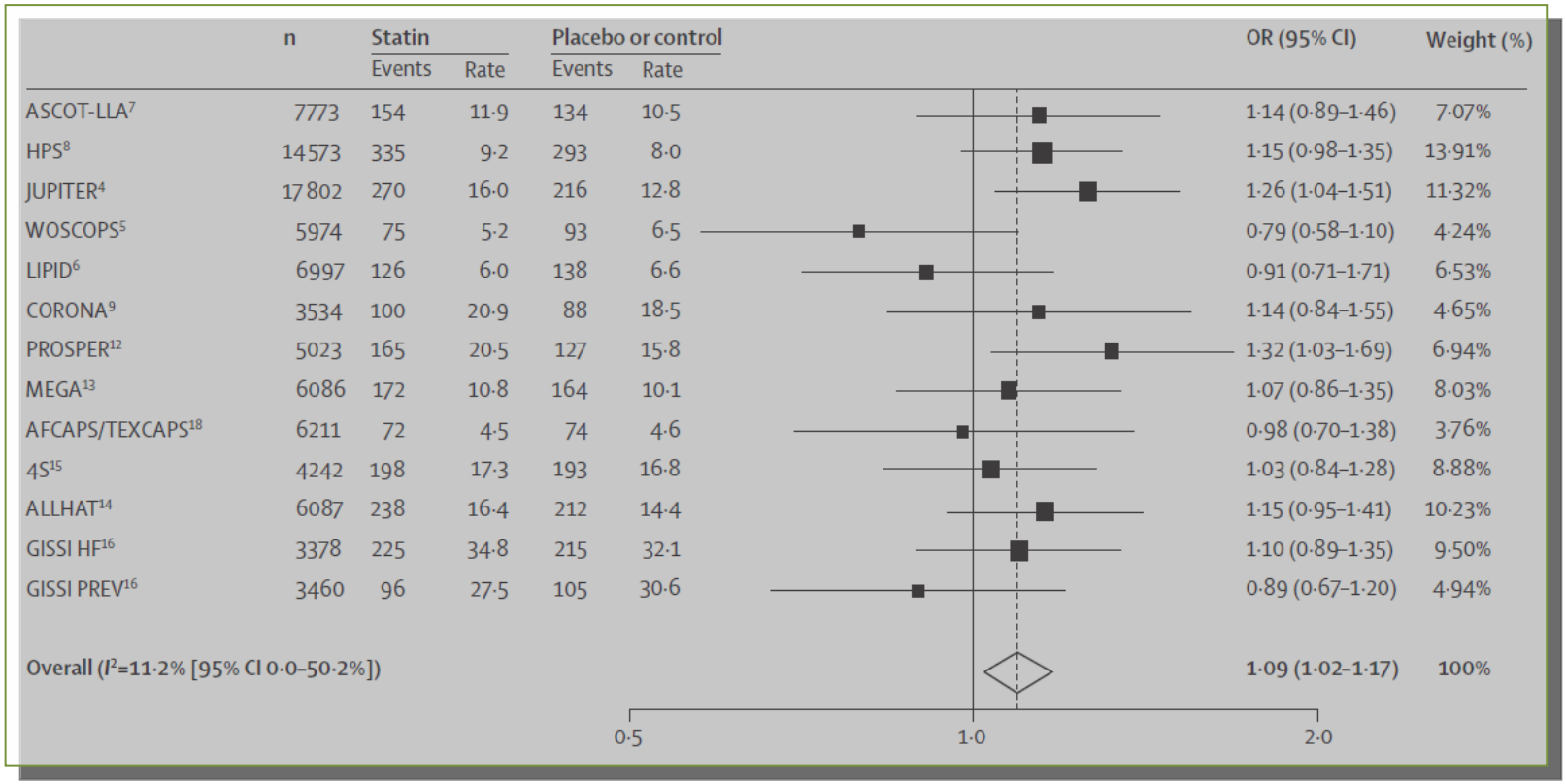
HbA1c decreased after 104 weeks of treatment with PITAVASTATIN

eGFR increased after 104 weeks of treatment with PITAVASTATIN



Kimura K et al. J Ath Throm 2010; 17: 601-9
Tamio T et al. Expert Opin. Pharmacother. 2010 11:817-828

