成大醫院
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LDL-C goal attainment:

Role of aggressive approach with low dose dual combination

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Presenter Disclosure Information

Name: Yi-Heng Li

Within the past 12 months, the presenter had a financial interest/arrangement or affiliation with the organization listed below.

Company Name:	Relationship:
Pfizer	Consultant/Speaker bureau
Sanofi-Aventis	Consultant/Speaker bureau
Astra Zeneca	Consultant/Speaker bureau
Daiichi Sankyo	Consultant/Speaker bureau
Takeda	Consultant/Speaker bureau

LDL goal attainment

- Current international lipid guideline
- 全民健康保險降膽固醇藥物給付規定
- Current strategy
- Conclusions

2011 European Guidelines: Task Force for the Management of Dyslipidaemias of the ESC and EAS

Patient group	LDL-C treatment goal
Very high CV risk • **Established CVD**, **type 2 diabetes, type 1 diabetes with target organ damage, moderate-to-severe CKD** or a SCORE level of ≥10%	**<1.8 mmol/L (~<70 mg/dL) and/or ≥50% reduction when target level cannot be reached**
High CV risk • Markedly elevated single risk factors, a SCORE level of ≥5% to <10%	<2.5 mmol/L (~<100 mg/dL)
Moderate CV risk • SCORE level >1% to ≤5%	<3.0 mmol/L (~<115 mg/dL)

SCORE = Systematic Coronary Risk Estimation

Eur Heart J. 2011;32:1769-1818.

2011 ESC/EAS dyslipidemia guideline

● Very high risk (CVD, DM, CKD, >10%)

Subjects with any of the following:

1. **Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction (MI), ACS, coronary revascularization [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)] and other arterial revascularization procedures, ischemic stroke, PAD.**
2. **Patients with type 2 diabetes, patients with type 1 diabetes with target organ damage (such as microalbuminuria).**
3. **Patients with moderate to severe CKD [glomerular filtration rate (GFR) < 60 mL/min/1.73 m2).**
4. **A calculated 10 year risk SCORE ≥10%.**

***LDL <70 or 50% reduction for very high risk pts-- IA**

U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Home > Drugs > Drug Safety and Availability

Drugs

FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury

Safety Announcement

Relative LDL-lowering Efficacy of Statin and Statin-based Therapies

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin*	Simva	%↓ LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----		-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----		-----	-----	20 mg	10/40 mg	-----	55%
	-----		-----	-----	40 mg	10/80 mg	-----	63%

Crestor 10mg = Atorva 40mg= Vytorin 10/20mg

Recommendations	Class[a]	Level[b]	Ref[c]
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A	15, 16, 17
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

2013 ADA guideline recommendations: Dyslipidemia/Lipid Management

Treatment recommendations and goals

- **In individuals without overt CVD**
  - **Primary goal is an LDL cholesterol <100 mg/dL (2.6 mmol/L) (B)**
- **In individuals with overt CVD**
  - **Lower LDL cholesterol goal of <70 mg/dL (1.8 mmol/L), using a high dose of a statin, is an option (B)**

Treatment recommendations and goals

- **If targets not reached on maximal tolerated statin therapy**
  - **Alternative therapeutic goal: reduce LDL cholesterol ~30–40% from baseline (B)**

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Secondary Prevention: Achieving an Optimal Atherogenic Cholesterol Level

- The optimal LDL-C in patients with established ASCVD is < 70 mg/dL (1.8 mmol/L) (or non-HDL-C of < 100 mg/dL [2.6 mmol/L])
- Most patients with ASCVD deserve maximal statin therapy when it is tolerated
- To achieve an LDL-C < 70 mg/dL (1.8 mmol/L) some patients will require add-on drugs to statins (i.e. ezetimibe and/or bile acid resins)

NCEP ATP III Guidelines 2004

Patient group	LDL-C treatment goal
CHD or CHD risk equivalents (10-year risk >20%) • **Very high risk***	<100 mg/dL **<70 mg/dL**
Multiple (2+) risk factors†	<130 mg/dL
0–1 risk factor	<160 mg/dL

***For patients considered to be at very high risk a goal of <70 mg/dL is considered a 'reasonable clinical strategy'.**
†Risk factors = cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL-C (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years, CHD in female first-degree relative <65 years), and age (men ≥45 years; women ≥55 years).

- **Very high risk**

Established CVD plus:

- **Multiple major risk factors(especially diabetes)**
- **Severe and poorly controlled risk factors**
- **Multiple risk factors of the metabolic syndrome**
- **Acute coronary syndromes**

Circulation 2004;110:227-239.

