Balancing Efficacy and Safety in Treating Dyslipidemia Patients

效能與安全性的絕佳平衡

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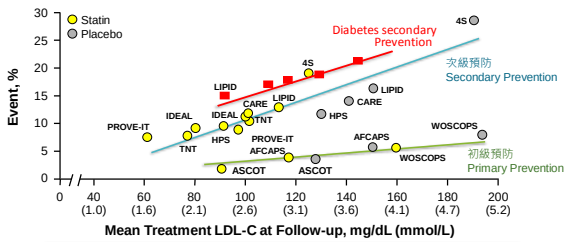
2020/03/11

主要內容

- 積極治療血脂的重要性-血脂治療指引
- 亞洲族群重要的心血管試驗-REAL-CAD study
- Pitavastatin療效與安全性的實證醫學

LDL-C與冠狀動脈心臟病(CAD/CHD)發生率呈正相關



It is estimated that 1% reduction in LDL-C levels, the relative risk for major CHD events is reduced by approximately 1%

IDEAL=Incremental Decrease in Endpoints through Aggressive Lipid Lowering; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; AFCAPS=Air Force Coronary Atherosclerosis Prevention Study; WOSCOPS=West of Scotland Coronary Prevention Study.
Adapted from Rosenson RS. *Expert Opin Emerg Drugs.* 2004;9(2):269–279; LaRosa JC, et al. *N Engl J Med.* 2005;352(14):1425–1435; Pedersen TR, et al. *JAMA.* 2005;294(19):2437–2445.

2017台灣高風險病人血脂治療指引 (High risk)


2017 Taiwan lipid guidelines for high risk patients

七大醫學會：
中華民國血脂及動脈硬化學會、中華民國心臟學會、臺灣介入性心臟血管醫學會、台灣腦中風學會、中華民國糖尿病學會、中華民國糖尿病衛教學會、台灣腎臟醫學

J Formos Med Assoc. 2017 Apr;116(4):217-248.

2019年健保給付規範(108/2/1)

將急性冠心症候群、高風險心血管疾病者的LDL-C治療目標下修到70mg／dL以下

	非藥物治療	起始藥物治療血脂值	血脂目標值	處方規定
1. 有急性冠狀動脈症候群病史 2. 曾接受心導管介入治療或外科冠狀動脈搭橋手術之冠狀動脈粥狀硬化 患者(108/2/1)	與藥物治療可並行	LDL-C≧70mg/dL	LDL-C＜70mg/dL	第一年應每3-6個月抽血檢查一次，第二年以後應至少每6-12個月抽血檢查一次，同時請注意副作用之產生如肝功能異常，橫紋肌溶解症。
心血管疾病或糖尿病患者	與藥物治療可並行	TC≧160mg/dL 或 LDL-C≧100mg/dL	TC＜160mg/dL 或 LDL-C＜100mg/dL	
2個危險因子或以上	給藥前應有3-6個月非藥物治療	TC≧200mg/dL 或 LDL-C≧130mg/dL	TC＜200mg/dL 或 LDL-C＜130mg/dL	
1個危險因子	給藥前應有3-6個月非藥物治療	TC≧240mg/dL 或 LDL-C≧160mg/dL	TC＜240mg/dL 或 LDL-C＜160mg/dL	
0個危險因子	給藥前應有3-6個月非藥物治療	LDL-C≧190mg/dL	LDL-C＜190mg/dL	

心血管疾病定義：
(一)冠狀動脈鈣化硬化病人：心絞痛病人，有心導管證實或缺氧性心電圖變化或負荷性試驗陽性反應者(附檢查報告)
(二)缺血型腦血管疾病病人包含：
1.腦梗塞。
2.暫時性腦缺血患者(TIA)。（診斷須由神經科醫師確立）
3.有症狀之頸動脈狹窄。（診斷須由神經科醫師確立）

危險因子定義：
1. 高血壓
2. 男性≥45歲，女性≥55歲或停經者
3. 有早發性冠心病家族史(男性≦55歲，女性≦65歲)
4. HDL-C<40mg/dL
5. 吸菸(因吸菸而符合起步治療準則之個案，若未戒菸而要求藥物治療，應以自費治療)。

2.6.1 全民健康保險停藥期間藥物給付規定表

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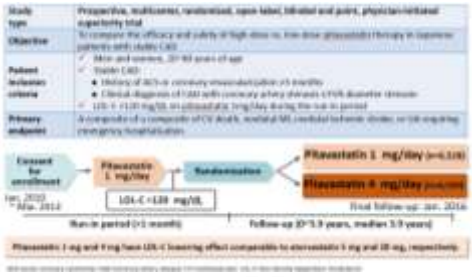
REAL-CAD Study

Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease

A prospective, multi-center, randomized, open-label, blinded endpoint, physician-initiated trial to determine whether **high-dose as compared with low-dose** pitavastatin therapy within the approved dose range could **reduce CV events** in Japanese patients with **stable CAD**.

Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

Study design



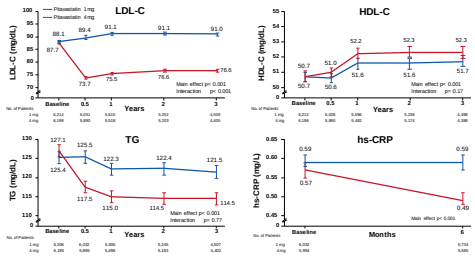
Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

Baseline Characteristics

Variables	Pitavastatin 1 mg (N=6,214)	Pitavastatin 4 mg (N=6,199)
Age — years	68.1±8.3	68.0±8.3
Male sex	83%	83%
BMI — kg/m²	24.6±3.4	24.6±3.3
Hypertension	75%	76%
Diabetes mellitus	40%	40%
Current smoking	16%	17%
History of ACS	72%	72%
ACS within 1 year before randomization	24%	24%
Coronary revascularization	91%	90%
Revascularization within 1 year before randomization	28%	28%
Ischemic stroke	7%	7%
Peripheral vascular disease	7%	7%
CKD (eGFR <60 mL/min/1.73m²)	36%	35%
Aspirin	93%	92%
DAPT	45%	44%
Statins before enrollment	91%	91%

Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

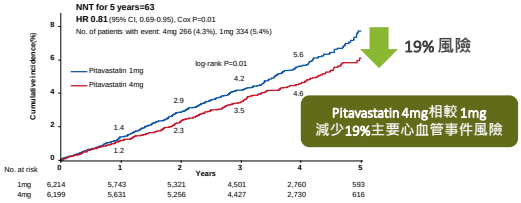
Significant reduction in lipid parameters



Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

Primary endpoint: CV death/MI/ischemic stroke/UA

Pitavastatin 4 mg/day significantly reduced the primary endpoint vs. pitavastatin 1 mg/day.

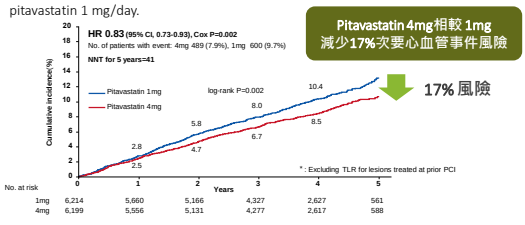


CAD=coronary artery disease; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; MI=myocardial infarction; UA=unstable angina.

Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

Secondary endpoint: Primary endpoint + coronary revascularization*

Pitavastatin 4 mg/day significantly reduced the secondary composite endpoint vs. pitavastatin 1 mg/day.



* Excluding TLR for lesions treated at prior PCI.
CI=confidence interval; HR=hazard ratio; PCI=percutaneous coronary intervention; TLR=target lesion revascularization.

Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

Other secondary endpoints

Outcomes	No. of patients with event (%) 1 mg (n=6,214)	4 mg (n=6,199)	HR(95% CI)	P Value
Death from any cause	260 (4.2)	207 (3.3)	0.81 (0.68-0.98)	0.03
CV death	112 (1.8)	86 (1.4)	0.78 (0.59-1.04)	0.09
MI	72 (1.2)	40 (0.6)	0.57 (0.38-0.83)	0.004
Ischemic stroke	83 (1.3)	84 (1.4)	1.03 (0.76-1.40)	0.84
Hemorrhagic stroke	30 (0.5)	43 (0.7)	1.46 (0.92-2.33)	0.11
Unstable angina requiring emergency hospitalization	90 (1.4)	76 (1.2)	0.86 (0.63-1.17)	0.34
Coronary revascularization (Any)	626 (10.1)	529 (8.5)	0.86 (0.76-0.96)	0.008
Coronary revascularization (non-TLR)	356 (5.7)	277 (4.5)	0.79 (0.68-0.92)	0.003
Coronary revascularization (TLR)	319 (5.1)	276 (4.5)	0.88 (0.75-1.03)	0.12