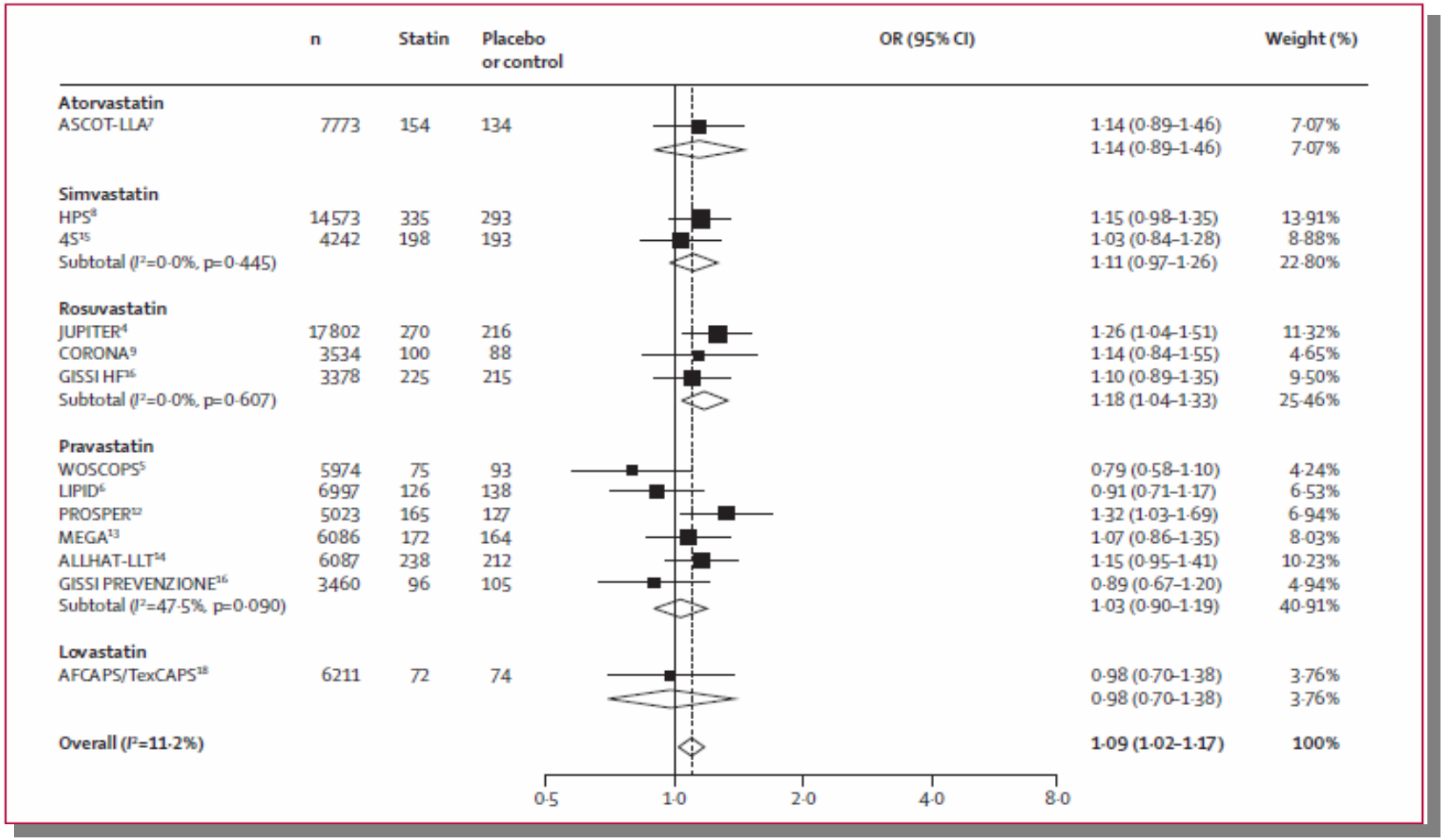
Association between statin therapy and incident diabetes in 13 major cardiovascular trials



