Perception vs. Evidence

*B*alancing *safety* and *efficacy* in *statin* users

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與病人的溝通

- **Responding to patients with poor adherence**
  - **Statin intolerance**
  - **Myths and phobia** of taking western drugs
  - Told by other experts…

- **Issues** about myalgia, abnormal liver function, NODM, cognitive impairment, diarrhea, insomnia

Case: A 65-year-old woman

Meta-analysis

Prevalence of statin intolerance

- RCTs at the PubMed, Medline, and Cochrane Central Register of Controlled Trials (CENTRAL) databases
- Included if they had ≥1,000 participants, had patients who were followed up for ≥1 year, and reported rates of drug discontinuation
- Random effects model. 22 studies (statins = 66,024, placebo = 63,656), with mean follow-up of 4.1 years
- The rates of discontinuation: 13.3% (8,872 patients) for statin-treated patients and 13.9% (8,898 patients) for placebo-treated patients → **no** significant difference between the placebo and statin arms (odds ratio [OR] = 0.99, 95% confidence interval [CI] = 0.93 to 1.06)
- The rates of **myopathy**: also similar between the statins and placebos (OR = 1.2, 95% CI = 0.88 to 1.62, p = 0.25).

Am J Cardiol. 2017 Sep 1;120(5):774-781.

Proposed statin myalgia clinical index score

Table 1 Proposed statin myalgia clinical index score

Clinical symptoms—new or increased unexplained muscle symptoms	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Nonspecific asymmetric—intermittent	1
Temporal pattern	
Symptoms onset <4 wk	3
Symptoms onset 4–12 wk	2
Symptoms onset >12 wk	1
Dechallenge	
Improves on withdrawal—<2 wk	2
Improves on withdrawal—2–4 wk	1
Does not improve upon withdrawal—>4 wk	0
Challenge	
Same symptoms reoccur on rechallenge—<4 wk	3
Same symptoms reoccur on rechallenge—4–12 wk	1
Statin myalgia clinical index score (total points)	
Probable	9–11
Possible	7–8
Unlikely	<7





J Clin Lipidol. 2017 Feb;11(1):24-33.

Clinical factors potentially predisposing to statin-associated muscle symptoms

Table 3 Clinical factors potentially predisposing to statin-associated muscle symptoms

Advanced age
Female gender
Asian ethnicity
Low body mass index (frailty)
Pre-existing muscle/joint/tendon conditions
Chronic pain disorders
Diabetes mellitus
Obesity
Neuromuscular conditions
Chronic renal or hepatic disease
Hypothyroidism
Vitamin D deficiency
Severe trauma (eg, major surgery)
Physical exertion
Family history of myalgia—with or without statin therapy
Interacting agents—potentially increasing statin serum concentrations
Amiodarone
Azole antifungals—multiple agents
Cyclosporine
Gemfibrozil
Diltiazem
Verapamil
Macrolide antibiotics—clarithromycin, erythromycin
Protease inhibitors—multiple agents
Excess grapefruit/juice consumption
Other medications/factors associated with musculoskeletal symptoms
Substances of abuse—alcohol, amphetamines, caffeine, cocaine, heroin
Colchicine
Cyclosporine
Antiviral agents—zidovudine, ritonavir, didanosine
Corticosteroids
Antimalarials—hydroxychloroquine
Antipsychotics—haloperidol, risperidone
Daptomycin
Danazol
Dipeptidyl peptidase-4 (DPP-4) inhibitors—primarily arthralgia

J Clin Lipidol. 2017 Feb;11(1):24-33.

Distinguishing between the musculoskeletal symptoms observed with these agents and SAMS is often difficult

- CK elevation
- Acute and rapidly evolving
- Accompanied with neuropathic features

J Clin Lipidol. 2017 Feb;11(1):24-33.

*K*ey points about **SAMS** for clinicians

•**What are SAMS?** Muscle pain, weakness and aches, usually **symmetrical and proximal**, affecting the thighs, buttocks, calves and back muscles. **Not** normally associated with marked creatine kinase (CK) elevation.

•**When do SAMS occur?** Tend to occur early (within 4–6 weeks of starting a statin), after an increase in statin dose, or with initiation of an interacting drug.

•**Who is at risk of SAMS?** The very elderly (>80 years), notably female, or with low body mass index or of **Asian** descent, with a history of muscle disorders, or concurrent conditions (e.g. acute infection, impaired renal or hepatic function, diabetes, HIV) or concomitant interacting medications.

•**How did the EAS Consensus Panel define SAMS?** By the nature of muscle symptoms, and their temporal association with statin initiation, discontinuation, and response to repetitive statin **re-challenge**.

•**What determines management of SAMS?** The magnitude of CK elevation, and the patient's global cardiovascular risk

Eur Heart J. 2018 Jul 14;39(27):2526-2539

Comparison of all statins at NTUH

Parameter	Rosuva		Atorva		Pitava		Prava		Fluva	
Half-life, h	19 任何時間服用		3~14 任何時間服用		11 (任何時間)		1.8 (**睡前**服用)		1 (晚上服用)	
Metabolic enzyme (S, substrate; I, inhibitor)	2C9,2C19 (none)		3A4(S)		2C9 minimally, Glucuronidation		Sulfation (none)		2C9(I)	
Food effect on bioavailability	None		↓13%		None		↓ 30%		↓15-25%	
Hydrophilic/ hydrophobic	**Hydrophilic**		Hydrophobic		Equivocal		**Hydrophilic**		Hydrophobic	
LDL-C reduction, %	**10 mg**	47%	**10mg**	38%	**2mg**	38%	10mg	20%	80mg	30%
	20mg	52%	20mg	43%	4mg	43%	20mg	24%		
	40mg	55%	40mg	48%			**40mg**	30%		
HDL-C increase%	7.7%~10%		5.7%~2%		5%~8.2%		3.2%~5.5%		3.2%~5.5%	
TG reducce, %	20%~26%		20%~28%		11%~18%		8%~13%		8%~13%	
Elimination, % **Urine** **Feces**	10 90		4 96		15 79		20 70		5 95	

Parameter	Rosuva	Atorva	Prava	Fluva
Half-life, h	19 (任何時間服用)	3~14 (任何時間服用)	1.8 (睡前服用)	1 (任何時間服用)
Metabolic enzyme (S, substrate; I, inhibitor)	**2C9**,2C19 (none)	**3A4(S)**	**Sulfation (none)**	**2C9**(I)
Food effect on bioavailability	與燕麥至少間隔2-4小時	葡萄柚汁；增加藥品副作用；與燕麥至少間隔2-4小時	與燕麥至少間隔2-4小時	與燕麥至少間隔2-4小時
Hepatoselectivity (log ratio)	3.3	2.2	**3.3**	1.3
LDL-C reduction, %	10 mg **46%** 20mg **52%** 40mg **55%**	10mg **37%** 20mg **43%** 40mg **48%**	10mg **20%** 20mg **24%** 40mg **30%**	80mg **30%**
HDL-C increase%	7.7%~10%	5.7%~2%	3.2%~5.5%	3.2%~5.5%
TG reduction, %	20%~26%	20%~28%	8%~13%	8%~13%
Elimination, % Urine Feces	10 90	4 96	20 70	5 95

Step-by-step approach to managing SAMS in the highly intolerant – (1)

Table 2 Step-by-step approach to managing SAMS in the highly intolerant

Exclude other common causes of musculoskeletal symptoms such as physical exertion, hypothyroidism, and concurrent illness.

- Attempting to identify true intolerance
  - Use the statin myalgia clinical index score, or other resources, to help with clinical assessment and rule out other etiologies of musculoskeletal complaints.
- Reviewing and modifying the medication profile
  - Review for agents that can raise statin serum concentrations.
  - Evaluate for other agents as etiologies for musculoskeletal symptoms.
  - Switch triglyceride-lowering agents with potential for myalgia (eg, fibrate) to those with low myalgia potential (eg, omega-3 fatty acids).
- Can supplements elevate the statin threshold?
  - Replete low vitamin D concentrations and consider statin reintroduction once fully repleted.
  - Consider a short-term trial of ubiquinol, begin 2 wk before statin reintroduction, discontinue if no response.
- Dietary intake and musculoskeletal symptoms
  - Emphasize the importance of a heart-healthy diet.
  - Evaluate for high intake of grapefruit/juice.
  - Assess for dietary sources that may worsen musculoskeletal symptoms (eg, gluten, excess intake of artificial ingredients).
- Reintroducing a statin and isolating adverse events
  - Use shared decision-making when reintroducing statin therapy.
  - Begin QWK dosing with a long half-life statin and have patient self-monitor for patterns of myalgia corresponding with the dosing day. Gradually titrate as tolerated to BIW and QOD dosing.
  - Consider "pulse-dosing" for patients with cumulative development of muscle symptoms.

J Clin Lipidol. 2017 Feb;11(1):24-33.

Step-by-step approach to managing SAMS in the highly intolerant – (2)

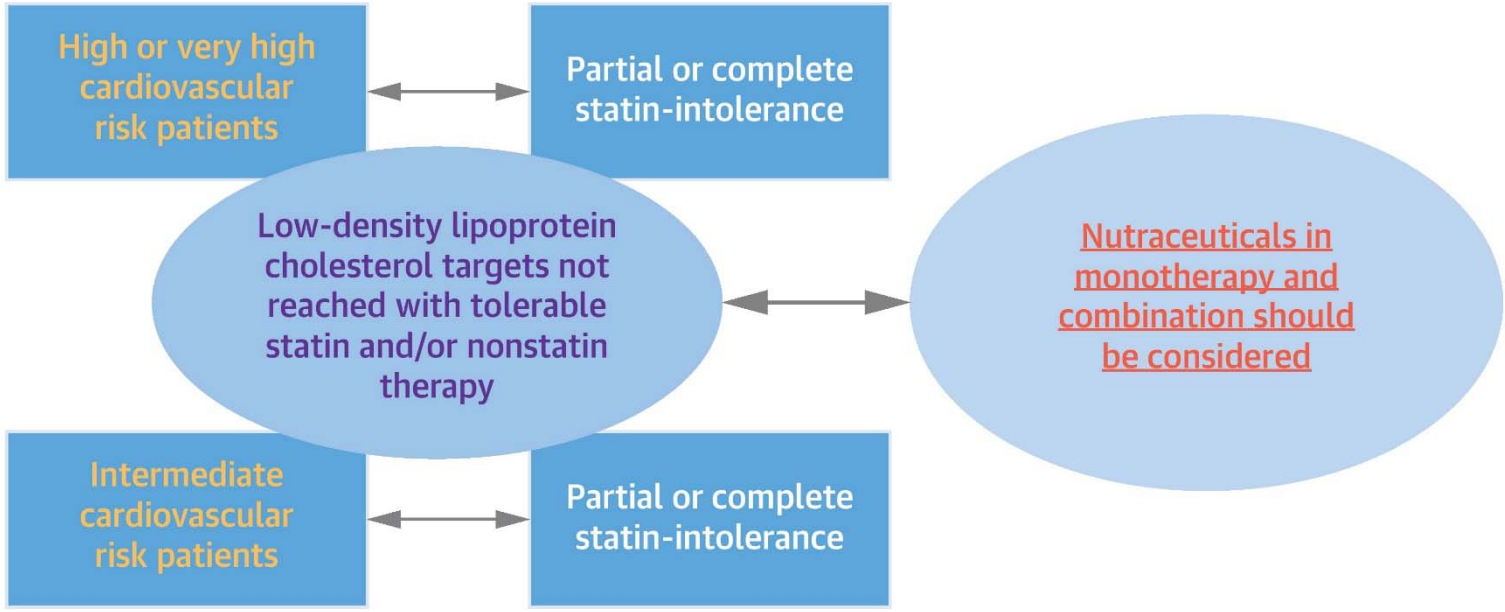
- Ezetimibe—not a statin and exploiting the flat dose–response
  - Counsel patients that ezetimibe is a nonstatin with low potential for systemic effects including myalgia.
  - Tablet-split (½ tablet) and use intermittent dosing, especially in patients ezetimibe intolerant, and gradually increase dosing frequency as tolerated. May consider ezetimibe on statin "off-days."
- Nonstatins—beyond ezetimibe
  - BARs are considered second-line alternatives to ezetimibe that are unlikely to cause muscle symptoms and may improve glycemic markers.
  - Consider a PCSK9 inhibitor in high-risk patients (eg, clinical ASCVD and/or baseline LDL-C ≥190 mg/dL). If <50% overall LDL-C reduction, may use before ezetimibe or BAR if clinical ASCVD and baseline LDL-C ≥190 mg/dL.
  - Niacin and fibrates—no clear indication for LDL-C lowering in statin-intolerant patients.
- Alternative therapy options
  - Supplements containing phytosterols and viscous fiber (fiber laxatives) are safe and provide modest (~10%) LDL-C reductions when added to statin therapy.
  - Consideration may be given to using a quality red yeast rice supplement, but product inconsistency and potential citrinin content may be of concern. Lovastatin component may trigger muscle symptoms.
- Realistic goals
  - Intensify treatment and control of other modifiable cardiovascular risk factors.
  - For the highest cardiovascular risk patients, PCSK9 inhibitors may achieve the recommended >50% LDL-C reduction or <70 mg/dL LDL-C target.
  - Intermittent statin dosing + ezetimibe generally provides LDL-C reductions >30%.
  - For patients completely statin intolerant and not candidates for PCSK9 therapy, approximate LDL-lowering of 30% can usually be achieved with combination nonstatin therapy.

