Key Pharmacological Aspects & Pleiotropic Effects of Anti-dyslipidemic Drugs

Pongsatorn Meesawatsom
BPharm., MSc.(Pharmacology)
Department of Pharmacology
Faculty of Pharmacy
Mahidol University

Selected pharmacologic agents available for treating dyslipidemias

Drugs	% LDL decease	% HDL increase	% TG decrease
Statins	18-55	5-15	7-30
Ezetimibe	15-20	1	8
Ezetimibe + simvastatin	30-60	9	20
Nicotinic acid*	2-25	15-35	20-50
Nicotinic acid +statin	30-42	20-30	32-44
Fibrates*	5-20	10-15	20-50
Bile-acid sequestrants	10-20	1-2	Possible increase
Omega-3 fatty acid	5-10	1-3	25-30

*Small dense LDL also decreased

HMGCoA reductase Inhibitors (Statins)

LDL Reduction of statins

Drug	LDL Reduction by Dose (% Change from Baseline)				
	5 mg	10 mg	20 mg	40 mg	80 mg
Pravastatin	—	-20	-24	-30	-36
Fluvastatin	—	—	-22	-25	-35
Simvastatin	-26	-30	-38	-41	-47
Atorvastatin	—	-37	-43	-48	-51
Rosuvastatin	-40	-46	-52	-55	—
Simvastatin + Ezetimibe	—	-45	-52	-55	-60

Drug	Reduction by Dose (% Change from Baseline)		
	1 mg	2 mg	4 mg
Pitavastatin	-34	-42	-47

Efficacy and safety characteristics of statins

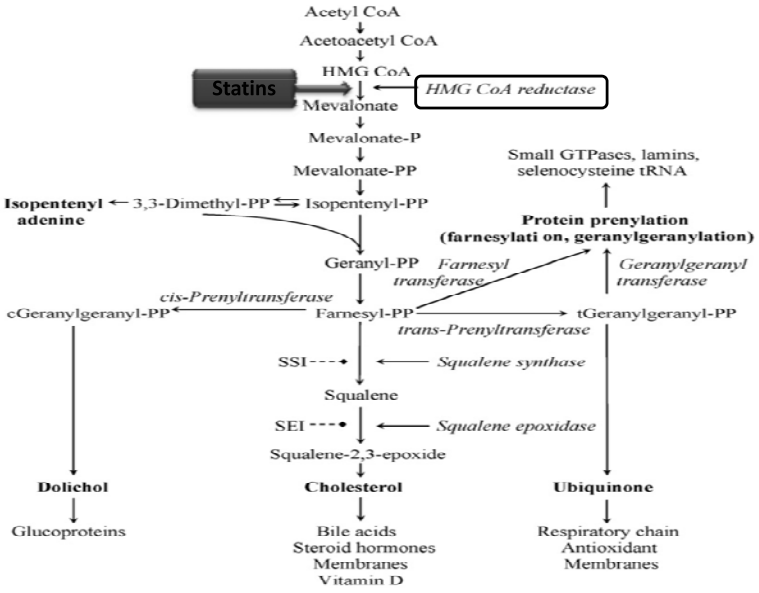
Licensed dose range (% LDL cholesterol reduction)*		Metabolism	Most important drug interactions increasing myopathy risk†
Lovastatin	20–80 mg daily	Mainly CYP3A4	Potent inhibitors of CYP3A4‡,
Simvastatin	10–80 mg	Mainly CYP3A4	Potent inhibitors of CYP3A4
Pravastatin	20–80 mg daily	Sulfation, biliary, and urinary excretion	
Fluvastatin	40–80 mg daily	CYP2C9 (some CYP2C8 and CYP3A4)	Inhibitors of CYP2C9
Atorvastatin	10–80 mg daily	CYP3A4	Potent inhibitors of CYP3A4
Rosuvastatin	5–40 mg daily	Minimal metabolism (via CYP2CP and some CYP2C19) and biliary excretion	
Pitavastatin	2–4 mg daily	Minimal metabolism (via CYP2C8 and CYP2C9), lactonisation, and bilary excretion	Unclear

Lancet 2007; 370: 1781–90.

Important drug interactions of statins

- ❖Pharmacodynamics
  - ★Colchicine+ Statins
- ❖Pharmacokinetics
  - ★CYP3A4 Inhibitors + simvastatin/atorvastatin
  - ★CYP2C9 Inhibitors + fluvastatin
  - ★OATP1B1 inhibitors+ all statins (minimal effect on fluvastatin)