	n	Statin		Placebo or control		OR (95% CI)	Weight (%)
		Events	Rate	Events	Rate		
ASCOT-LLA[7]	7773	154	11·9	134	10·5	1·14 (0·89–1·46)	7·07%
HPS[8]	14573	335	9·2	293	8·0	1·15 (0·98–1·35)	13·91%
JUPITER[4]	17802	270	16·0	216	12·8	1·26 (1·04–1·51)	11·32%
WOSCOPS[5]	5974	75	5·2	93	6·5	0·79 (0·58–1·10)	4·24%
LIPID[6]	6997	126	6·0	138	6·6	0·91 (0·71–1·71)	6·53%
CORONA[9]	3534	100	20·9	88	18·5	1·14 (0·84–1·55)	4·65%
PROSPER[12]	5023	165	20·5	127	15·8	1·32 (1·03–1·69)	6·94%
MEGA[13]	6086	172	10·8	164	10·1	1·07 (0·86–1·35)	8·03%
AFCAPS/TEXCAPS[18]	6211	72	4·5	74	4·6	0·98 (0·70–1·38)	3·76%
4S[15]	4242	198	17·3	193	16·8	1·03 (0·84–1·28)	8·88%
ALLHAT[14]	6087	238	16·4	212	14·4	1·15 (0·95–1·41)	10·23%
GISSI HF[16]	3378	225	34·8	215	32·1	1·10 (0·89–1·35)	9·50%
GISSI PREV[16]	3460	96	27·5	105	30·6	0·89 (0·67–1·20)	4·94%
Overall (I^2=11·2% [95% CI 0·0–50·2%])						**1·09 (1·02–1·17)**	**100%**

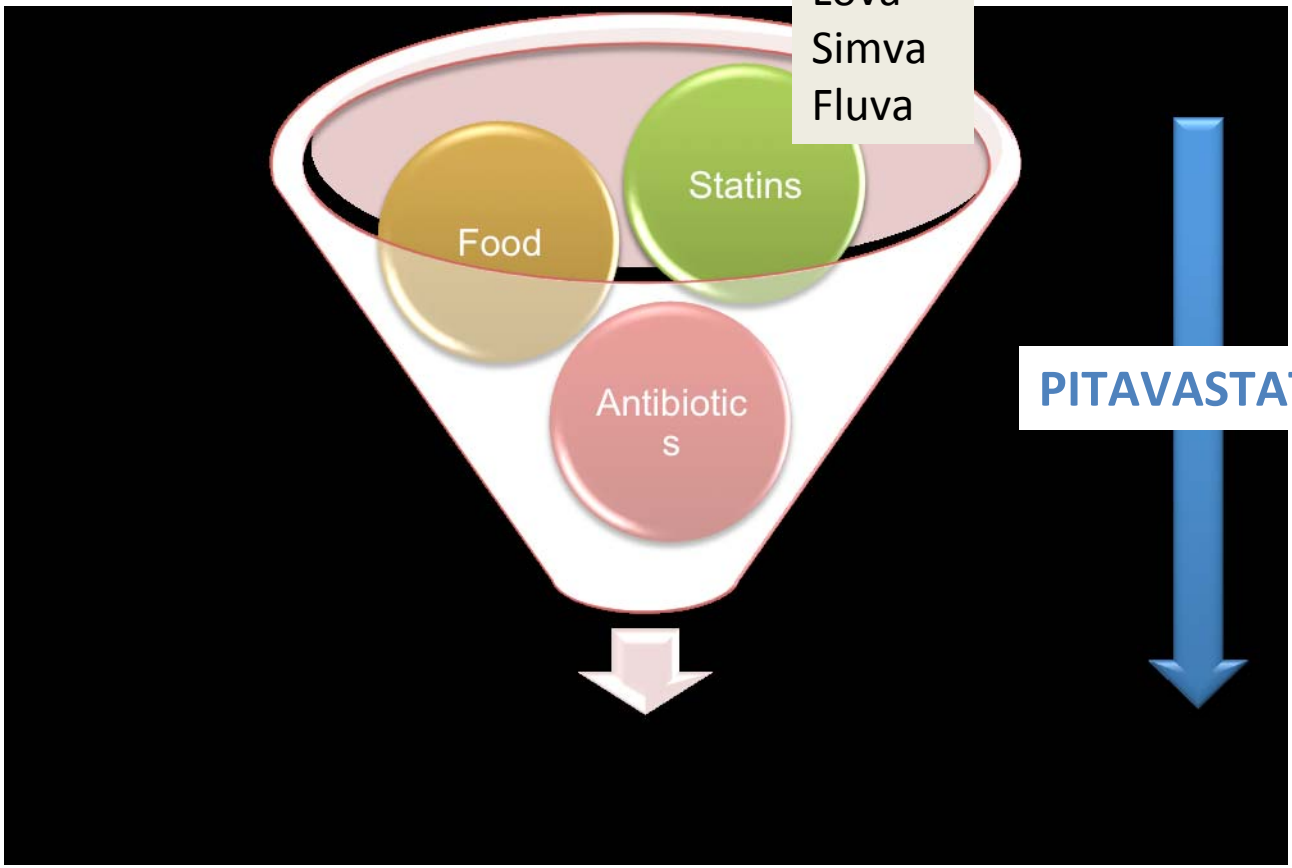
Naveed Sattar et al. Lancet 2010, 375: 735-42