ASCVD, atherosclerotic cardiovascular disease; BARs, bile acid resins; BIW, twice weekly; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; QOD, every other day; QWK, every week; SAMS, statin-associated muscle symptoms.

J Clin Lipidol. 2017 Feb;11(1):24-33.

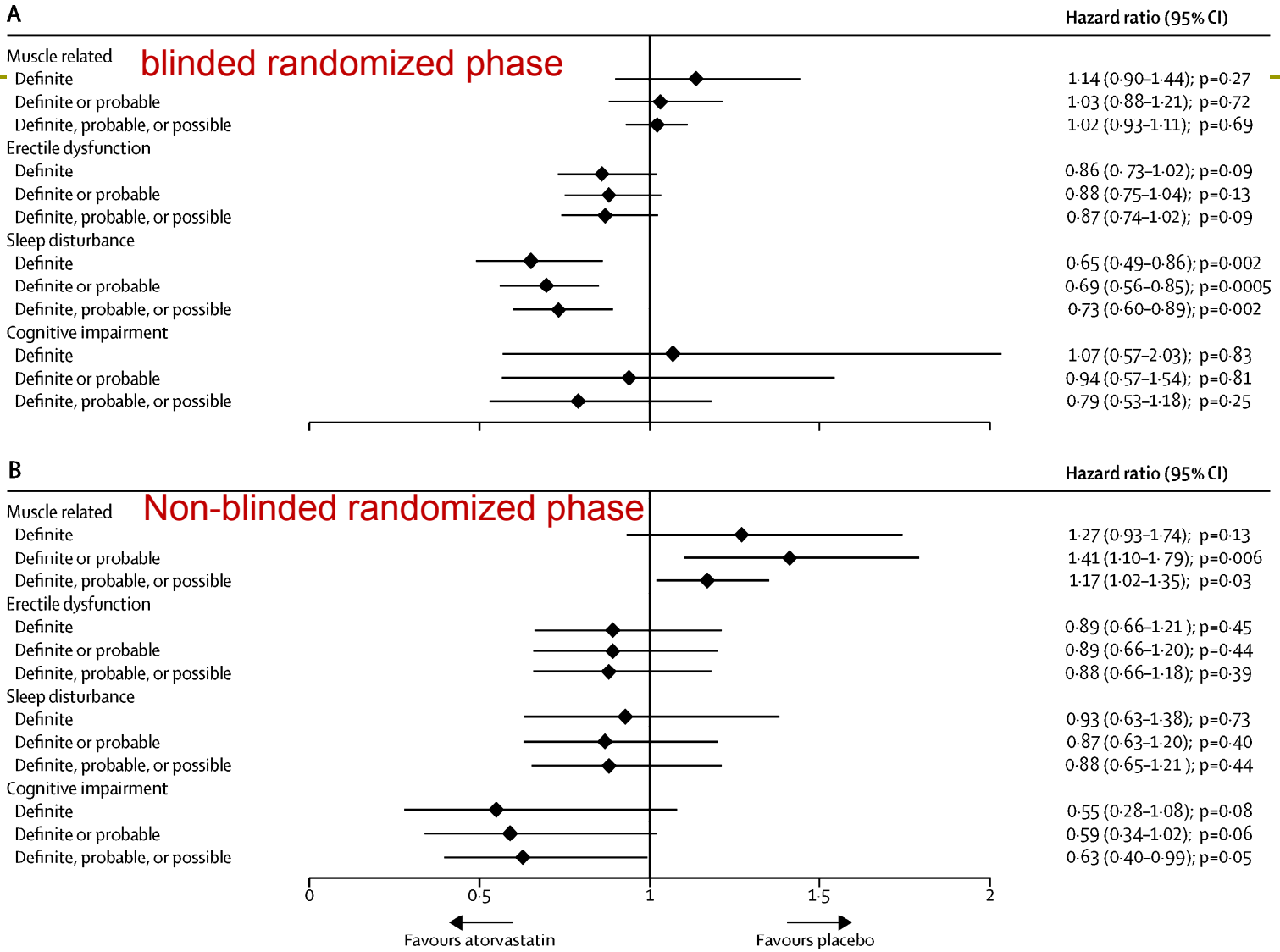
JACC State-of-the-Art Review

CENTRAL ILLUSTRATION: Role of Nutraceuticals in Statin-Intolerant Patients



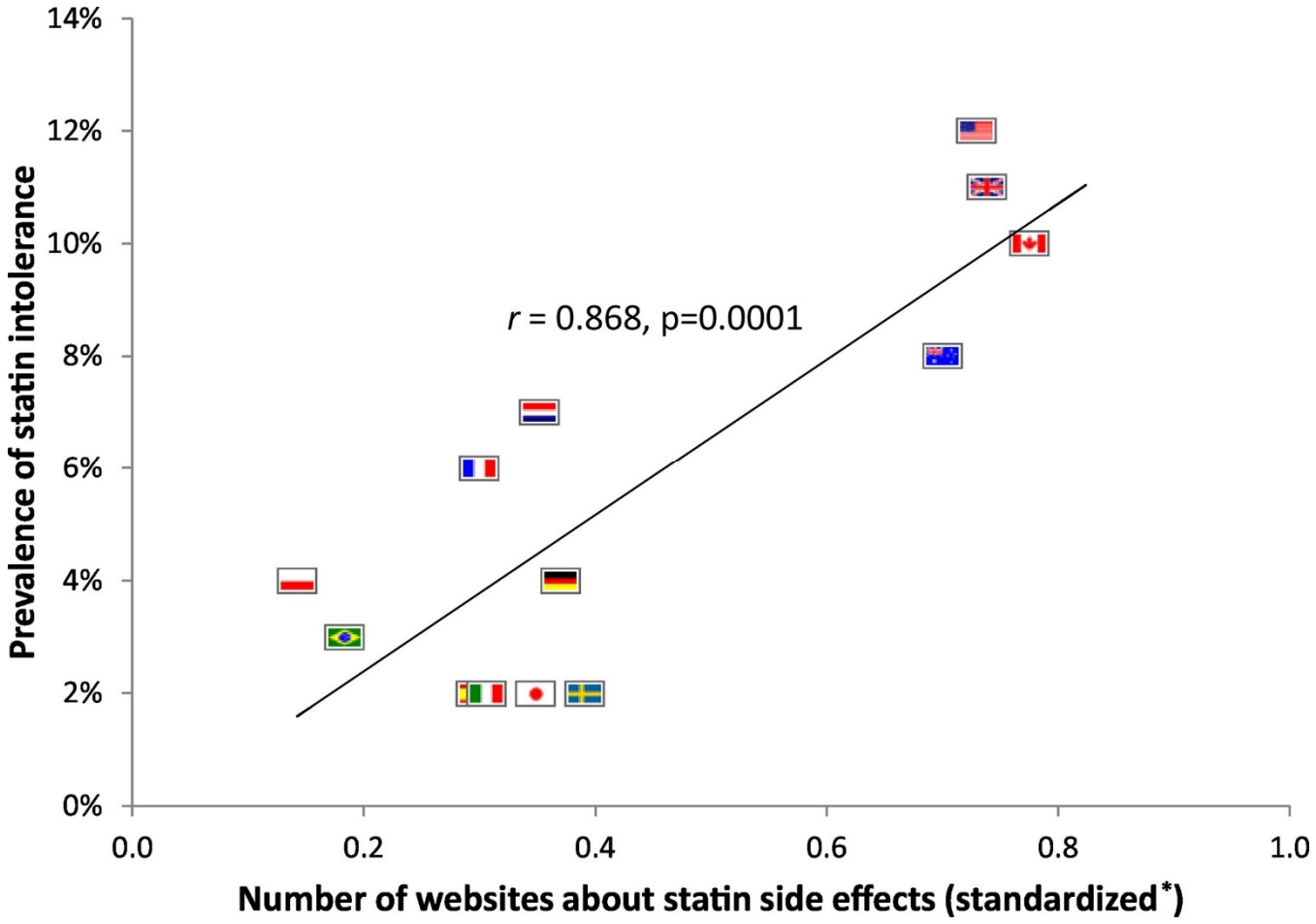
Banach, M. et al. J Am Coll Cardiol. 2018;72(1):96–118.

Nocebo effect



Lancet. 2017 Jun 24;389(10088):2473-2481.

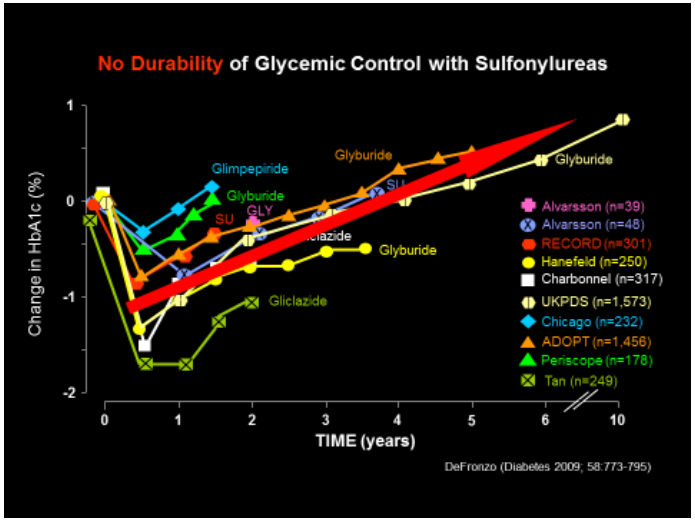
Does **Googling** lead to statin intolerance?