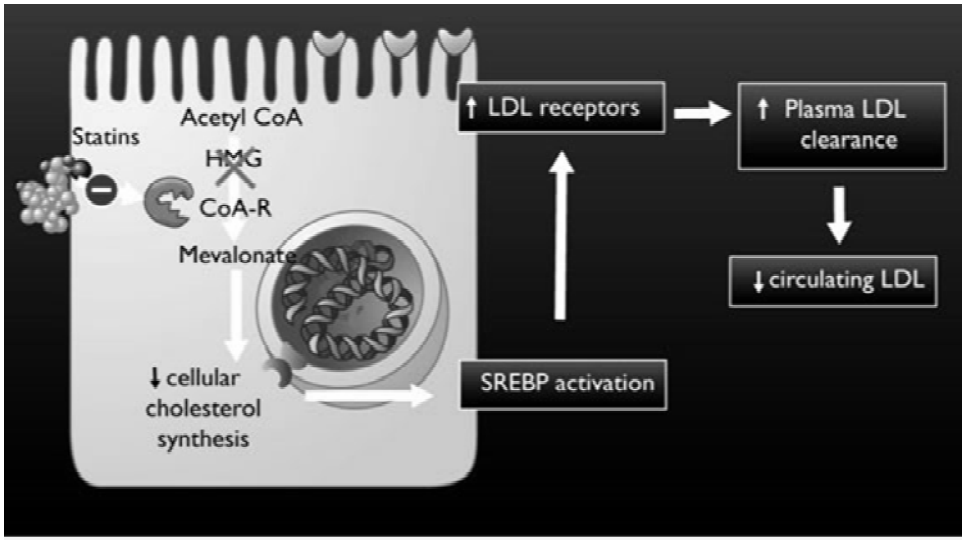
The biosynthetic pathway of cholesterol and other co-metabolites



PP=Pyrophosphate, **SSI**=Squalene Synthase Inhibitors, **SEI**=Squalene Epoxidase Inhibitors

Atherosclerosis 2009;202:18–28.

Statins: Molecular mechanisms of action of LDL reduction



SREBP = sterol regulatory element binding protein

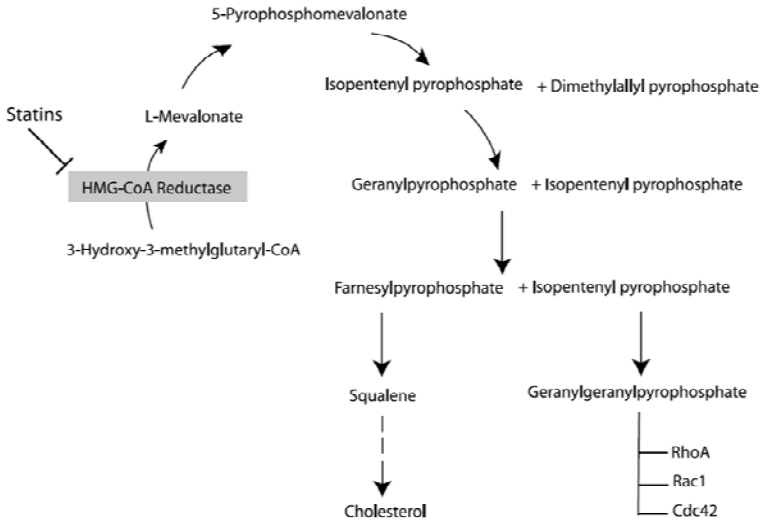
Currently proposed mechanisms of statins

- ❖Lipid improving effects
  - ★Inhibition of HMG-CoA which are rate-limiting step enzyme in cholesterol synthesis in hepatocyte →LDL receptor upregulation
- ❖Pleiotropic effects
  - ★HMG-CoA inhibition dependent mechanisms
  - ★HMG-CoA inhibition independent mechanisms
    - Direct block β**2 integrin leukocyte function antigen-1 (LFA-1)**

Pleiotropic effects of statin

- ❖Improve endothelial function
- ❖Antiproliferative effect on smooth muscle
- ❖Anti-inflammatory effect
  - ★Systemic inflammatory state
  - ★Local plaque inflammation
- ❖Plaque stabilization
- ❖Increase circulating endothelial progenitor cell

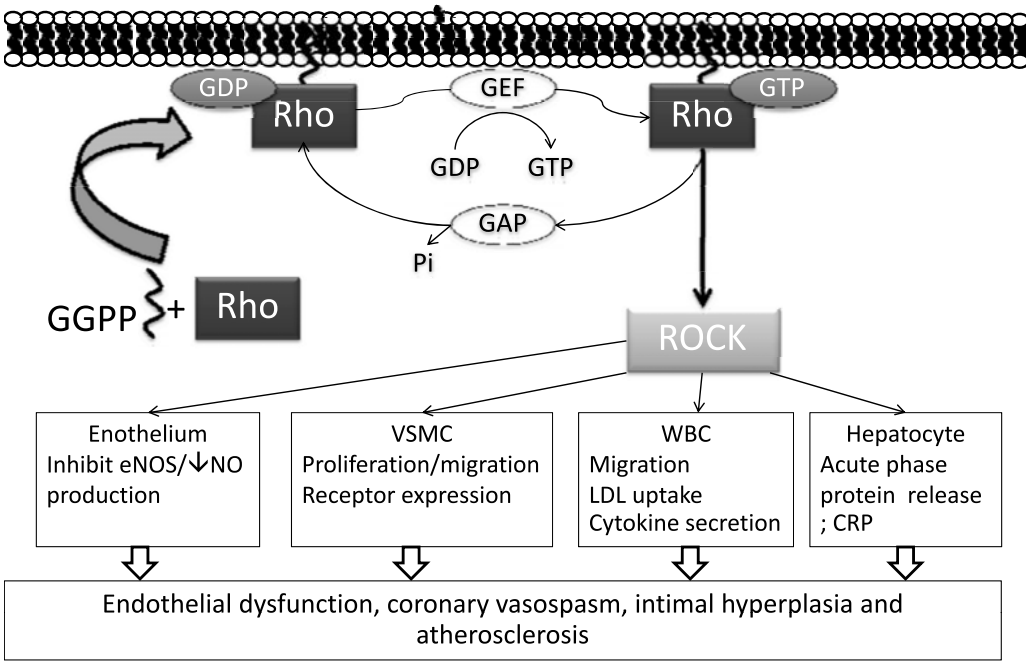
Statins inhibit synthesis of isoprenoids



Circ J 2010;74(5):818-26.