Association between statin therapy and incident diabetes in 13 major cardiovascular trials



Naveed Sattar et al. Lancet 2010, 375: 735-42

Safety and tolerability

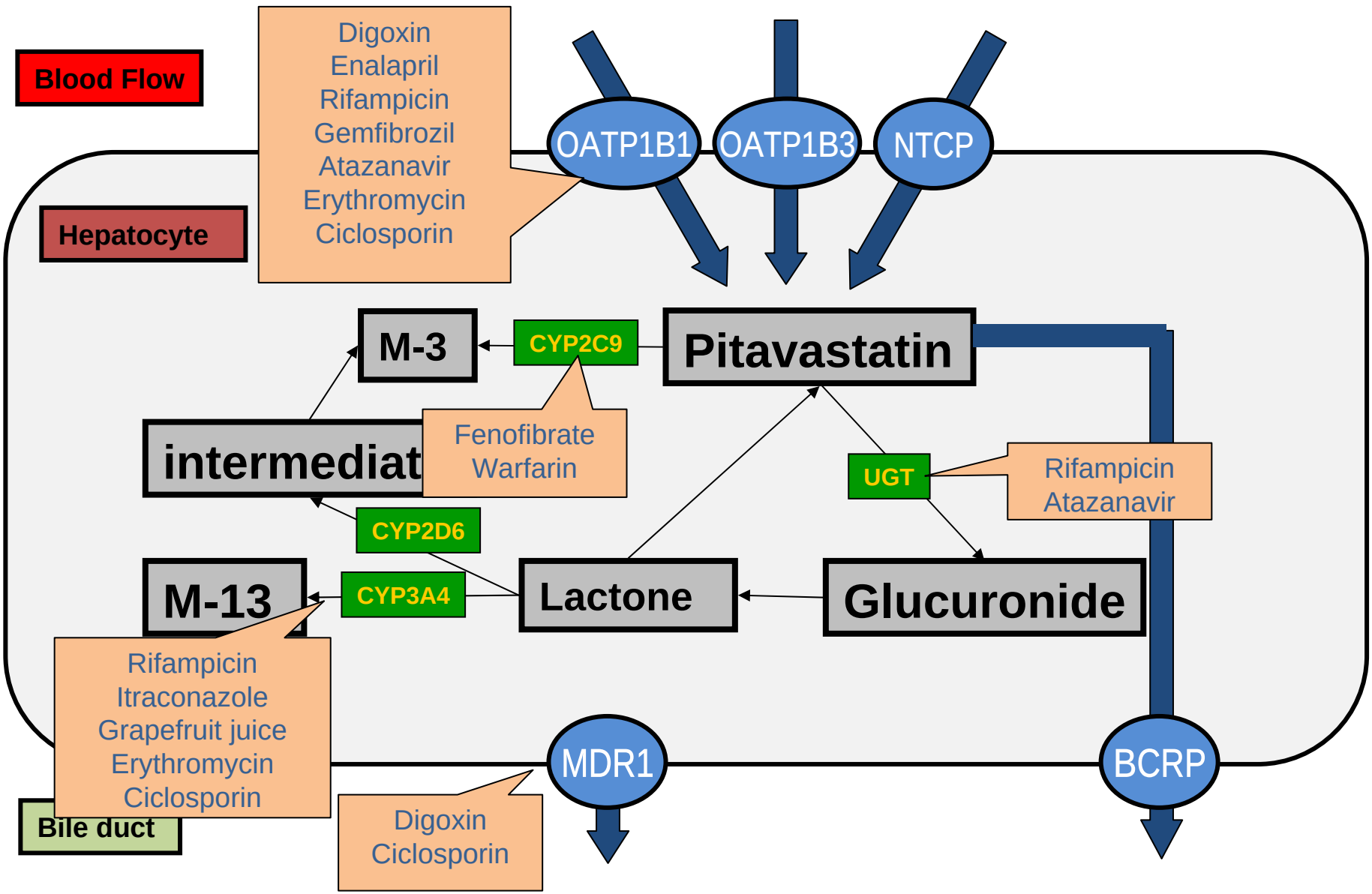


Atorva
Lova
Simva