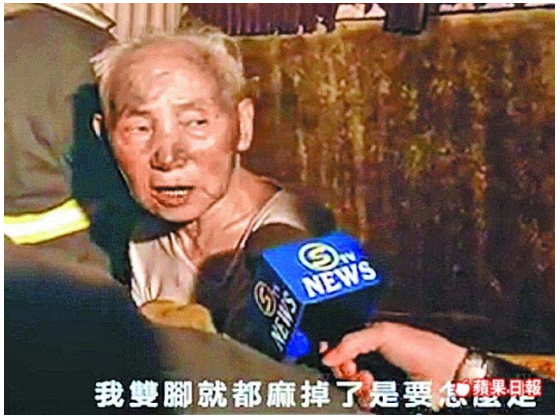


Int J Cardiol. 2018 Jul 1;262:25-27

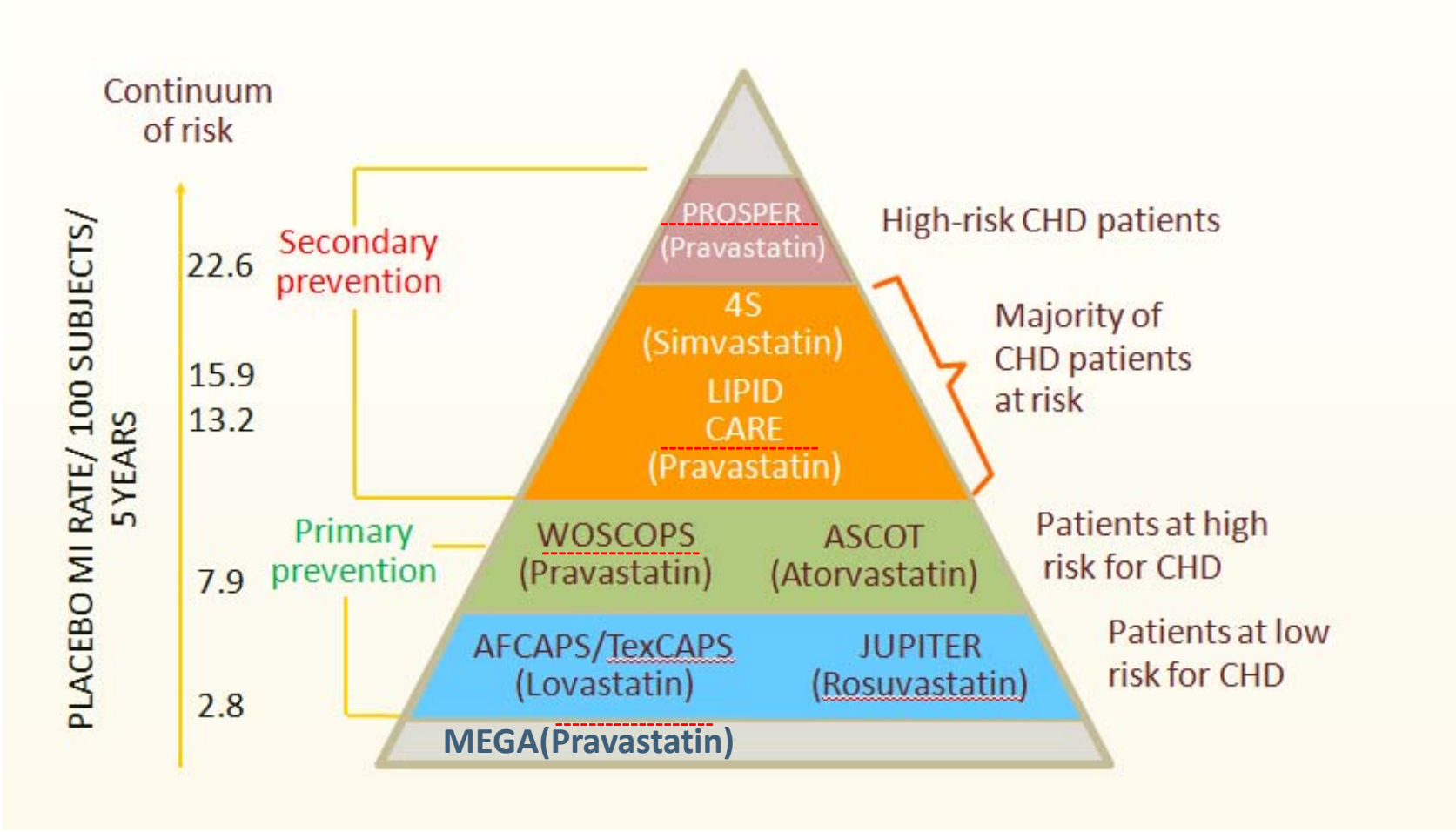
Myths & unmet needs

- Phobia of taking western drugs
  - 暫不想吃三高藥物(怕有去無回)，但想吃顧循環通血路。
  - 西藥傷腰子？





Landmark Trials

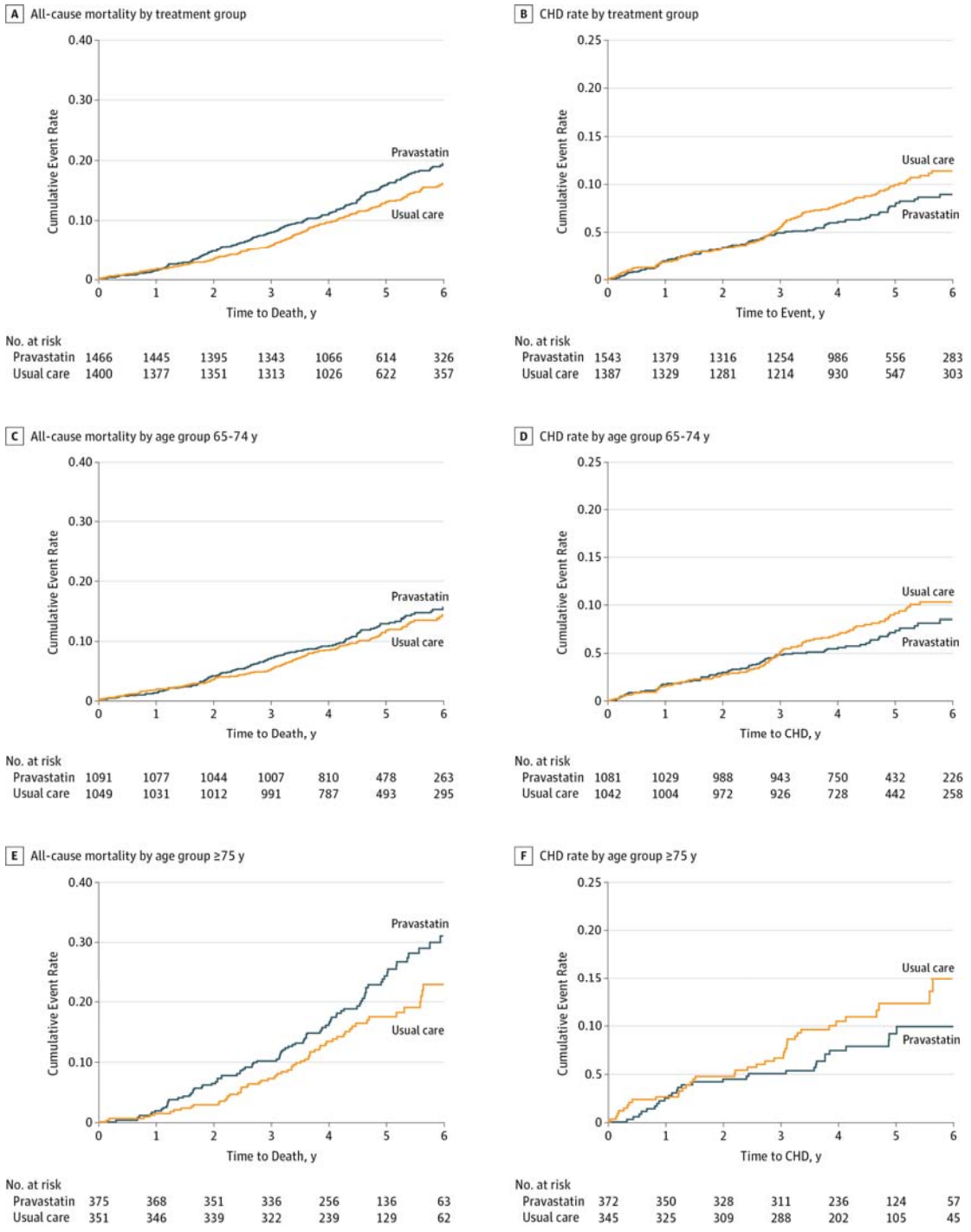


Major Pravastatin Clinical Outcome Trials

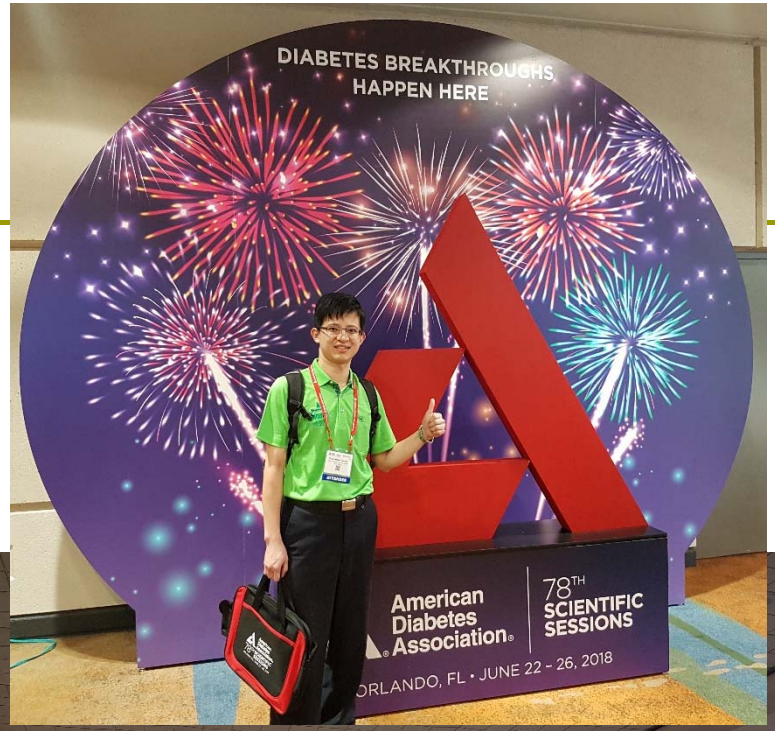
Study	Study Drug	# of patients	Duration	Primary endpoint
Primary prevention				
WOSCOPS	Pravastatin 40mg/day	6,959 (men)	5yrs	NFMI / CHD Death 31% Reduction (P < 0.001)
MEGA	Pravastatin 10-20mg/day	7,832 (2,476 men; 5,356 women)	5.3yrs	CHD reduction 33% (P = 0.01)
Secondary prevention				
CARE	Pravastatin 40mg/day	4,159 (3,583 men; 576 women)	5yrs	Nonfatal (NF) MI / CHD Death 24% Reduction (P=0.003)
LIPID	Pravastatin 40mg/day	9,014 (7,498 men; 1,516 women)	6yrs	CHD Death 24% Reduction (P < 0.001)
PROSPER	Pravastatin 40mg/day	5,804 (48% men; 52% women/ 70-82 years)	3.2yrs	CHD death, Nonfatal MI, Fatal or Nonfatal Stroke 15% (P=0.014)

H. Nakamura, Lancet 2006 368 1155-1163/ Shepherd et al. NEJM 1995;333:1301-7. Sacks et al. NEJM 1996;335:1001-9.
LIPID Study Group. NEJM 1998;339:1349-57/ PROSPER Study Group ,Lancet. 2002; 360:1623-30

No benefit was found when a statin was given for primary prevention to older adults.