ACC/AHA/NHLBI Cholesterol Guideline 2013

Four Major Statin Benefit Patient Groups
Individuals with clinical ASCVD
Individuals 40-75 years with diabetes with LDL-C 70-189 mg/dL
Individuals without clinical ASCVD or diabetes who are 40-75 years with LDL-C 70-189 mg/dL
Individuals with primary elevation of LDL-C > 190 mg/dL

- **Clinical ASCVD**
  - Acute coronary syndromes
  - Histroy of MI or stable or unstable angina
  - Coronary or other arterial revascularization
  - Stroke, TIA or peripheral arterial disease presumed to be of atherosclerotic origin

Circulation 2013;November 13 on line.

ACC/AHA/NHLBI Cholesterol Guideline 2013

High-, moderate-, and low-intensity statin therapy (used in the RCTs)

High-intensity statin therapy:

Daily dose lowers LDL-C on average, by approximately ≥50%

Atorvastatin 40-80 mg, Rosuvastatin 20-40 mg

Moderate-intensity statin therapy:

Daily dose lowers LDL-C on average, by approximately 30% to <50%

Atorvastatin 10-20 mg, Rosuvastatin 5-10 mg, Simvastatin 20-40 mg, Pravastatin 40-80 mg, Lovastatin 40 mg, Fluvastatin XL 80 mg, Fluvastatin 40 mg bid, Pitavastatin 2-4 mg

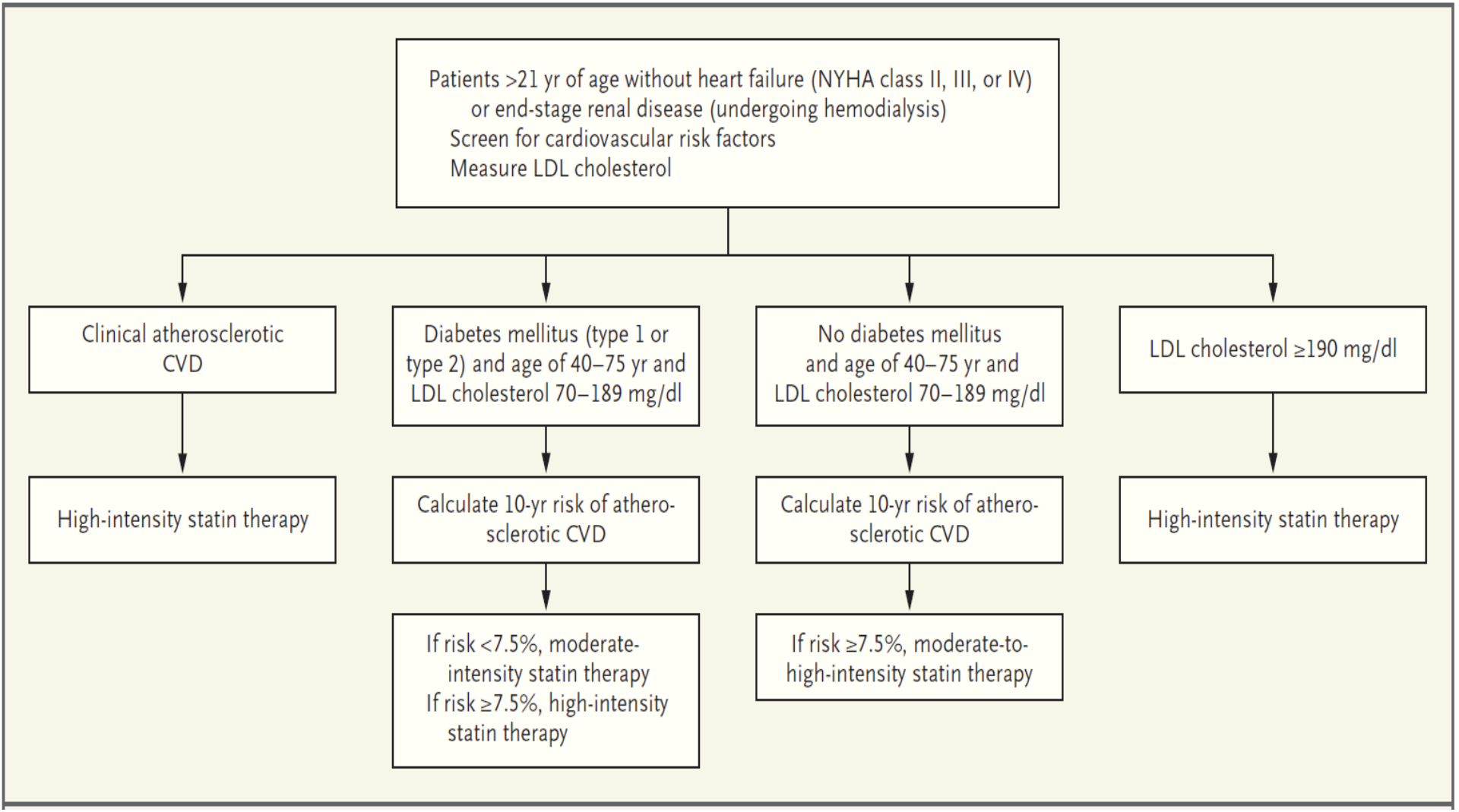
Low-intensity statin therapy:

Daily dose lowers LDL-C on average, by approximately <30%

Simvastatin 10 mg, Pravastatin 10-20 mg, Lovastatin 20 mg, Fluvastatin 20-40 mg, Pitavastatin 1 mg

Circulation 2013;November 13 on line.

ACC/AHA/NHLBI Cholesterol Guideline 2013



N Engl J Med 2013;November 27 on line.

ACC/AHA/NHLBI Cholesterol Guideline 2013

A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals

1. **The Expert Panel was unable to find RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.**

2. **The appropriate intensity of statin therapy should be used to reduce ASCVD risk in *those most likely to benefit*.**

Circulation 2013;November 13 on line.

Monitoring statin therapy

- Measure lipid panel 4 to 12 weeks after initiation of statin therapy to determine patient's adherence
- Thereafter, assessments should be performed every 3 to 12 months as clinically indicated
- LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence – they are not to be used as performance standards

Circulation 2013;November 13 on line.

Statin safety recommendations

- **Moderate-intensity statin therapy should be used in place of high-intensity statin therapy when patient characteristics predispose to statin associated adverse effects (eg, muscle disorders, unexplained ALT elevations >3 times ULN, use of concomitant drugs, age >75 years)**
- **Additional characteristics that may modify the decision to use higher statin intensities may include history of hemorrhagic stroke or Asian ancestry**

Circulation 2013;November 13 on line.

LDL goal attainment

- Current international lipid guideline
- 全民健康保險降膽固醇藥物給付規定
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- Conclusions

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全民健康保險降血脂藥物給付規定表
(2008/7/1~2013/7/31)

血脂異常之起步治療準則		血脂濃度		≧2個危險因子(如附註二)	TC/HDL-C > 5 或 HDL-C< 40mg/dl	治療目標	處方規定
無心血管疾病患者（如附註一）	給予下列情況之一時，應治療三至六個月非藥物	TC	≧200mg/dl	ˇ	×	< 200mg/dl	如非藥物治療未達治療目標，得使用降血脂藥物(請附三個月前及本次血脂檢查數據)，接受藥物治療後，應每三至六個月抽血檢查一次，同時請注意副作用產生，如肝功能異常或橫紋肌溶解症等，如已達治療目標得考慮減量至最低有效劑量，並持續衛教治療。(91/9/1、93/9/1、97/7/1)
			≧240mg/dl	×	×	< 240mg/dl	
		LDL-C	≧130mg/dl	ˇ	×	< 130mg/dl	
			≧160mg/dl	×	×	< 160mg/dl	
		TG ≧200mg/dl (需同時合併有TC/HDL-C>5或是HDL-C<40mg/dl)(91/9/1)		×	ˇ	< 200mg/dl (87/4/1)	
有心血管病患者疾病或糖尿	同時予以非藥物治療	TC ≧200mg/dl		×	×	< 160mg/dl (87/7/1)	接受藥物治療後，應每三至六個月抽血檢查一次，同時請注意副作用產生，如肝功能異常或橫紋肌溶解症等，**如已達治療目標得考慮減量至最低有效劑量**，並持續追蹤治療。(93/9/1、97/7/1)
		LDL-C ≧130mg/dl		×	×	**≦100mg/dl (87/7/1)**	
		TG ≧200mg/dl (需同時合併有TC/HDL-C>5或是HDL-C<40mg/dl) (91/9/1)		×	ˇ	< 150mg/dl (87/7/1)	

血中三酸甘油酯高於500mg/dl，具有罹患急性胰臟炎危險者，得使用降血脂藥物。(87/4/1、93/9/1)

(ˇ)需符合此項條件
(x)不需符合此項條件

附註一：心血管疾病：
(一)冠狀動脈粥狀硬化患者
有心導管檢查證實(附檢查報告、醫院名稱及日期)。
曾患心肌梗塞有心電圖(附心電圖)或住院證實(附檢查醫院名稱及日期)。
心絞痛病患，有缺氧性心電圖變化或運動試驗陽性反應者(附檢查報告)。
(二)**腦血管病變患者**
腦梗塞。
腦內出血(不含其他顱內出血)。
陣發性腦缺血患者(TIA)其頸動脈超音波證實有粥腫樣變化併有70%以上阻塞者。
(三)周邊血管粥狀硬化有缺血性症狀且經血管都卜勒超音波或血管攝影證實者。
附註二：危險因子：
1.高血壓2.糖尿病3.男性≧45歲4.有早發性冠心病家族史5.女性≧55歲或停經沒有雌激素療法者
6.吸菸(因吸菸而符合起步治療準則之個案，如要求藥物治療，應以自費治療)。