Fluva

PITAVASTATIN

Rosu
Prava

Distribution and metabolism of pitavastatin



Hirano M, et al. *J Pharmacol Exp Ther* 2004;311:139-146

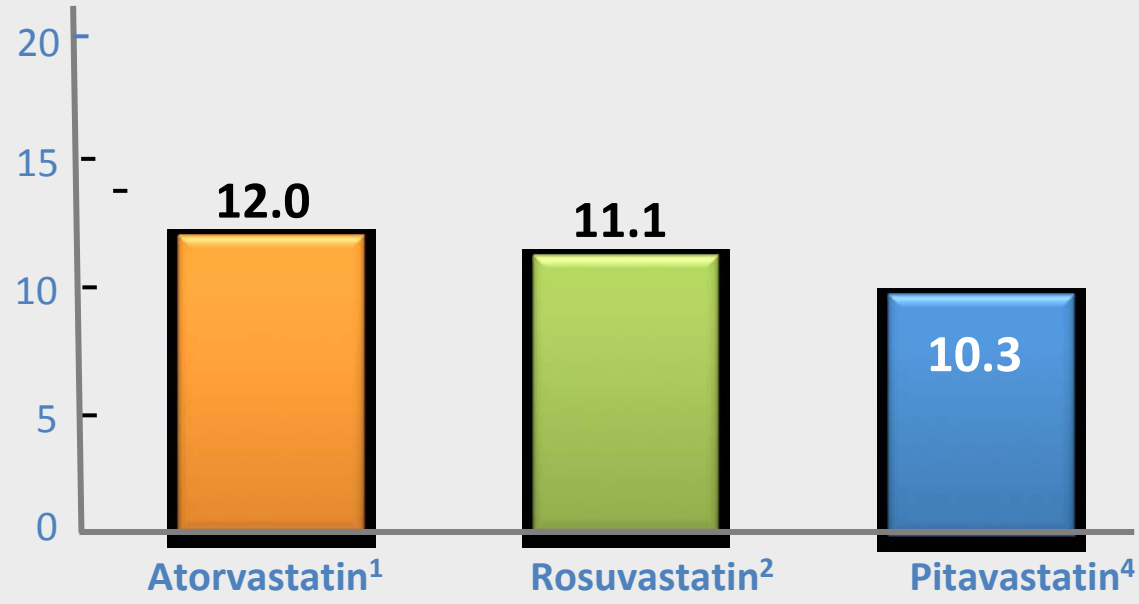
Pitavastatin: Minimal drug-drug interactions