JAMA Intern Med. 2017 Jul 1;177(7):955-965.


DIABETES BREAKTHROUGHS
HAPPEN HERE
American
Diabetes
Association.
78TH
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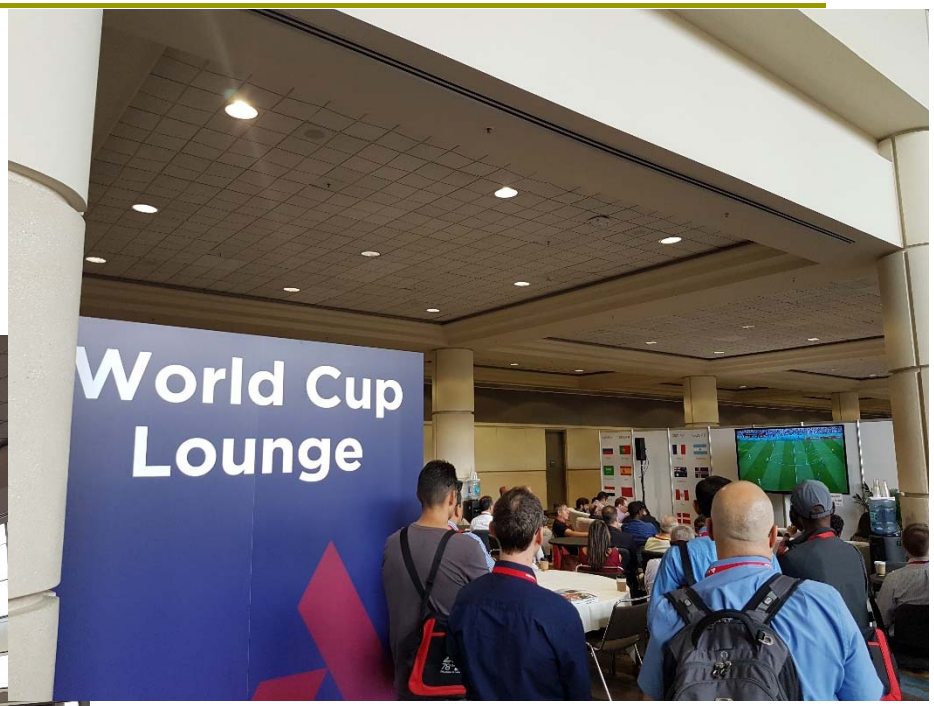
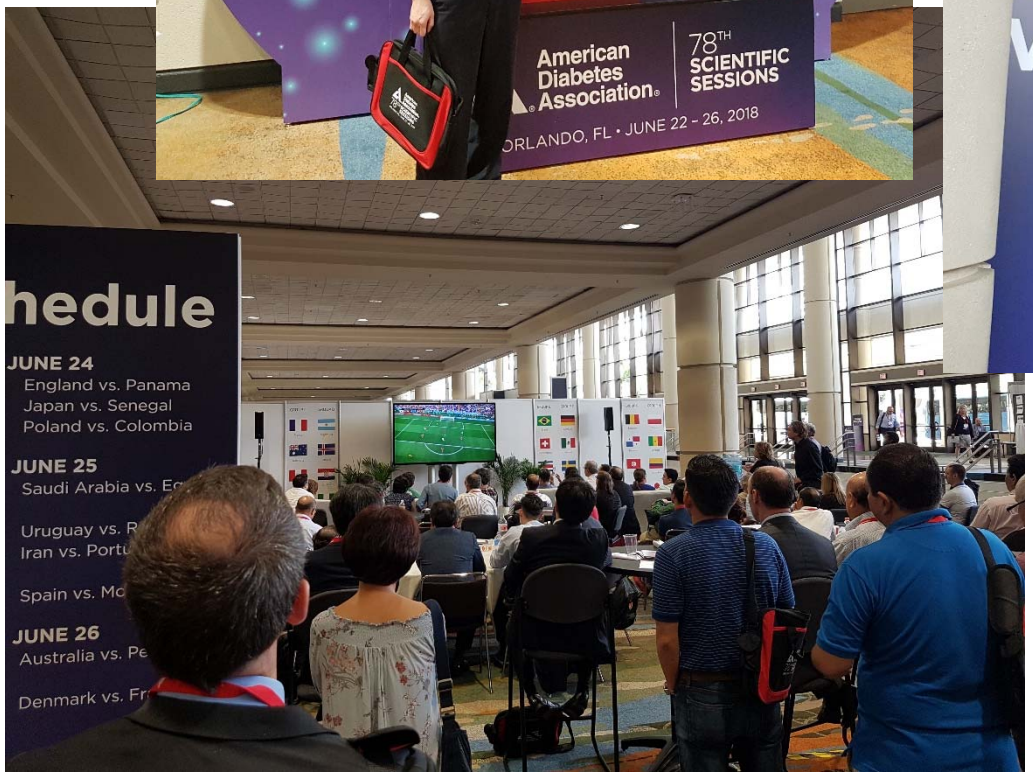
SESSIONS
ORLANDO, FL • JUNE 22 – 26, 2018

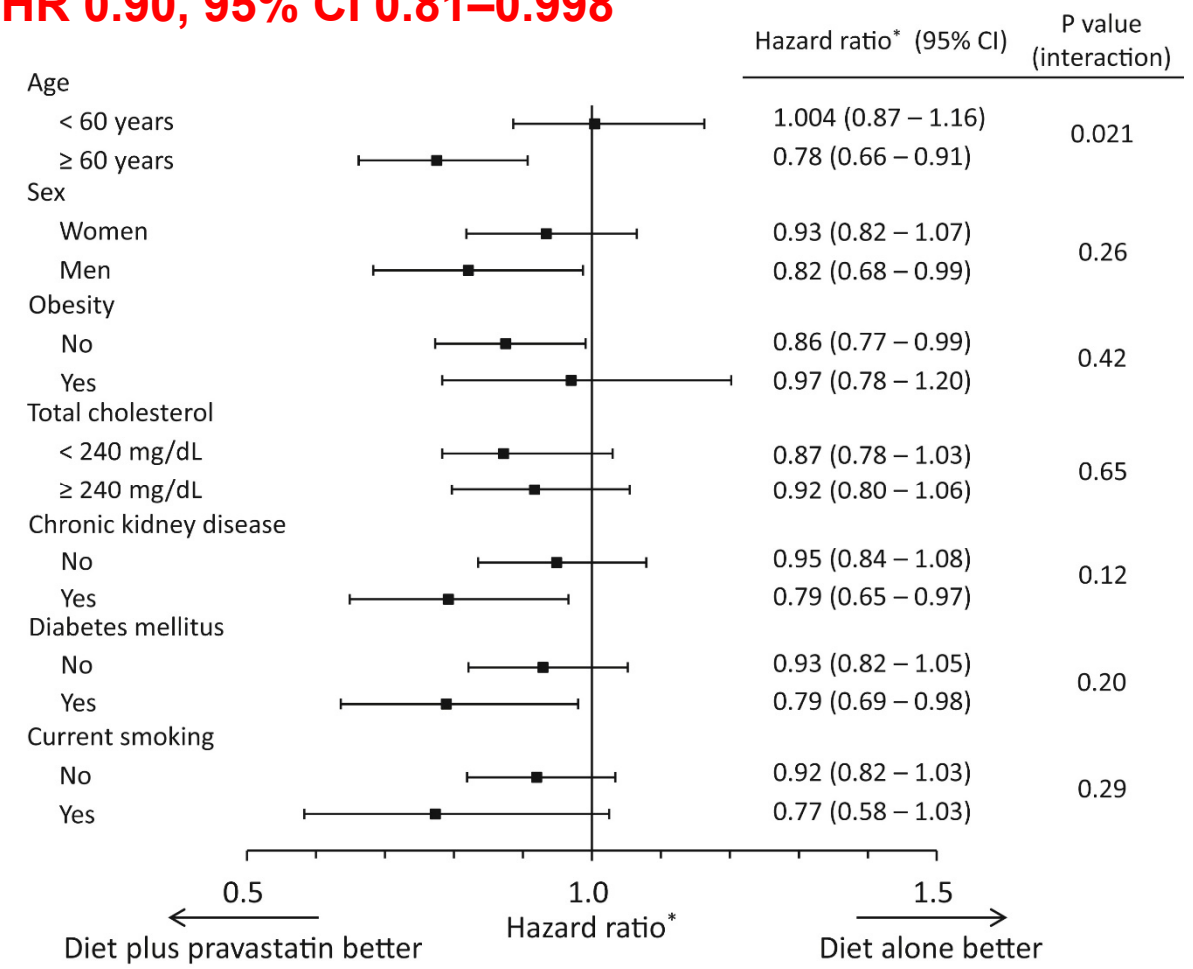

World Cup
Lounge


hedule
JUNE 24
England vs. Panama
Japan vs. Senegal
Poland vs. Colombia
JUNE 25
JUNE 26