4 mg Better ← 1 mg Better →

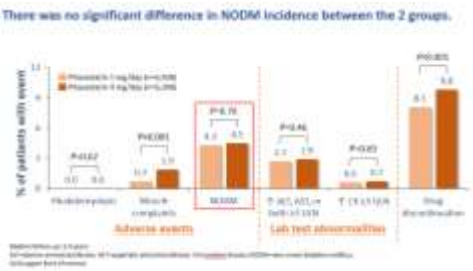
Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

REAL-CAD demonstrate significant reduction in all-cause mortality

Trial	Therapy	Follow-up (years)	Mean LDL-C reduction in aggressive arm (mg/dL)	Composite primary endpoint in aggressive arm vs. moderate arm	Deaths in aggressive arm vs. moderate arm
REAL-CAD	Pitavastatin 4 mg vs. Pitavastatin1 mg	3.9	15	-19% P=0.01	-19% P=0.03
PROVE-IT	Atorvastatin 80 mg vs. pravastatin 40 mg	2	33	-16% P=0.005	-28% P=0.07
IDEAL	Atorvastatin 80 mg vs. simvastatin 20–40 mg	4.8	23	-11% P=0.07	-2% P=0.81
IMPROVE-IT	Simvastatin vs. simvastatin + ezetimibe	6	16	-6.4% P=0.016	-1% P=0.78
TNT	Atorvastatin 80 mg vs. Atorvastatin 10 mg	4.9	24	-22% P<0.001	+1.0% P=0.92
FOURIER	Statin vs. statin + evolocumab	2.2	56	-15% P<0.001	+4.0% P=0.54

CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol.
FOURIER=Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; IDEAL=Initiating Dialysis Early and Late; IMPROVE-IT=Improved Reduction of Outcomes: Vytorin Efficacy International; PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy; REAL-CAD=Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease; TNT=Treatment to New Targets.
Barter PJ. Circulation. 2018;137(19):2013-5.

Safety outcomes



Taguchi I, et al. Circulation. 2018;137(19):1997-2009.

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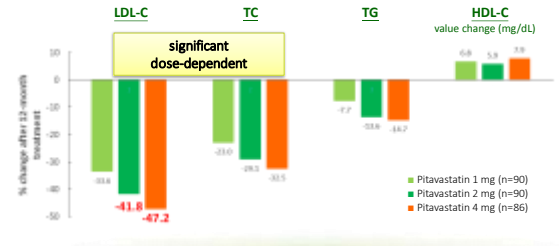
Pitavastatin有效降低LDL-C達41%、47%

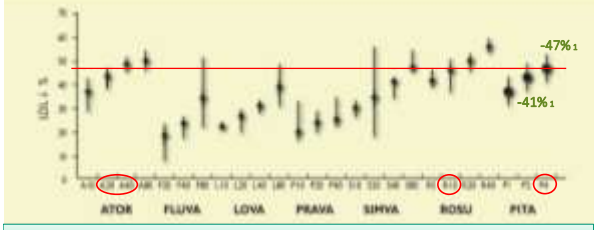
經過12個月的治療後，Pitavastatin 1~4mg 有效降低LDL-C, TC , TG，以及顯著提升HDL-C



Saito Y, et al. Arzneim-Forsch/Drug Res. 2002;52(4):251-5.

2016 ESC/EAS Guidelines

Statin降LDL-C的效果與劑量相關(dose dependent)，且不同的statin效果存在差異



Pitavastatin 4 mg ≒ Atorvastatin 20 mg ≒ Rosuvastatin 10mg[3]

1. Ther Adv Chronic Dis. 2011 Mar; 2(2): 101–117.
2. European Heart Journal (2016) 37, 2999–3058
3. Mukhtar RY, et al. Int J Clin Pract. 2005;59(2):239-52.