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全民健康保險降膽固醇藥物給付規定表 2013-8-1

	非藥物治療	起始藥物治療血脂值	血脂目標值	處方規定
心血管疾病或糖尿病病人	與藥物治療可並行	TC≧160 mg/dl或LDL-C≧100 mg/dL	TC＜160 mg/dl或LDL-C＜100 mg/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。
2個危險因子或以上	給藥前應有3-6個月非藥物治療	TC≧200 mg/dl或LDL-C≧130 mg/dL	TC＜200 mg/dl或LDL-C＜130 mg/dL	
1個危險因子	給藥前應有3-6個月非藥物治療	TC≧240 mg/dl或LDL-C≧160 mg/dL	TC＜240 mg/dl或LDL-C＜160 mg/dL	
0個危險因子	給藥前應有3-6個月非藥物治療	LDL-C≧190 mg/dL	LDL-C＜190 mg/dL	

心血管疾病定義：

(一)冠狀動脈粥狀硬化病人： 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：(經神經科醫師確定診斷之下列病人)

1.腦梗塞
2.暫時性腦缺血患者(TIA)
3.有症狀之頸動脈狹窄

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

2013 全民健康保險降血脂藥物給付規定

1.心血管疾病或糖尿病患者，起始治療LDL-C由≧130mg/dl降為100mg/dl，目標＜100mg/dl

→Achieve ideal goal

2. 刪除達到治療目標需“減量至最低有效劑量”

→Treat to goal at one time and keep it

LDL goal attainment

- Current international lipid guideline
- 全民健康保險降膽固醇藥物給付規定
- Current strategy
- Conclusions

My current strategy:

1. Obtain lipid profile and other blood chemistry data
2. Determine patients' cardiovascular risk & clinical conditions
3. Determine LDL goal & calculate LDL lowering percentage
4. Determine risk of side effects
5. Choose adequate drug

Relative LDL-lowering Efficacy of Statin and Statin-based Therapies

Atorva	Fluva	Pitava	Lova	Prava	Rosuva	Vytorin*	Simva	%↓ LDL-C
-----	40 mg	1 mg	20 mg	20 mg	-----	-----	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	-----	-----	20 mg	38%
20 mg	-----	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	-----		-----	-----	10 mg	10/20 mg	80 mg	47%
80 mg	-----		-----	-----	20 mg	10/40 mg	-----	55%
	-----		-----	-----	40 mg	10/80 mg	-----	63%

Crestor 10mg = Atorva 40mg= Vytorin 10/20mg

Statin safety recommendations

- **Moderate-intensity statin therapy should be used in place of high-intensity statin therapy when patient characteristics predispose to statin associated adverse effects (eg, muscle disorders, unexplained ALT elevations >3 times ULN, use of concomitant drugs, age >75 years)**
- **Additional characteristics that may modify the decision to use higher statin intensities may include history of hemorrhagic stroke or Asian ancestry**

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Case

- A 46 y/o male was referred to my clinic for LDL 245, no evident S/S
- He has no HT, no DM and does not smoke
- His 256 CT and carotid Duplex showed atherosclerosis
- His father died of heart attack at the age of 50
- His BUN Cre GOT GPT are normal, AC sugar is 99
- What is your choice of lipid lowering therapy?

Case

- I started with aspirin and atorvastatin 40 mg qd
- One month later, LDL dropped to 130
- But mild myalgia was noted, no CK and GOT elevation
- What is your suggestion?

Case

- I stopped atorvastatin and changed to Vytorin 10/20 mg qd
- One month later, LDL became 134
- No more myalgia was noted and CK and GPT were OK
- What is your further suggestion?

Case

- I kept Vytorin for another 3 months
- Three months later, LDL became 138
- I decided to change Vytorin to Rosuvastatin 10 mg qd
- One month later, LDL became 140 and I added ezetimibe 10 mg.
- One month later, LDL dropped to 108

LDL goal attainment

- Current international lipid guideline
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Conclusions

- International guidelines suggest 70 as the LDL target in high risk patients
- New ACC/AHA guideline use statin-intensity approach
- For LDL goal attainment: Rosuva 10 mg = Atorva 40mg = Vytorin 10/20 mg
- Watch out for side effects of high dose statin
- Add-on ezetimibe is helpful for LDL goal attainment