MEGA

Pravastatin reduced the risk of developing HTN

HR 0.90, 95% CI 0.81–0.998



J Clin Lipidol. 2017 Jul - Aug;11(4):998-1006

Case: A 65-year-old woman

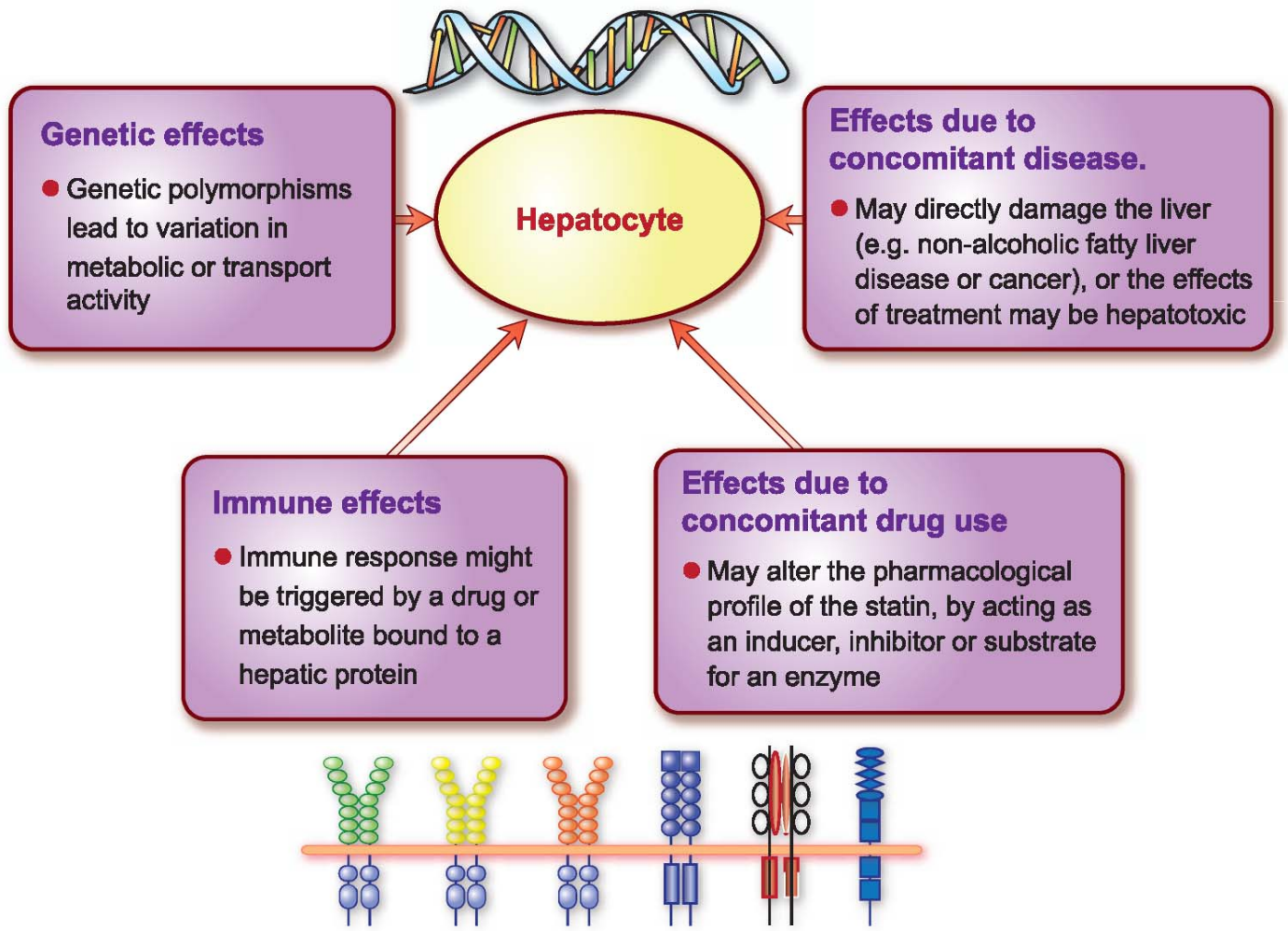
Stop and Think

- **The concern of NAFLD / NASH**

- 102-05

Hogsmeade

Factors that may affect *susceptibility* to *d*rug induced liver injury



Eur Heart J. 2018 Jul 14;39(27):2526-2539

Digestive and Liver Disease 44 (2012) 451–452

Contents lists available at SciVerse ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Commentary

If steatosis is the atherosclerosis of the liver, are statins the "aspirin" for steatosis?

Amedeo Lonardo, Paola Loria*

Operating Unit Metabolic Internal Medicine, University of Modena and Reggio Emilia, Italy

Dig Liver Dis. 2012 Jun;44(6):451-2

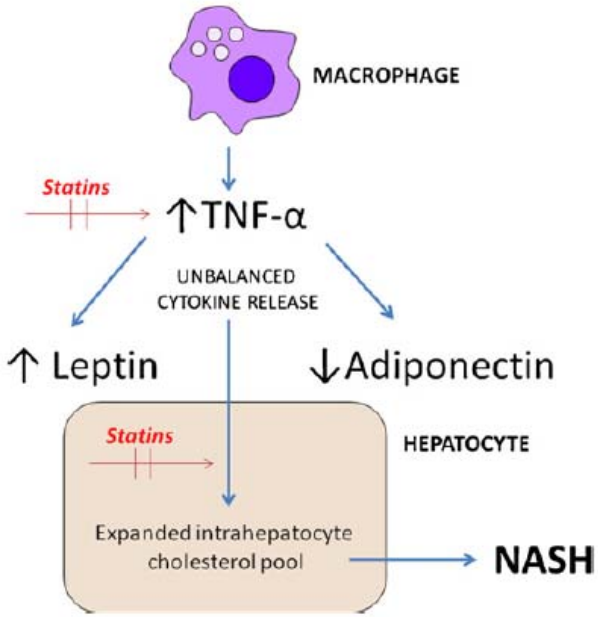


Fig. 1. Putative mechanism of action of statins in reversing the development of non-alcoholic steatohepatitis. Macrophage activation perturbs the proportion of released pro-inflammatory cytokines including increased TNF-α and leptin and decreased adiponectin levels [6]. In its turn, the inflammatory cytokine profile appears to promote expansion of the cholesterol pool within the hepatocyte [17–19]. The potential sites of action of statins along this biochemical cascade are highlighted in red.

Table 1 Hepatic safety and efficacy of lipid-lowering agents in patients with NAFLD or NASH and their effect on hepatic steatosis and fibrosis

Lipid-lowering agent	Author [ref]	Duration of study in months	Effect on serum liver enzyme activity	Effect on steatosis	Effect on fibrosis
Simvastatin	Abel et al. [29]	6	Improved	NS	NS
Simvastatin	Nelson et al. [30]	12	Improved partially	Ameliorate	Yes
Lovastatin	Mihaila et al. [31]	4	Improved	Ameliorate	NS
Pravastatin	Rallidis et al. [32]	6	Improved	Ameliorate	Yes
Pravastatin	Lewis et al. [33]	9	Improved	NS	NS
Pitavastatin	Hyogo et al. [34]	12	Improved partially	Ameliorate	NS
Atorvastatin	Gomez-Dominguez et al. [35]	6	Improved	NS	NS
Atorvastatin	Athyros et al. [36]	36	Improved	NS	NS
Atorvastatin	Kiyici et al. [37]	6	Improved	Ameliorate	NS
Atorvastatin	Kimura et al. [40]	12	Improved	Ameliorate	Yes
Atorvastatin	Athyros et al. [38]	12	Improved	Ameliorate	NS
Atorvastatin	Georgescu and Georgescu [39]	7 ± 1	Improved	Ameliorate	NS
Atorvastatin	Kimura et al. [40]	12	Improved	Ameliorate	NS
Atorvastatin	Samy et al. [41]	8	Improved	Ameliorate	NS
Rosuvastatin	Antonopoulos et al. [42]	8	Improved	NS	NS
Clofibrate	Laurin et al. [44]	12	Improved	NS	NS
Gemfibrozil	Basaranoglu et al. [45]	1	Improved	NS	NS
Fenofibrate	Fernandez-Miranda et al. [46]	12	Improved	NS	NS
Niacin	Fabbrini et al. [49]	4	Improved	NS	NS
Ezetimibe	Yoneda et al. [54]	6	Improved	Ameliorate	NS
Ezetimibe	Chan et al. [55]	4	Improved	Ameliorate	NS
Ezetimibe	Park et al. [56]	24	Improved	Ameliorate	NS
PUFA	Cappani et al. [61]	12	Improved	Ameliorate	NS
PUFA	Spadaro et al. [62]	6	Improved	Ameliorate	NS
PUFA	Tanaka et al. [64]	12	Improved	Ameliorate	Yes
PUFA and olive oil	Sofi et al. [65]	12	Improved	NS	NS
PUFA	Zhu et al. [66]	6	Improved	Ameliorate	NS

Dig Liver Dis. 2012 Jul;57(7):1773-81.

Key points

- Antiviral therapies directed against HBV and HCV are universally effective in primary and secondary prevention of hepatocellular carcinoma (HCC), but are associated with substantial costs and adverse effects
- Statin use is associated with decreased risk of HCC, potentially by inhibiting Myc activation and through inhibition of the mevalonate pathway
- In patients with diabetes, the use of metformin might reduce the risk of HCC through mTOR inhibition, whereas insulin and insulin-secreting agents might increase the risk of HCC
- Aspirin has also been shown to decrease risk of hepa… HCC in animal models, with early epidemiological stu… favourable association
- Dietary agents, such as coffee, vitamin E, fish rich in … fatty acids and dietary polyphenols, might also have a… against HCC
- Randomized controlled trials for chemopreventive age… and ethically challenging; prospective cohort studies t… confounders might be well-suited to inform us about th…

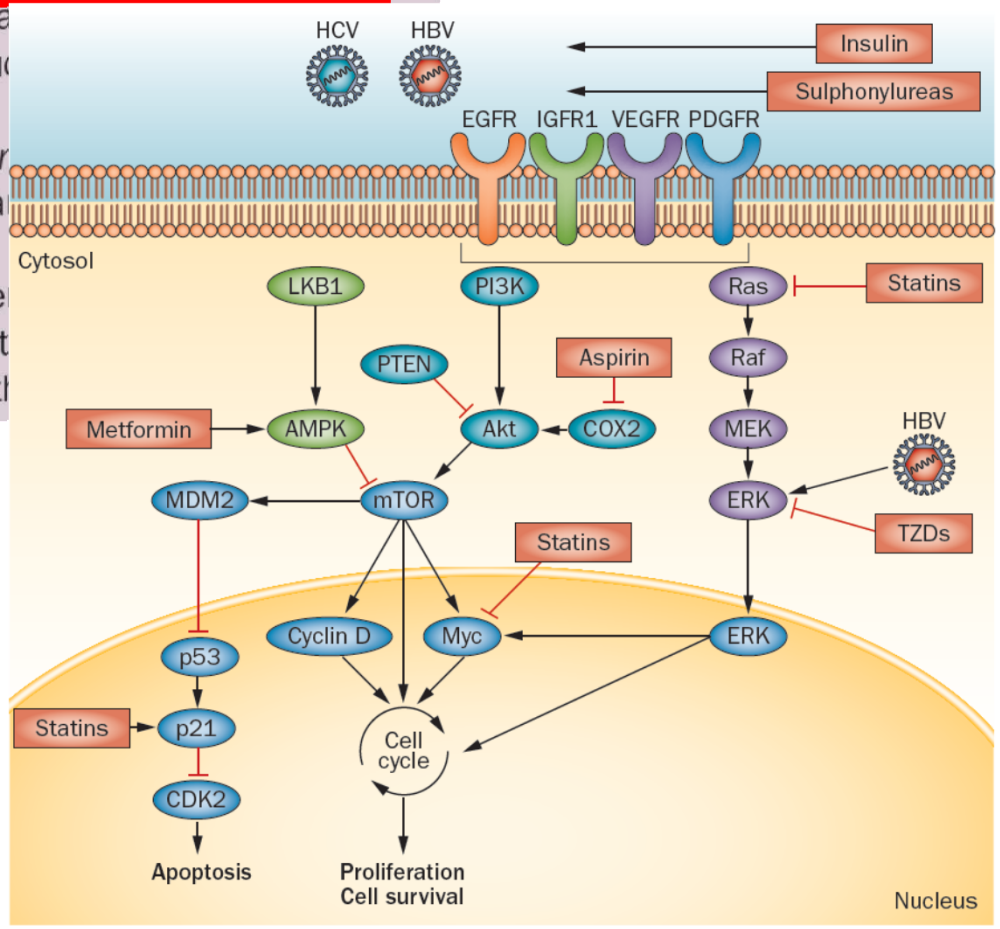


Figure 1 | Pathogenesis of HCC and targets for chemopreventive agents. Receptor

Nat Rev Gastroenterol Hepatol. 2014 Jan;11(1):45-54.

Statin use need NOT be avoided
in patients with preexisting liver dysfunction such as nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, compensated cirrhosis, and compensated chronic liver disease if its use is clearly indicated.

J Pharm Bioallied Sci. 2016 Jan-Mar;8(1):23-8.
Statins and its hepatic effects: Newer data, implications, and changing recommendations.

Retrospective Cohort Studies of Statins in patients with *cirrhosis*

Table 1. Retrospective Cohort Studies and Randomized Clinical Trials of Statins in patients with cirrhosis.