2018 AHA Statin Intensity Classification

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering*	≥50%	30%–49%	<30%
Statins	Atorvastatin 40 mg(+) 80 mg Rosuvastatin 20 mg (40 mg	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§	Simvastatin 10 mg
	–	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

Grundy SM, et al. 2018 Cholesterol Clinical Practice Guidelines

Racial Differences in the Cholesterol-Lowering Effect of Statin

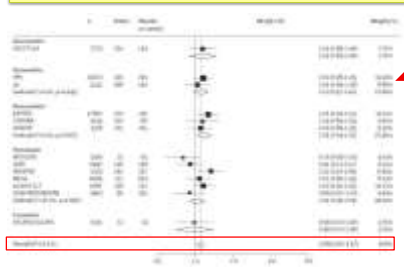
In Japanese patients, a lower dose of statins has demonstrated similar relative risk reduction of cardiovascular events to a higher dose of statins in Western patients.
The differences in response to statins between Asians and Westerners were observed for all statins except for pitavastatin.

Maximum dose of statins in Japan and U.S.

Taiwan(mg)	20	4	40	40	40	80

Statin類藥物對新生糖尿病的風險

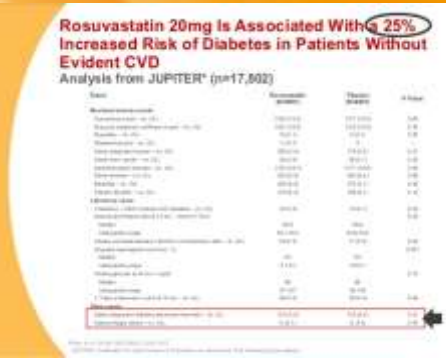
Meta-analysis 研究發現Statin有些微增加新生糖尿病的風險



+9%
(OR=1.09)
risk of new-onset DM
Statin therapy

CI=confidence interval; DM=diabetes mellitus; OR=odds ratio
Sattar N, et al. Lancet. 2010;375(9716):735-42.

Rosuvastatin 增加25% DM



2012年FDA網站警語

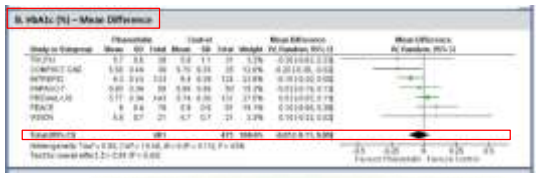
The FDA is making several changes to the labels of statins following a comprehensive review, the agency announced on Tuesday: http://www.fda.gov/Safety/MedWatch/Safe ... 293670.htm

•Incident diabetes and increased blood glucose are possible with statin use. Several meta-analyses found an increased risk for diabetes (9%–13%) **in patients taking statins.**

•Reversible memory loss and confusion are possible, though rare. The FDA said there is no evidence that these side effects lead to significant cognitive decline later.
•Routine monitoring of the liver enzyme alanine aminotransferase is no longer required, although testing before statin initiation and as clinically indicated is still recommended. The agency has concluded that serious liver injury among patients taking statins is rare and cannot be prevented with routine monitoring.
•Use of lovastatin is now contraindicated with strong CYP3A4 inhibitors — including itraconazole and erythromycin — to reduce the risk for rhabdomyolysis. Lovastatin's new label also lists dose limitations and several other drugs to avoid.

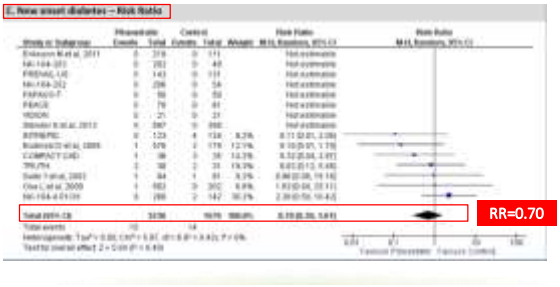
Pitavastatin 與對照組相比不易影響病人HbA1c Meta-analysis of RCT

Effect of pitavastatin on glucose, HbA1c and incident diabetes: A meta-analysis of randomized controlled clinical trials in individuals without diabetes



Vallejo-Vaz AJ, et al. Atherosclerosis. 2015;241(2):409-18.