Protein prenylation

- ❖The *posttranslational modification process* that *isoprenoid intermediates are incorporated to specific proteins* in which play role in
  - ★Anchoring to target membrane
  - ★Contraction
  - ★Proliferation and migration
  - ★Signaling pathway
  - ★Gene expression
  - ★Cytoskeletal maintenance



Pathological roles of small GTP binding proteins

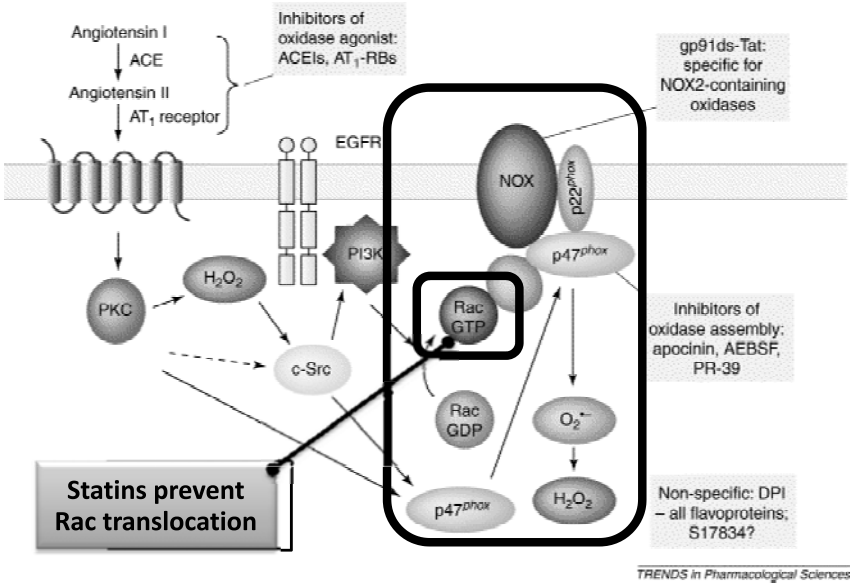
GTP binding proteins	Cellular effects	Effects on atherothrombosis
RhoA /ROCK	Inhibit eNOS ↑ ET-1 expression ↑ AT_1 receptor expression	Endothelial dysfunction Vasoconstriction
	↑ PAI-1 expression, ↓ t-PA expression	Prothrombosis
	↑ MMP	More vulnerable plaque
Rac-1	Activation of IL-6 receptor protein signaling, STAT3 → ↑ CRP release	Various effects of CRP
	Increase NADPH oxidase (NOX) activity → ↓NO availability	Endothelial dysfunction
Ras	NF-κB activation	Leucocyte activation Plaque inflammation and progression

Endothelial-Derived Nitric Oxide

- ❖Mediates vasodilation
- ❖Inhibits platelet aggregation
- ❖Inhibits SMC chemotaxis
- ❖Inhibits vascular SMC proliferation
- ❖Attenuates monocyte adhesion
- ❖Decreases LDL oxidation

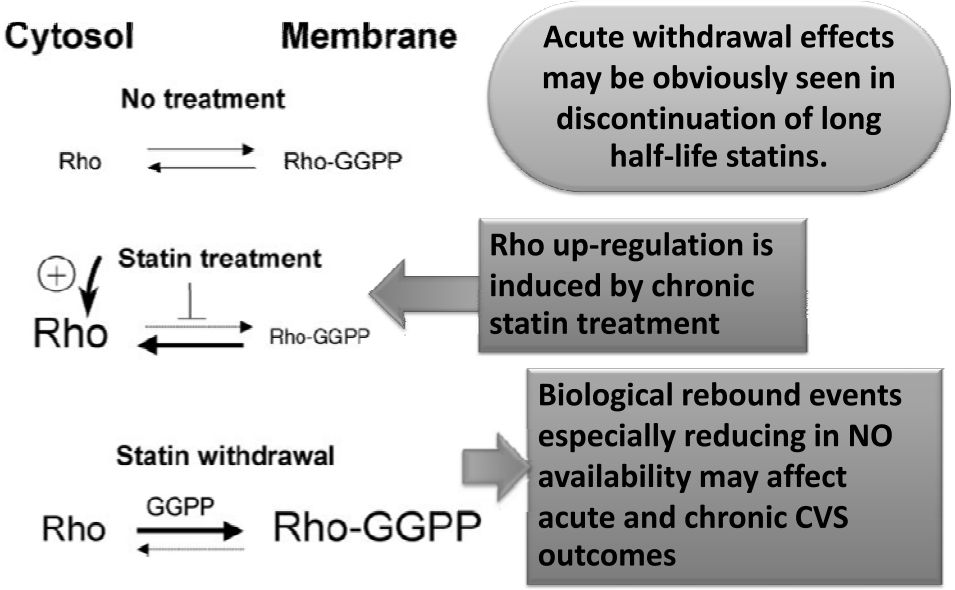
Endothelium dysfunction may result from increased production of reactive oxygen species and decreased availability of nitric oxide

Agents Affecting NOXs activation



TIPs 2003;24:471-8.