Retrospective Cohort Studies

Study	Patients source	Patients description	Study Design	Number of patients	Type of statin	Follow up period	Endpoints	Results	Comments
F. Chang Hepatology 2017	Taiwan National Health Insurance	Hepatitis B, Hepatitis C and Alcohol related cirrhosis	Retrospective cohort study	1,174 statin users vs. 6,453 non statin users	NA	Approx median of follow up of 3 years	Decompensation Death HCC development	Prevented decompensation aHR 0.39 (0.30-0.50) Decreased mortality aHR 0.46 (0.34-0.63) Decreased HCC aHR 0.52(0.35-0.76)	Lower risk of ascites, variceal bleeding and hepatic encephalopathy Analysis by etiology in HBV, HCV and OH cirrhosis. Dose-response relationship
Bang Aliment Pharmacol Ther 2017	Danish National Patient Registry	Alcohol related cirrhosis	Retrospective cohort study	794 statin users vs 4,623 non users	Simvastatin 79% Atorvastatin 8% Rosuvastatin 6%	Approx median of follow up of 4 years	Decompensation Death	Prevented decompensation HR 0.29 (0.24-0.34) Decreased mortality HR 0.57 (0.45-0.71)	Adjusted by adhesion to treatment but not for liver function scores. HE not evaluated
Mohanty Gastroentero logy 2016	US Veterans Health Admin	Hepatitis C related compensated cirrhosis	Retrospective cohort study	1,323 statins users vs 12,522 non statin users	Simvastatin 85% Lovastatin 10% Pravastatin 3% Rosuvastatin 1% Fluvastatin 1%	Median of 2.5 years for statin users, 1.5 years for non-users	Decompensation Death	Prevented decompensation aHR 0,55 (0,39-0,77) Decreased mortality aHR 0,56 (0,46-0,69)	Adjusted for liver tests and scores. Lower risk of ascites and variceal hemorrage
Kumar Dig Dis Sci 2014	Partners Research Patient Data Registry	NASH, OH, Hepatitis C and Hepatitis B related cirrhosis	Retrospective cohort study	81 statin users vs. 162 non statin users	Simvastatin 49% Atorvastatin 30%	3 Years for statin users, 2.5 years for non-statin users	Decompensation Death	Prevented decompensation HR 0.58 (0.34-0.98) Decreased mortality HR 0.66 (0.33-0.86)	Low number of patients included, risk of selection and reporting biass. Biopsy proven cirrhosis
C. M-Feagans Aliment Pharmacol Ther 2013	US Veterans Health Admin	Hepatitis C and alcohol related cirrhosis	Retrospective cohort study	2,468 statin users vs. 16,408 non statin users	Simvastatin 90% Lovastatin 9%	3.3 years	Infections	Prevented infections aHR 0,67 (0,47-0,95)	Adjusted for age and comorbidities. No data of liver function

J Hepatol. 2018 Jul 31. doi: 10.1016/j.jhep.2018.07.019. [Epub ahead of print]

RCTs of Statins in patients with *cirrhosis*

Randomized Clinical Trials

Study	Patients source	Patients description	Study Design	Number of patients	Type of statin	Follow up period	Endpoints	Results	Comments
Abraldes, Gastroenterology, 2009	University Hospitals	Cirrhosis and portal hypertension (HVPG>12 mmHg)	Multicenter randomized Clinical Trial (3 centers)	27 patients on statin treatment vs. 28 patients on placebo	Simvastatin	One month	Change in HVPG	Decreased HVPG from 18.5 to 17.1 (p=0.003) , not decrease in placebo group	Simvastatin administration improved quantitative tests of liver funtion (indiocyanine green clearance) Non severe adverse events related to medication
P. Pollo-Flores, Digestive and Liver Disease, 2015	University Hospital	Cirrhosis and portal hypertension (HVPG>5 mmHg)	Single center randomized Clinical Trial	14 patients under statins treatment vs. 20 patients on placebo	Simvastatin	Three months	Change in HVPG	Reduced HVPG in patients under statin treatment compared to placebo: -2 vs. 0mmHg, p=0.02	Previous variceal bleeding independent variable associated with response to simvastatin Non severe adverse events related to medication
Abraldes, Gastroenterology, 2016	University Hospitals	Cirrhosis and variceal bleeding 5-10 days before inclusion	Multicenter randomized Clinical Trial (14 centers)	69 patients under statin treatment vs. 78 patients on placebo	Simvastatin	Two years	Composite endpoint (rebleeding or death) Death	Not significant decrease in risk of rebleeding or death Decreased mortality HR 0.39(0.15-0.98)	Decrease in liver related death Not significant decresae in the primary endopoint or in specific complications of cirrhosis
Bishnu, Eur J Gastroenterol Hepatol, 2018	University Hospital	Cirrhosis and portal hypertension	Single center randomized Clinical Trial	11 patients atorvastatin + propranolol vs. 12 placebo + propranolol	Atorvastatin	One month	Change in HVPG	Decreased HVPG 4.81 ± 2.82 vs. 2.58 ± 1.88 mmHg	No significant differences in clinical outcomes after one year follow-up

J Hepatol. 2018 Jul 31. doi: 10.1016/j.jhep.2018.07.019. [Epub ahead of print]

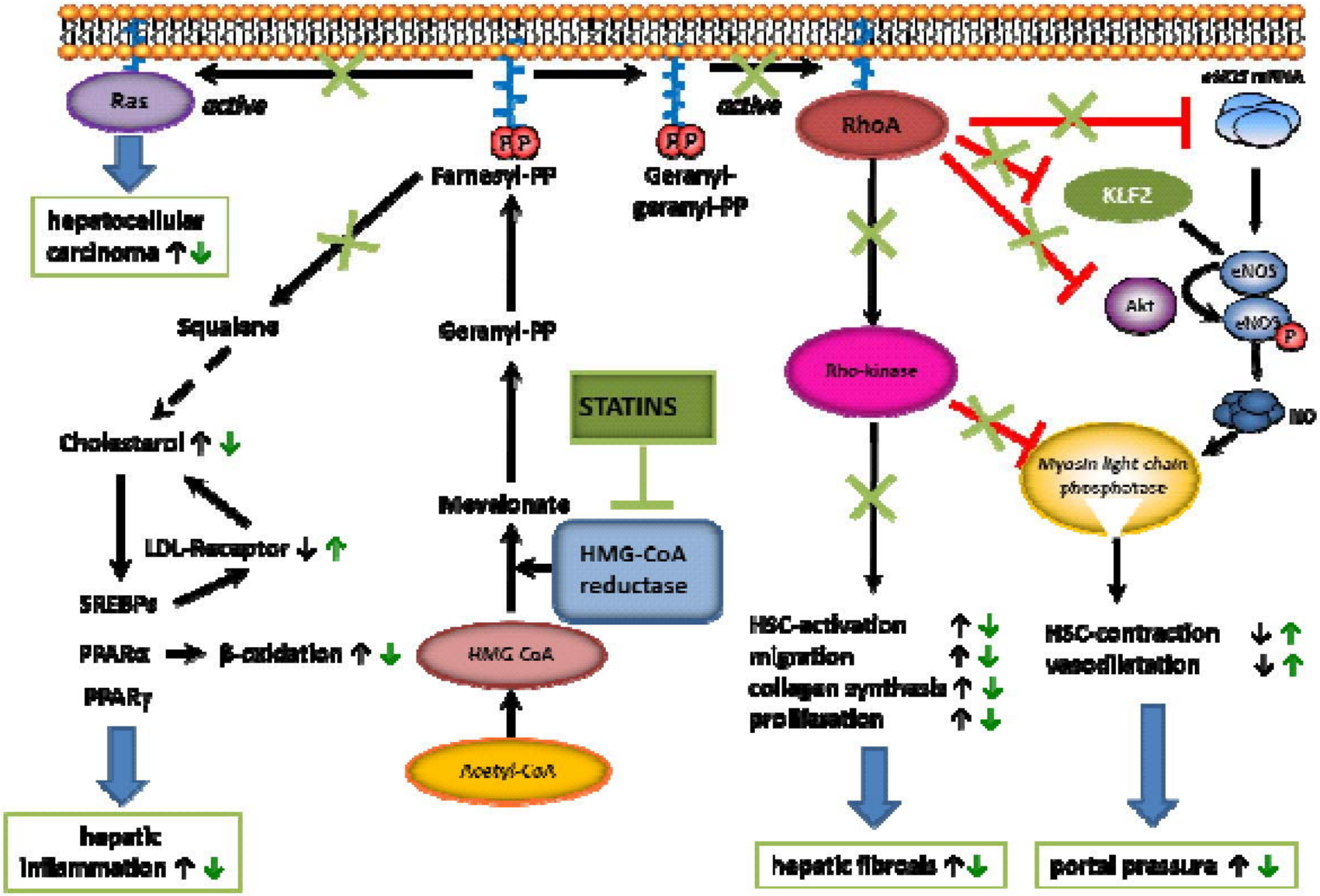
Statins: old drugs as new therapy for liver diseases?

- **Pre-cirrhotic conditions**: statins may have beneficial effects by preventing disease progression.

- **Cirrhosis**: statins have shown potential beneficial effects by decreasing portal hypertension and risk of decompensation and may improve survival.

- RCTs in large series of patients are needed to confirm safety and beneficial effects of statins in patients with cirrhosis.

J Hepatol. 2018 Jul 31. doi: 10.1016/j.jhep.2018.07.019. [Epub ahead of print]



J Hepatol. 2018 Jul 31. doi: 10.1016/j.jhep.2018.07.019. [Epub ahead of print]

Stop and Think

The concern of new-onset DM

- 102-05

食品藥物管理局
Food and Drug Administration

藥求安全・食在安心

新　聞　稿

日期	101.2.29	單位	藥品組	編號	
標題	食品藥物管理管理局說明降膽固醇 statin 類藥品用藥安全資訊				

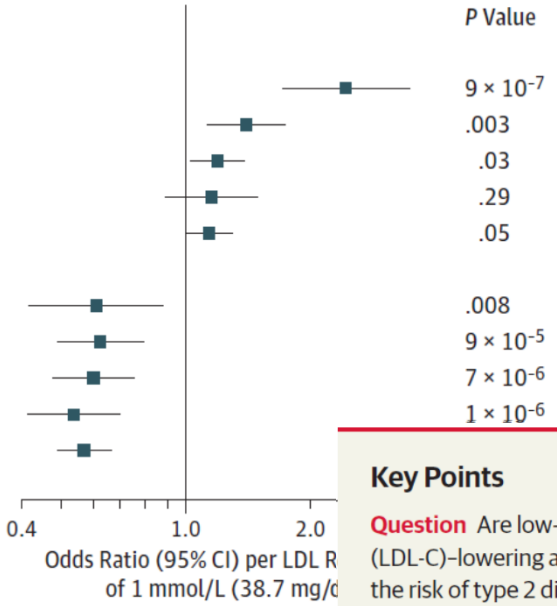
最近美國食品藥物管理局於回顧 statin 類藥品之上市後安全資訊及多個臨床試驗結果報告，作出以下建議 (1)肝功能監測：病人於開始使用 statin 前，需監測肝功能指數，服藥期間若出現疑似肝功能異常之臨床症狀時，需再次檢測肝功能指數；(2)於仿單中新增不良事件訊息：部分報告顯示，該類藥品可能導致非嚴重且停藥後可恢復之可逆性認知障礙（例如失憶、混亂），及些微增加血糖及糖化血色素(HbA1c)上升之風險；惟美國食品藥物管理局認為該類藥品對心血管之臨床效益仍高於些微血糖上升之風險 (3) lovastatin 藥物交互作用：lovastatin 併用 CYP3A4 抑制劑藥品時會產生交互作用，而提高橫紋肌溶解症之不良反應風險。

JAMA | Original Investigation

Association Between Low-Density Lipoprotein Cholesterol–Lowering Genetic Variants and Risk of Type 2 Diabetes
A Meta-analysis

Figure. Association of Low-Density Lipoprotein Cholesterol (LDL-C)–Lowering Genetic Variants With Coronary Artery Disease and Type 2 Diabetes