Pitavastatin與對照組相比較無增加新生糖尿病風險
Meta-analysis of RCT



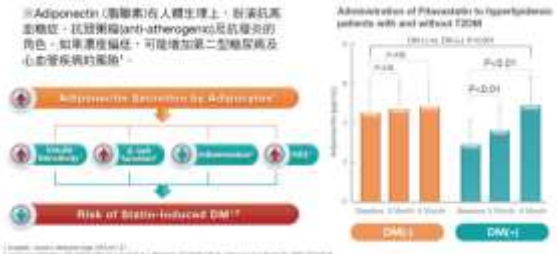
CI=confidence interval; DM=diabetes mellitus; RR=risk ratio.
Vallejo-Vaz AJ, et al. Atherosclerosis. 2015;241(2):409-18.

Zulitor 4mg 仿單記載:
Pitavastatin並未有明確造成糖尿病之徵兆

Diabetes Obes Metab. 2011 Nov;13(11):1047-55.

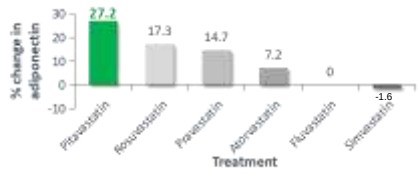
Pitavastatin可有效提高
糖尿病患者之Adiponectin

Advantage with Pitavastatin
Neutral effect on blood sugar



Effects of statins on plasma adiponectin

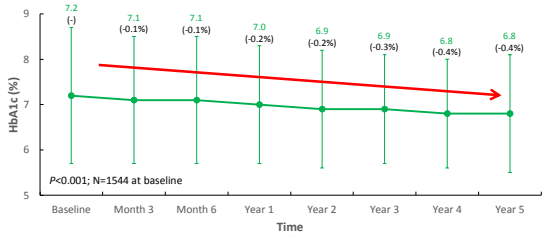
Pitavastatin exhibited a higher ability to increase plasma adiponectin level vs. other statins.



Arnaboldi L, Corsini A. Atheroscler Suppl. 2015;16:1-27.

LIVES study/LIVES study extension
No adverse effect on glucose metabolism

A significant decrease of HbA1c in DM patients was observed after long-term pitavastatin treatment.



DM=diabetes mellitus; HbA1c=hemoglobin A1c.
Teramoto T, et al. Jpn Pharmacol Ther 2011,39(9):789-803.

PIT-EM-1710003

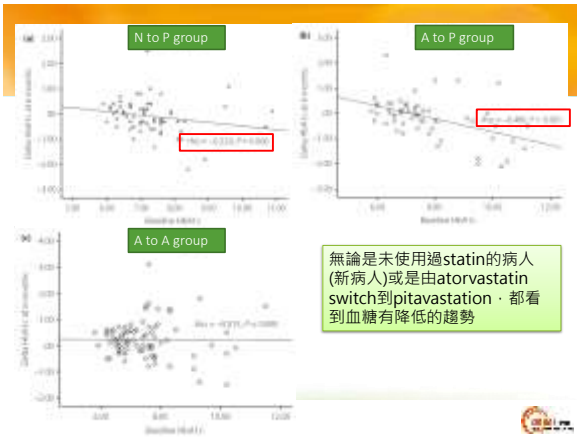

JDI Journal of Diabetes Investigation Open access

ORIGINAL ARTICLE

Pitavastatin improves glycated hemoglobin in patients with poorly controlled type 2 diabetes

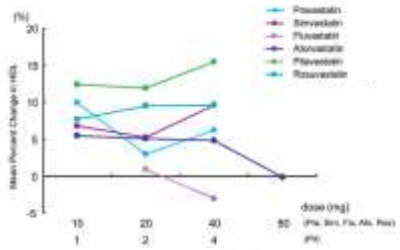
使用statin的
第二型糖尿病病人

只更改statin，糖尿病藥
不做任何調整



無論是未使用過statin的病人(新病人)或是由atorvastatin switch到pitavastation，都看到血糖有降低的趨勢

優異的HDL-C提升效果



ATO=atorvastatin; FLU=fluvastatin; PIT=pitavastatin; PRA=pravastatin; ROS=rosuvastatin; SIM=simvastatin.
Yamashita S, et al. J Atheroscler Thromb. 2010;17(5):436-51.