Withdrawal of statin treatment leads to overshoot activation of Rho GTPase



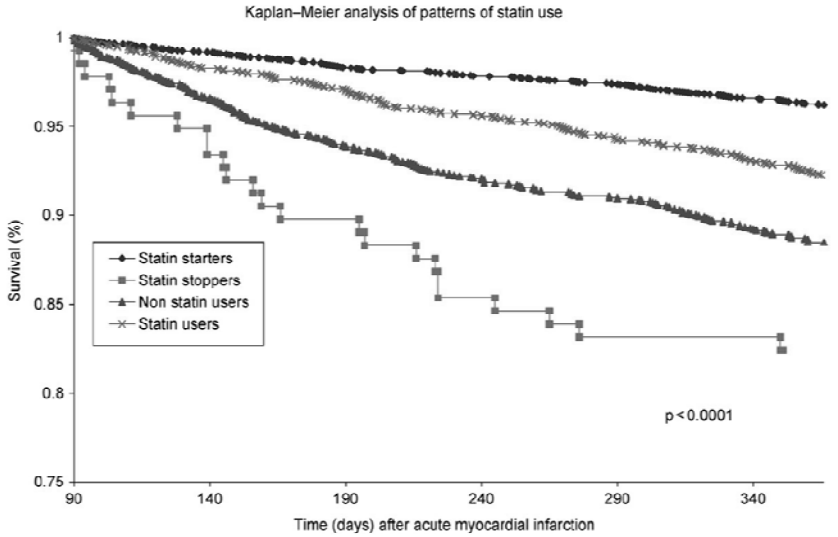
Acute withdrawal effects may be obviously seen in discontinuation of long half-life statins.

Rho up-regulation is induced by chronic statin treatment

Biological rebound events especially reducing in NO availability may affect acute and chronic CVS outcomes

Stroke 2006;37;2640-2643.

Kaplan–Meier analysis of effect of statin treatment patterns on 1-year all-cause mortality among survivors of a first acute myocardial infarction (AMI)



Eur Heart Journal 2008;29:2083–2091.

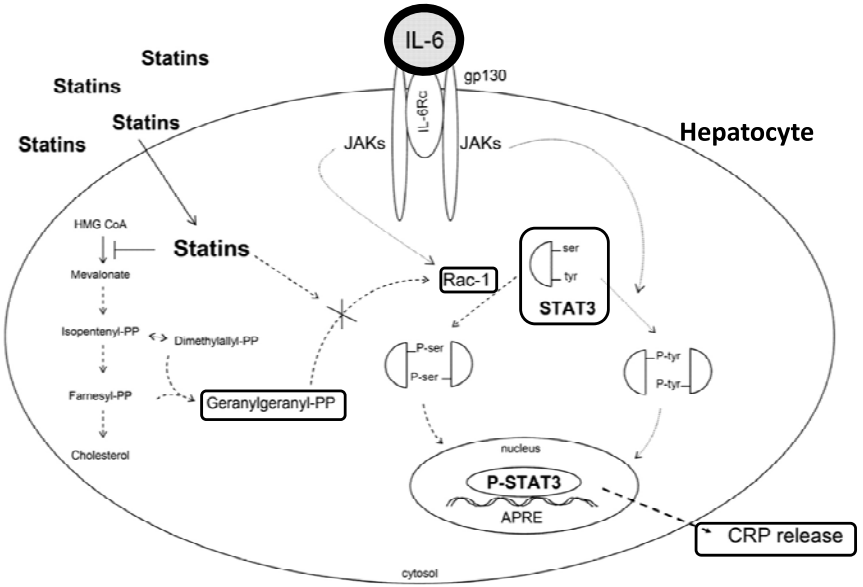
Long term outcomes of statin discontinuation in critical peroids

- Results of statin discontinuation
  - ★ in survivors of a first AMI was associated with higher all-cause mortality when compared with non-users[1]
  - ★ have a significantly increased mortality during the first year after the acute cerebrovascular event[2]

The medical professionals should be careful when reviewing patients' medications and the patients should have high adherence

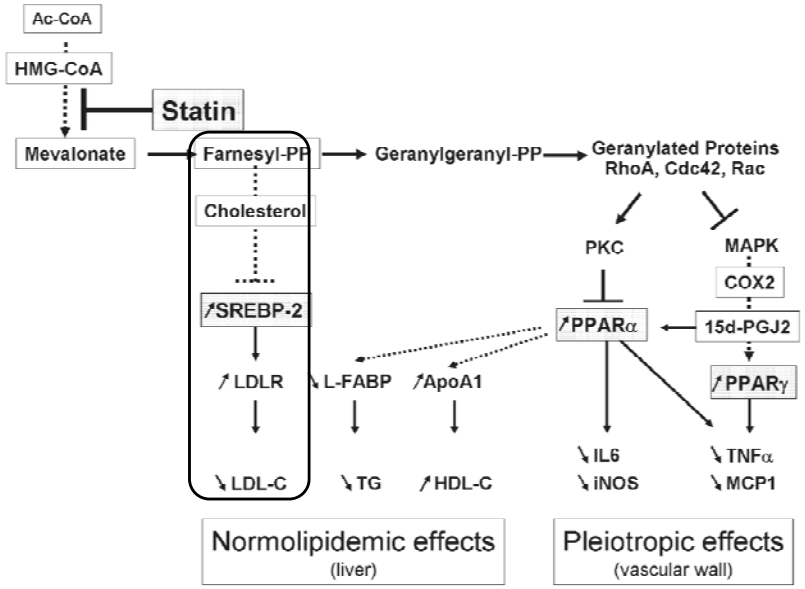
1. Eur Heart Journal 2008;29:2083–2091.
2. Stroke 2007;38:2652-2657

Proposed signaling pathways leading to statin-induced reduction of CRP release in hepatocytes



Arterioscler Thromb Vasc Biol 2005;25(6):1231-6.