	No. of Genetic Variants	Odds Ratio (95% CI)	*P* Value
Type 2 diabetes			
NPC1L1	2	2.42 (1.70-3.43)	9×10^{-7}
HMGCR	3	1.39 (1.12-1.73)	.003
PCSK9	1	1.19 (1.02-1.38)	.03
ABCG5/G8	1	1.15 (0.89-1.48)	.29
LDLR	1	1.13 (1.00-1.29)	.05
Coronary artery disease			
NPC1L1	2	0.61 (0.42-0.88)	.008
HMGCR	3	0.62 (0.49-0.79)	9×10^{-5}
PCSK9	1	0.60 (0.48-0.75)	7×10^{-6}
ABCG5/G8	1	0.54 (0.42-0.69)	1×10^{-6}
LDLR	1	0.57 (0.49-0.66)	



Coronary artery disease data are from 60 801 cases with coronary artery disease and 123 504 controls from the Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics (CARDIoGRAMplusC4D) Consortium.[19] Type 2 diabetes data are from 50 775 cases of type 2 diabetes and 270 269 controls from European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study,[13] the UK Biobank study,[14] and the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM).[15] In addition to
and DIAGRAM,[15] type 2 diab
included 11 studies (4496 ca
Swerdlow et al.[5] Therefore, t
association with type 2 diabe
320 946 controls. All results
(38.7-mg/dL) genetically pre

Key Points

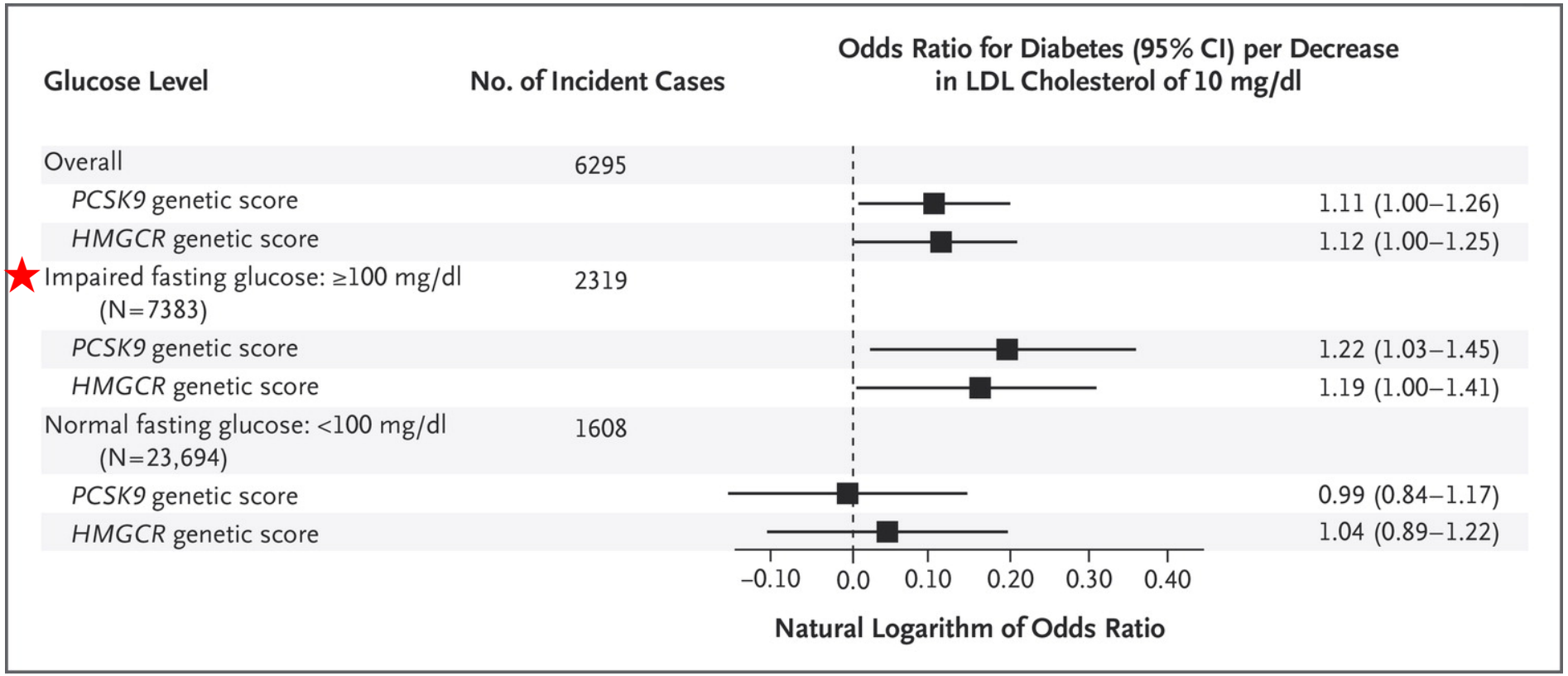
Question Are low-density lipoprotein cholesterol (LDL-C)–lowering alleles at *NPC1L1* or other genes associated with the risk of type 2 diabetes?

Findings In a meta-analysis of genetic association studies including 50 775 individuals with type 2 diabetes and 270 269 controls, LDL-C-lowering polymorphisms at *NPC1L1* were associated with a statistically significant odds ratio of 2.42 for type 2 diabetes per genetically predicted reduction of 1 mmol/L (38.7 mg/dL) in LDL-C. Low-density lipoprotein cholesterol–lowering polymorphisms at *HMGCR* and *PCSK9* were associated with a higher risk of diabetes.

Meaning These data provide insights into potential adverse effects of LDL-C-lowering therapy.

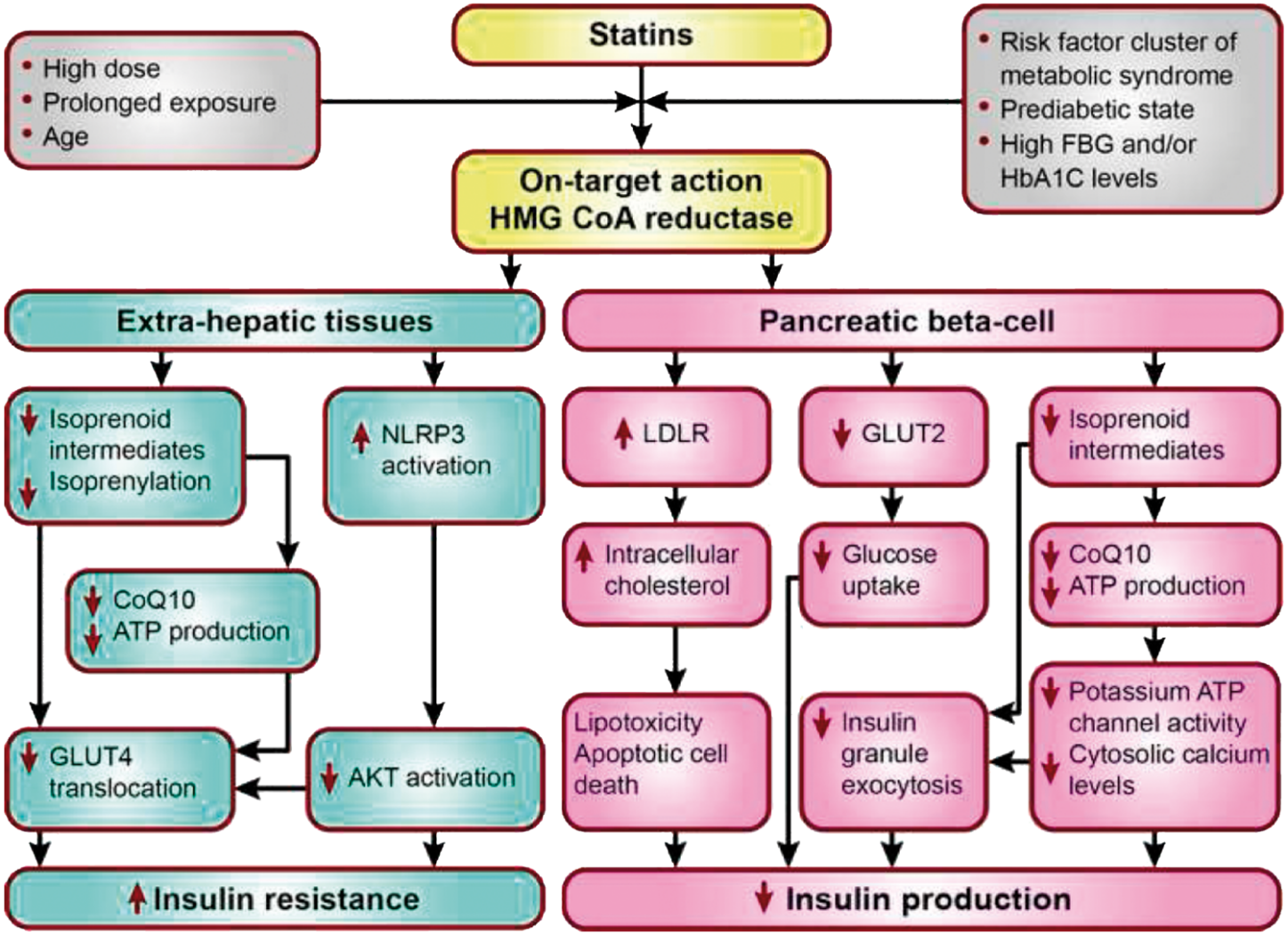
JAMA. 2016 Oct 4;316(13):1383-1391.

Effect of PCSK9 and HMGCR Scores on the Risk of Incident Diabetes



N Engl J Med 2016 Dec; 375:2144-2153

Factors favoring *diabetogenic* effects of statins

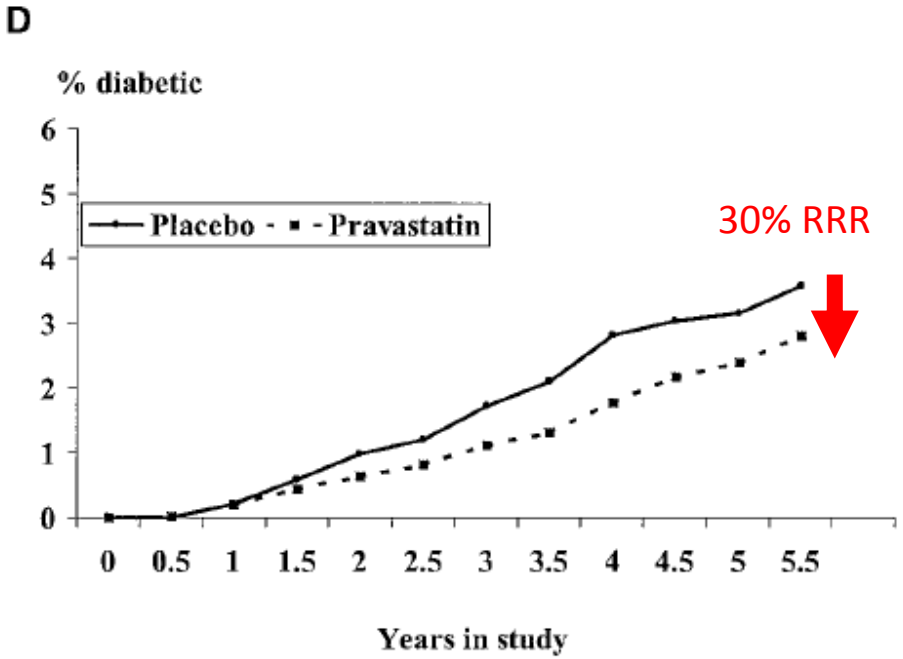


Eur Heart J. 2018 Jul 14;39(27):2526-2539

Pravastatin and the Development of Diabetes Mellitus

Evidence for a Protective Treatment Effect in the West of Scotland Coronary Prevention Study