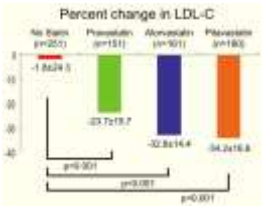
CIRCLE Study
觀察PCI術後的病人，Statin治療與心血管事件再發生的相關性

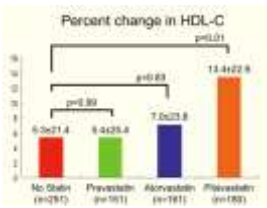
試驗類型	回溯性試驗
觀察族群	**Patients after PCI** (經皮冠狀動脈介入治療)
觀察重點	Statin對血脂治療的效果、與主要心血管不良事件(MACE)的相關性
病人數	743
觀察期間	2001-2008
地區	Kobe, Japan

Maruyama T, et al. Circ J. 2011;75(8):1951-9

CIRCLE Study

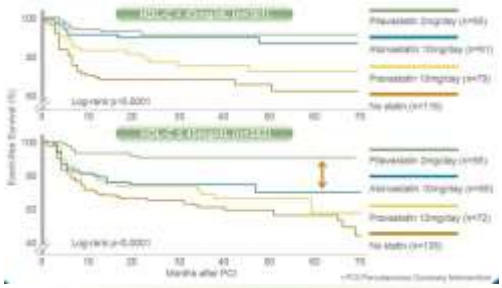
LDL-C相較於No-statin組皆有顯著下降　　只有**Pitavastatin的HDL-C**相較於No-statin**有顯著提升**





Maruyama T, et al. Circ J. 2011;75(8):1951-9

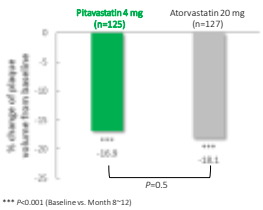
CIRCLE Study
觀察到PCI術後使用不同statin治療的Event-free Survival



*MACE=major adverse cardiac event; PCI=percutaneous coronary intervention.
Maruyama T, et al. Circ J. 2011;75(8):1951-9.

有效降低血管內斑塊體積，改善病患血管硬化程度

治療8~12個月之後，使用Pitavastatin 4mg的病人血管內斑塊體積明顯減少。



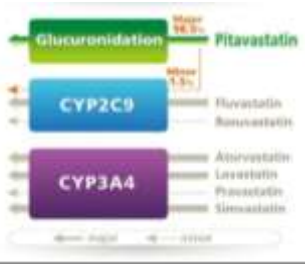
*** P<0.001 (Baseline vs. Month 8~12)

Hiro T, et al. J Am Coll Cardiol. 2009;54(4):293-302.

特殊代謝途徑，降低藥物交互作用風險

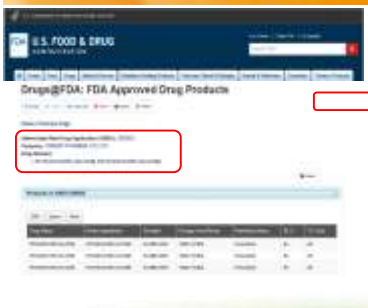
同時使用藥品數	交互作用機率
2	15%
5	40%
7	80%

Metabolic pathway of statin



ADR=adverse drug reaction; CYP=cytochrome P450; DDI=drug-drug interaction.
1. Corsini A, Ceska R. Curr Med Res Opin. 2011;27(8):1551-62.
2. Kawai Y, et al. Drug Des Devel Ther. 2011;5:283-97.

Zulitor (Pitavastatin 4mg) 獲USFDA 核准在美國上市



總結

1. 台灣2019年最新血脂治療藥物給付規定，將**高危險族群**的治療目標下修，建議**積極控制**低密度膽固醇，預防心血管事件發生。
2. **REAL-CAD研究證實，使用高劑量pitavastatin 4mg積極治療穩定型心血管疾病患者，可以降低心血管疾病發生風險。**
3. Pitavastatin 4mg可降低LDL-C 47%，對於糖尿病及非糖尿病患者的血糖影響小。
4. 且經特殊代謝途徑(不經過CYP3A4)，降低藥物交互作用風險，為醫師治療血脂異常患者(高重服藥病患)的理想選擇。

Zulitor patient type

1. Stable CAD 患者 (Ref: REAL CAD)
2. DM+CVD 患者 (Ref: REAL CAD)
3. Hypertension+CVD 患者 (Ref: REAL CAD)

4. 糖尿病患者(血糖波動高) (Ref:仿單- Zulitor 不影響血糖)
5. 多重服藥患者 (Ref:仿單-Zulitor 特殊代謝途徑)

6. PCI術後合併HDL<45 患者 (Ref: CIRCLE Study)

Thank you !!