Cross-talk of statins and PPARs



Trends Cardiovasc Med 2008;18:73–78.

Pleiotropic Effects of Statins on the Cardiovascular System

	Pleiotropic effects
Endothelial cells	Increased eNOS expression and activity[28,35,96]
	Increased expression of plasminogen activator and decreased expression of plasminogen activator inhibitor-1[97–99]
	Increased expression of PPAR[21,100]
	Decreased synthesis of endothelin-1[101,102]
VSMC	Reduced migration and proliferation[49,50,103,104]
	Increased apoptosis[105–107]
Platelets	Inhibition of platelet adhesion[108–110]
	Decreased biosynthesis of thromboxane A2[111–114]
Monocytes/Macrophages	Reduced macrophage cholesterol accumulation[115–117]
	Reduced macrophage proliferation and activity[118–120]
	Reduced secretion of MMP[121,122]
	Reduced secretion of MCP-1[123–125]
Stem cells	Increased mobilization of stem cells[126–128]

Circ J 2010;74(5):818-26.

The ACC/AHA/NHLBI consensus definitions of muscle-related side effects of statins (2002)

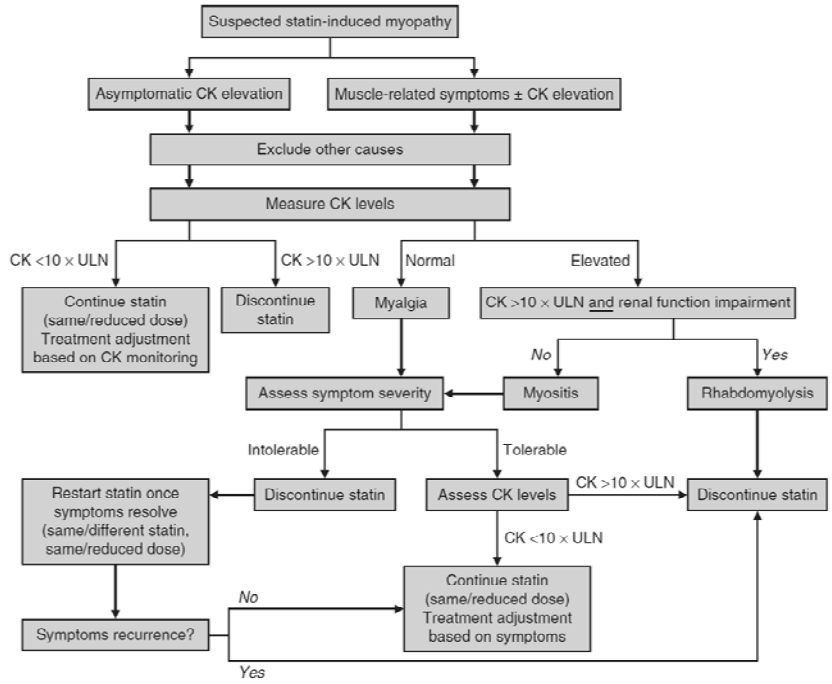
Condition	Definition
Myopathy	A general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
Myalgia	Muscle ache or weakness without CK elevation
Myositis	Muscle symptoms with increased CK levels
Rhabdomyolysis	Muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal) and with creatinine elevation (usually with brown urine and urinary myoglobin)

CK: creatine kinase.

Molecular and cellular effects of statins on the skeletal muscle cells leading to myopathy