Concomitant med	Con med→ pitavastatin	Pitavastatin →con med	Mechanism affected
Cyclosporine	**X**	–	OATP1B1, CYP3A4. MRP2, MDR1
Bezafibrate	O	–	OATP1B1
Fenofibrate	O	–	OATP1B1
Gemfibrozil	O	–	OATP1B1, CYP2C8
Grapefruit juice	O	–	CYP3A4
Warfarin	–	O	CYP2C9
Digoxin	O	O	MDR1, OATP1B3
Rifampicin	O	O	OATP1B1, UGT, CYP3A4
Enalapril	O	O	OATP1A2
Itraconazole	O	–	CYP3A4
Erythromycin	**X**	–	OATP1B1, OATP1B3

O: No/weak interaction
X: Moderate/strong interaction
–: Not tested

PGP = P-glycoprotein; OATP = organic anion-transporting polypeptides: UGT = Human UDP-glucuronosyltransferase; CYP = Cytochrome P450

Incidence of adverse drug reactions



Cases investigated (N)	4805	8795	19925
Cases with ADR (N)	576	978	2069

1. *Prog Med* 2005;25:131
2. *Prog Med* 2007;27:1159
3. *Jpn Pharmacol Ther* 2007;35:9
4. *Jpn Pharmacol Ther* 2008;36 (8):709-31

LIVES (LIVALO Effectiveness and Safety) study

Large-scale (n = 20,279), long-term (104 weeks), prospective postmarketing surveillance study of hypercholesterolemic patients treated with PITAVASTATIN

Adverse Reaction	Nº of incidences	Incidence rate (%)
Gastrointestinal	245	1.23
Myalgia	215	1.08
Myopathy	6	0.03
Rabdomyolisis	2	0.01
CK increase	545	2.74
ALT	356	1.79
AST	298	1.50
GGT	200	1

Evaluated Patients: : 19925

ADR : 2069 (10.38%)

Yuji Kurihara et al . *Jpn Pharmacol Ther* 2008;36 (8):709-31

LIVES (LIVALO Effectiveness and Safety) study

Table 5 Candidate risk factors for adverse drug reactions

Selected covariate		Hazard ratio	95% CI	*p*−value
Gender	Male/Female	1.081	(0.985 to 1.187)	0.102
Age	≧65/＜65	1.064	(0.975 to 1.162)	0.165
Familial hypercholesterolemia	Present/Absent	1.264	(0.913 to 1.748)	0.158
Concomitant liver disease	Present/Absent	1.324	(1.147 to 1.530)	＜0.001
Concomitant renal disease	Present/Absent	1.313	(1.067 to 1.616)	0.010
Concomitant diabetes mellitus	Present/Absent	1.197	(1.059 to 1.353)	0.004
History of drug allergy	Present/Absent	2.071	(1.688 to 2.541)	＜0.001
Concomitant use of SU	Present/Absent	0.892	(0.754 to 1.055)	0.182
Concomitant use of thiazolidine derivatives	Present/Absent	0.756	(0.595 to 0.961)	0.022
Concomitant use of biguanides	Present/Absent	0.705	(0.550 to 0.905)	0.006
Concomitant use of ARB	Present/Absent	0.869	(0.787 to 0.961)	0.006
Daily dosage upon first onset	2 mg/1 mg	0.921	(0.843 to 1.005)	0.065
	4 mg/1 mg	0.570	(0.335 to 0.971)	0.039

SU＝sulfonylureas. ARB＝angiotensin II receptor blockers.

Yuji Kurihara et al . *Jpn Pharmacol Ther* 2008;36 (8):709-31

•Pitavastatina es una estatina sintética, moderadamente lipofílica que se absorbe de forma amplia sin interacciones con la comida

•Prácticamente no se metaboliza y se excreta en su mayor parte por bilis y muy poco por orina.
•No interactúa con el CYP450 3 A4 por lo que tiene un buen perfil de compatibilidad con otros fármacos

•Desciende el c-LDL un 43%
•Eleva el c-HDL hasta un 14 %
•Disminuye triglicéridos un 17%

•Reduce PCR, oxidación y mejora la función endotelial

•Reduce y estabiliza la lesión ateromatosa

•Existen indicios de una acción positiva sobre el metabolismo hidrocarbonado

•Su perfil de tolerabilidad y toxicidad parecen óptimos y están avalados por un importante número de pacientes tratados en la actualidad.