Dilys J. Freeman, PhD; John Norrie, MSc; Naveed Sattar, PhD; R. Dermot G. Neely, MD; Stuart M. Cobbe, MD; Ian Ford, PhD; Christopher Isles, MD; A. Ross Lorimer, MD; Peter W. Macfarlane, PhD; James H. McKillop, MD; Christopher J. Packard, PhD; James Shepherd, PhD; Allan Gaw, MD, PhD



- Pravastatin treatment itself significantly influenced development of diabetes (hazard ratio 0.70, 95% CI 0.50 to 0.98; *P<0.036).*

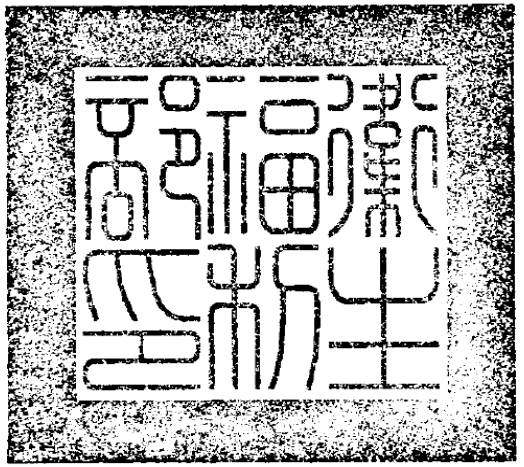
Freeman DJ et al. Circulation 2001; 103:357-362

衛福部公告：
(2014年4月3日)

基於**pravastatin**之化學特性與其他HMG-CoA還原酶抑制劑(statin類)不同，且近期有關含pravastatin成分藥品於糖尿病相關之醫學文獻顯示，使用含pravastatin成分藥品與使用安慰劑相比，**並未發現血糖增加等相關不良反應**，故中文仿單得**免刊載**衛福部於102年10月11日公告之公告事項第一項第一點第一款之「醣化血色素上升：病患接受HMG-CoA還原酶抑制劑(statin類)治療後，曾有醣化血色素及或空腹血漿血糖值上升的情況」的警語。

衛生福利部　公告

發文日期：中華民國103年4月3日
發文字號：部授食字第1036001343A號
附件：



主旨：含pravastatin成分藥品之中文仿單修訂相關事宜

依據：藥事法第48條。

公告事項：

一、基於pravastatin之化學特性與其他HMG-CoA還原酶抑制劑(statin類)不同，且近期有關含pravastatin成分藥品於糖尿病相關之醫學文獻顯示，使用含pravastatin成分藥品與使用安慰劑相比，並未發現血糖增加等相關不良反應，故含該成分藥品之中文仿單，得免刊載本部於102年10月11日部授食字第1021402914A號公告之公告事項第一項第一點第一款之「醣化血色素上升:病患接受HMG-CoA還原劑(statin類藥品)治療後，曾有醣化血色素及/或空腹血漿血糖值上升的情況」。

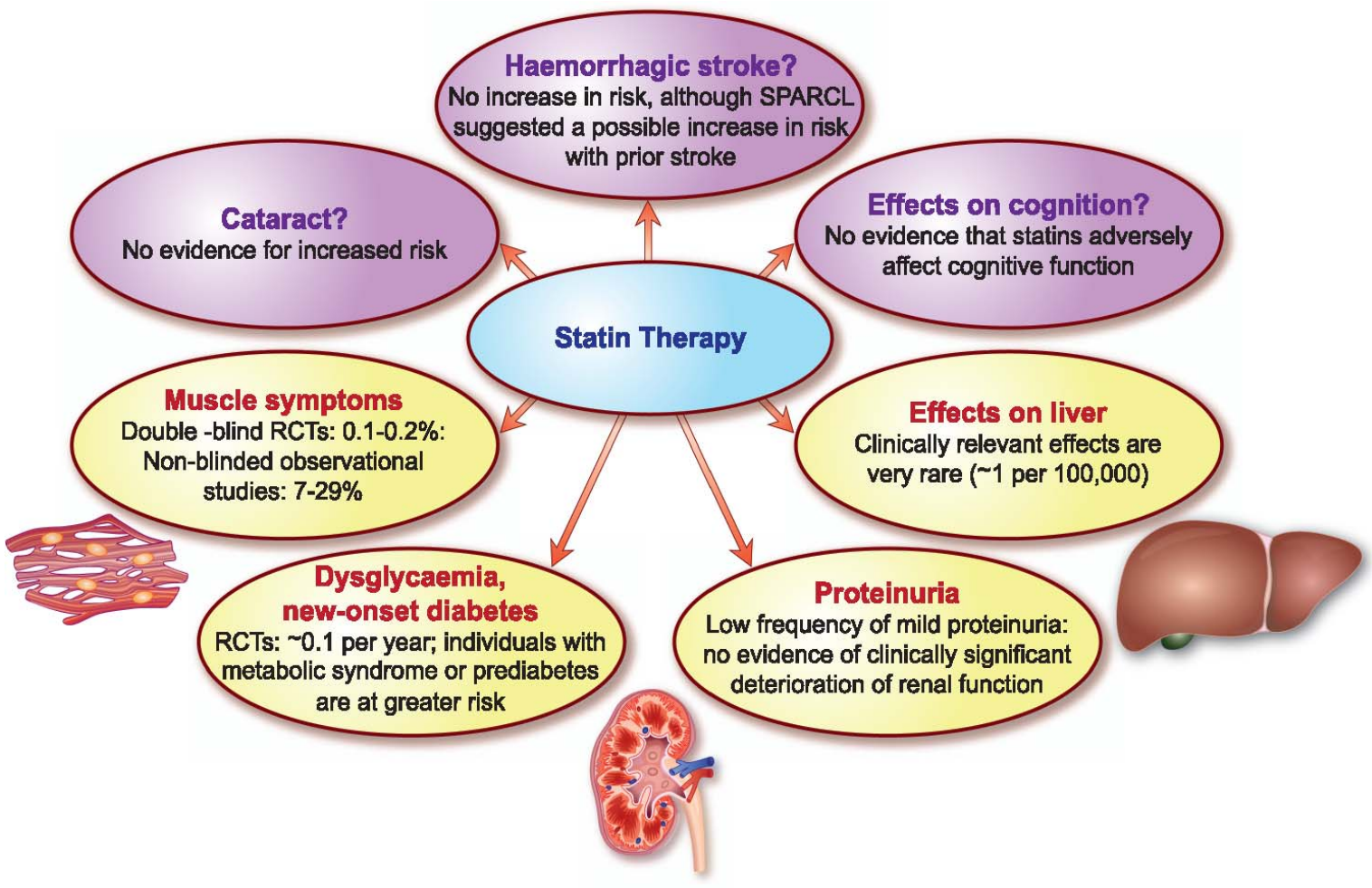
Case: A 65-year-old woman

*Pra*vastatin experience from CH Clinic

Patient report at the last visit: **89 patients**

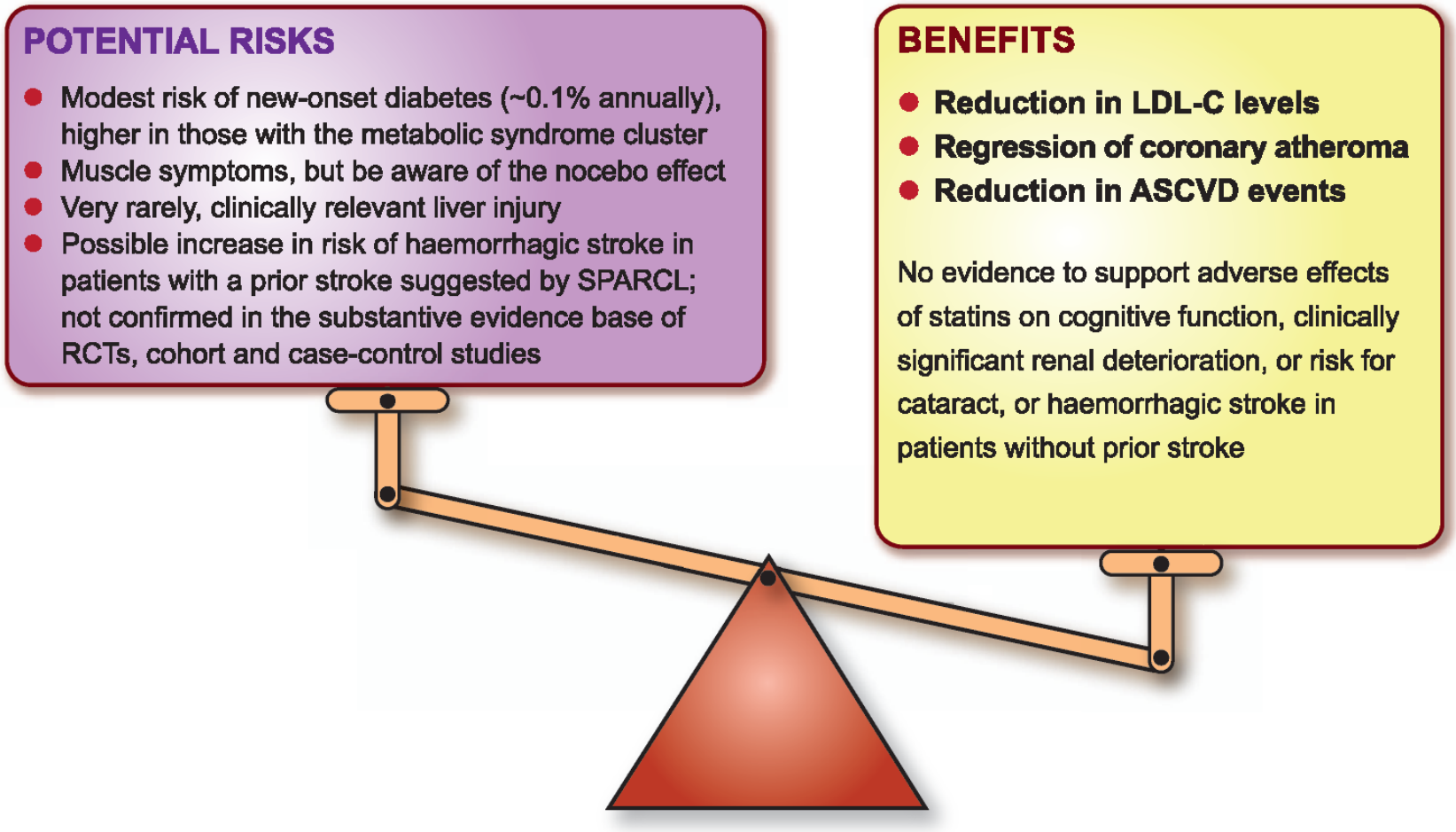
Composite adverse events:
SAMS, dysglycemia, and elevated ALT levels.

The relative prevalence of the main types of adverse effects reported with statin therapy



Eur Heart J. 2018 Jul 14;39(27):2526-2539

Highly favourable Benefit / Risk Ratio for statin therapy



Eur Heart J. 2018 Jul 14;39(27):2526-2539

*Pra*vastatin

Key Points

- **Pravastatin** benefit primary and secondary prevention of CHD events.
- **Myopathy concern**: hydrophilic. **Step by step approach**. Nocebo…
- **Drug-statin interaction:** little
- **Liver:** improving > deteriorating
- **CKD:** safe under right dosage
- **NODM:** Pravastatin has little concern.

戴資穎/ Tai Tzu Ying
郭婞淳 KUO, Hsing-Chun
文姿云wen,tzu-yun
李智凱 Chih Kai Lee