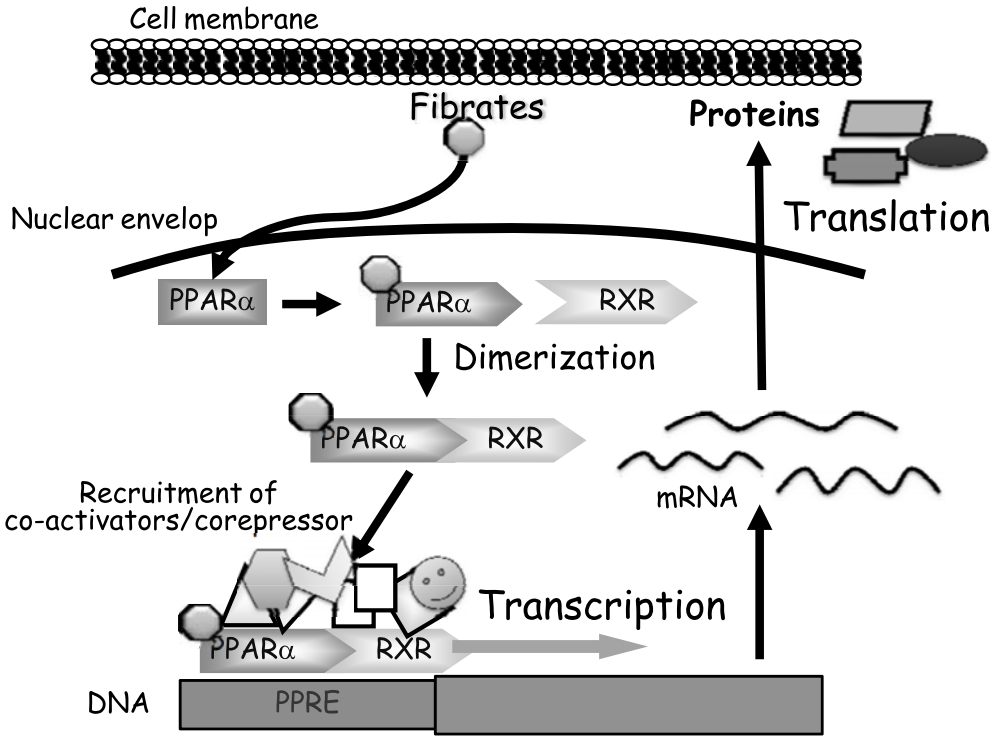
Molecule	Statin effect	Consequences at molecular level	Consequences at cellular level
Coenzyme Q10	Decreased synthesis	Impaired oxidative phosphorylation	Impaired energy production
Ras small GTPases	Dysprenylation	Impaired signal transduction	Deprivation of growth signals and impaired intracellular signaling
Rab small GTPases	Dysprenylation	Altered intracellular trafficking	Loss of physiologic cellular function and impaired translocation of receptors to the plasma membrane
Lamins	Dysprenylation	Nuclear fragility, eterochromatin disruption, impaired gene transcription	Susceptibility to mechanical stress and altered gene expression
Selenocysteine RNA	Dysprenylation	Premature termination of translation	Production of truncated and dysfunctional selenoproteins
Dolichols	Impaired post-translational N-glycosylation	Impaired expression of membrane receptors and alteration of structural proteins	Production of dysfunctional proteins and alteration or decrease of membrane receptors
Dystroglycans	Altered post-translational modification	Impaired extracellular matrix-cytoskeleton communication	Muscular dystrophy (?)

Atherosclerosis 2009;202:18-28.



Drug Saf 2010; 33 (3): 171-187

PPAR-α Agonists (Fibrates)



Key gene expression changed by PPAR-α agonists

- ❖ Increase HDL and enhance cholesterol ***reverse*** transport
  - ★↑Apo AI, Apo AII
  - ★↑ABCA1
  - ★↑SR-B1
- ❖ Decrease TG
  - ★↑LPL
  - ★↓Apo CIII
- ❖ Pleiotropic effects
  - ★↑ eNOS
  - ★↓ NF-κB
  - ★↓ TNF- α, IL-6, MCP-1
  - ★↓ VEGF and VEGF-2 receptor
  - ★↓ Factor VII, PAI-1
  - ★↓ CRP

Effects of Intensive Glycemic Control, Fenofibrate, and Intensive Blood-Pressure Control on Progression of Diabetic Retinopathy and Moderate Vision Loss

Treatment	Progression of Diabetic Retinopathy	Adjusted Odds Ratio (95% CI)	P Value	Moderate Vision Loss	Adjusted Hazard Ratio (95% CI)	P Value
	no./total no. (%)			*no./total no. (%)*		
Glycemia therapy		0.67 (0.51–0.87)	0.003		0.95 (0.80–1.13)	0.56
Intensive	104/1429 (7.3)			266/1629 (16.3)		
Standard	149/1427 (10.4)			273/1634 (16.7)		
Dyslipidemia therapy†		0.60 (0.42–0.87)	0.006		1.04 (0.83–1.32)	0.73
With fenofibrate	52/806 (6.5)			145/908 (16.0)		
With placebo	80/787 (10.2)			136/893 (15.2)		
Antihypertensive therapy		1.23 (0.84–1.79)	0.29		1.27 (0.99–1.62)	0.06
Intensive	67/647 (10.4)			145/749 (19.4)		
Standard	54/616 (8.8)			113/713 (15.8)		

* Moderate vision loss was defined as loss of visual acuity by three or more lines in either eye.
† Dyslipidemia therapy consisted of simvastatin plus either fenofibrate or placebo.

N Engl J Med 2010;363:233-44.

Fibrates in DM patients

- Combination statin–fibrate therapy offers complementary lipid-modifying efficacy in patients with type 2 diabetes
- Pharmacokinetic interaction between fenofibrate and commonly prescribed statins is minimal and translates to a low incidence of muscle toxicity, compared with gemfibrozil–statin combination therapy
- Combination therapy with fenofibrate and a statin is a logical treatment approach to the management of diabetic dyslipidaemia

Transporter-based drug interaction of gemfibrozil

- OATP1B1 (former called OATP-C)
  - ★ is protein product from SCL01B1 gene
  - ★ which plays role in hepatic uptaking of organic anion drugs
- All statins are substrate of OATP1B1
  - ★ + gemfibrozil → increase risk of myotoxicity
- Repaglinide is substrate of OATP1B1
  - ★ + gemfibrozil → increase risk of hypoglycemia

Involvement of selected protein isoforms in the metabolism of various statins

Protein	Atorvastatin	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Rosuvastatin
CYP						
CYP3A4	+	+	+	NR	NR	NR
CYP3A5	+	+	+	NR	NR	NR
CYP2C8	+	+	+	NR	+	NR
CYP2C9	+	+	+	NR	+	NR
CYP2C19	+	+	+	NR	+	NR
CYP2D6*	+	+	+	NR	NR	NR
ATP-binding cassette (ABC) protein						
ABCB1	+	+	+	+	NR	NR
ABCC2	+	+	+	+	NR	NR
ABCG2	NR	NR	NR	+	NR	NR
ABCB11	NR	NR	NR	+	NR	+
UGT						
UGT1A1	+	+	+	NR	+	NR
UGT1A3	+	+	+	NR	+	NR
UGT2B7	+	+	+	NR	NR	NR
SLC						
SLC15A1	NR	NR	NR	NR	+	NR
SLCO1A1	NR	NR	NR	NR	NR	NR
SLCO1B1	+	+	+	+	+	+
SLCO2B1	+	+	+	+	+	+
SLCO1B3	+	+	+	+	+	+
SLC22A6	NR	NR	NR	+	NR	NR
SLC22A8	NR	NR	NR	+	NR	NR

*Reports on the role of CYP2D6 are conflicting. Abbreviations: +, interaction; CYP, cytochrome P450; NR, not reported; SLC, solute carrier; UGT, uridine-diphosphate glucuronosyltransferase. Reproduced with permission from Expert Reviews Ltd. © Molokhia, M. *et al. Per. Med.* **5**, 481–494 (2008).[61]

Nat Rev Endocrinol 5, 507–518 (2009);

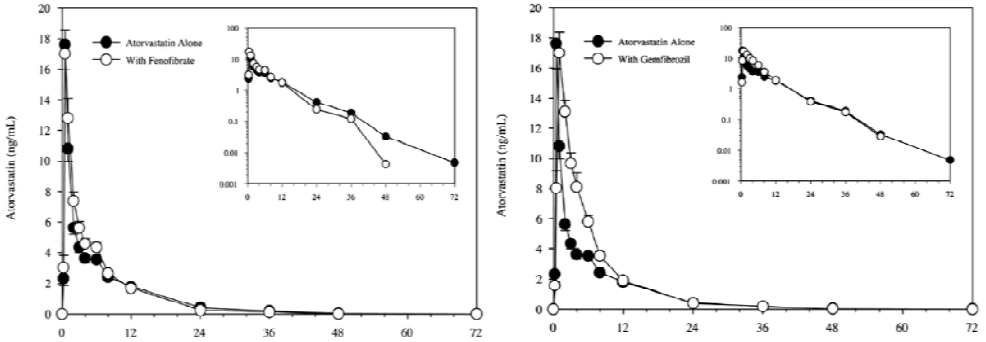
OATP1B1 inhibitors

- Gemfibrozil (not fenofibrate and bezafibrate)
- Cyclosporin
- Erythromycin, clarithromycin
- Ketoconazole
- Ritonavir

Inhibitors of CYP3A4

Mean plasma concentration–time profiles for atorvastatin 40 mg/day in combination with fenofibrate 160 mg/day or gemfibrozil 1200 mg/day

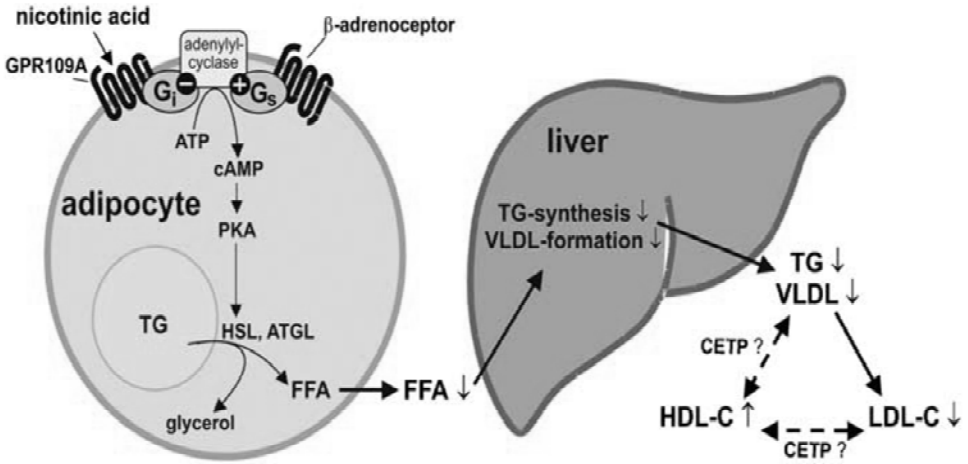
Design: Single-center, open-label, randomized, 6-sequence, 3-period, 3-treatment crossover study in 72 healthy volunteers



J Clin Pharmacol 2010; Apr 22, in press.

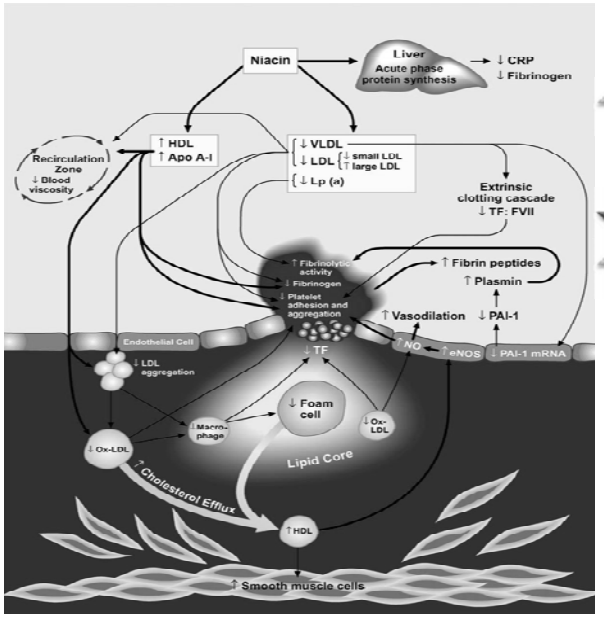
Niacin (Nicotinic acid)

Mechanism of nicotinic acid-induced changes in lipid metabolism



Br J Pharmacol 2008;153:s68-s75.

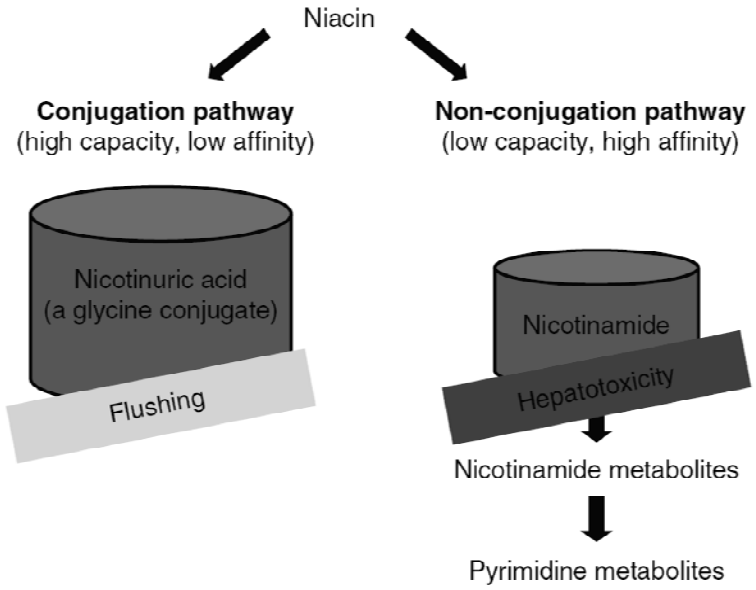
Antiatherothrombotic effects of niacin



- ↑ Atherosclerotic plaque stability
- ↓ Thrombogenesis
- ↑ Fibrinolysis

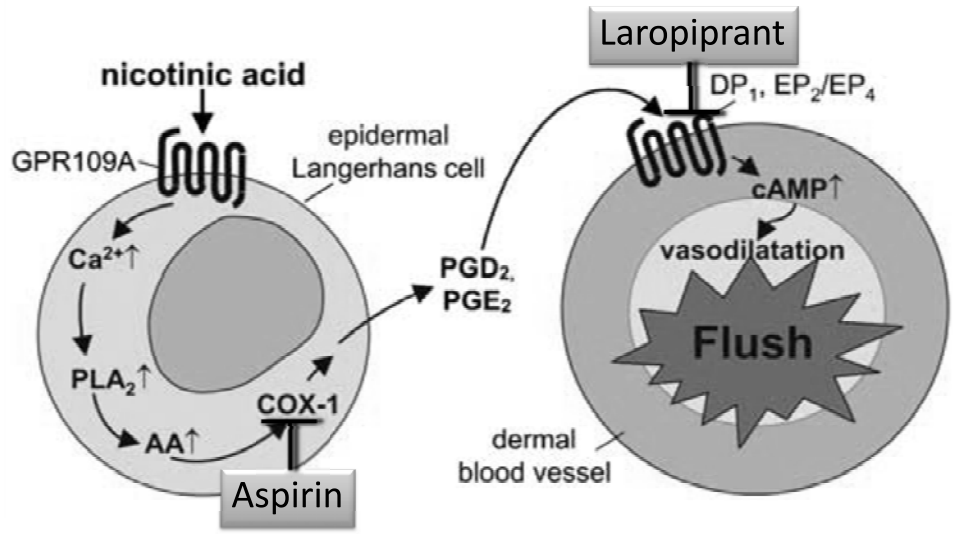
Atherosclerosis 2003;171:87–96.

Summary of niacin metabolism



Expert Opin Pharmacother 2008;9(16):2911-2920.

Proposed mechanism of the nicotinic acid-induced flushing response



Br J Pharmacol 2008;153:s68-s75.

Practical points for niacin

- ❖Pharmacological dose range 500-2000 mg
- ❖Flushing is minimized by using ER formulation
- ❖Avoid self treatment with niacin because of variability of niacin content in different preparation

- Pharmacists should advise patients who use niacin of the likelihood of flushing (the most common adverse event) and of steps that they can take to reduce the incidence of flushing.
- Patient counseling tips that may help manage flushing include:
  - Take niacin at bedtime.
  - Take niacin with a low-fat snack.
  - Take aspirin or ibuprofen about 30 minutes before taking niacin (with approval of the health care team).
  - Avoid alcoholic beverages, hot beverages, and spicy foods near the time of taking niacin. (This strategy remains unproven but may be helpful for some patients.)
  - Patients should rise slowly If they awaken while experiencing flushing, they should use caution if they decide to get out of bed.