Total Solution in Lipid Treatment of High Risk p't

代謝症候群與糖尿病患之混合型血脂症治療

LDL the lower the better?

安家診所
林正日醫師
2023/12/21

Outline

- Unmet need in the treatment of dyslipidemia
- Linicor- Niacin and Statin combination
  高風險病患混合型血脂治療首選
- Guideline recommendations
- Take home messages

Outline

Unmet need in the treatment of dyslipidemia

Linicor- Niacin and Statin combination

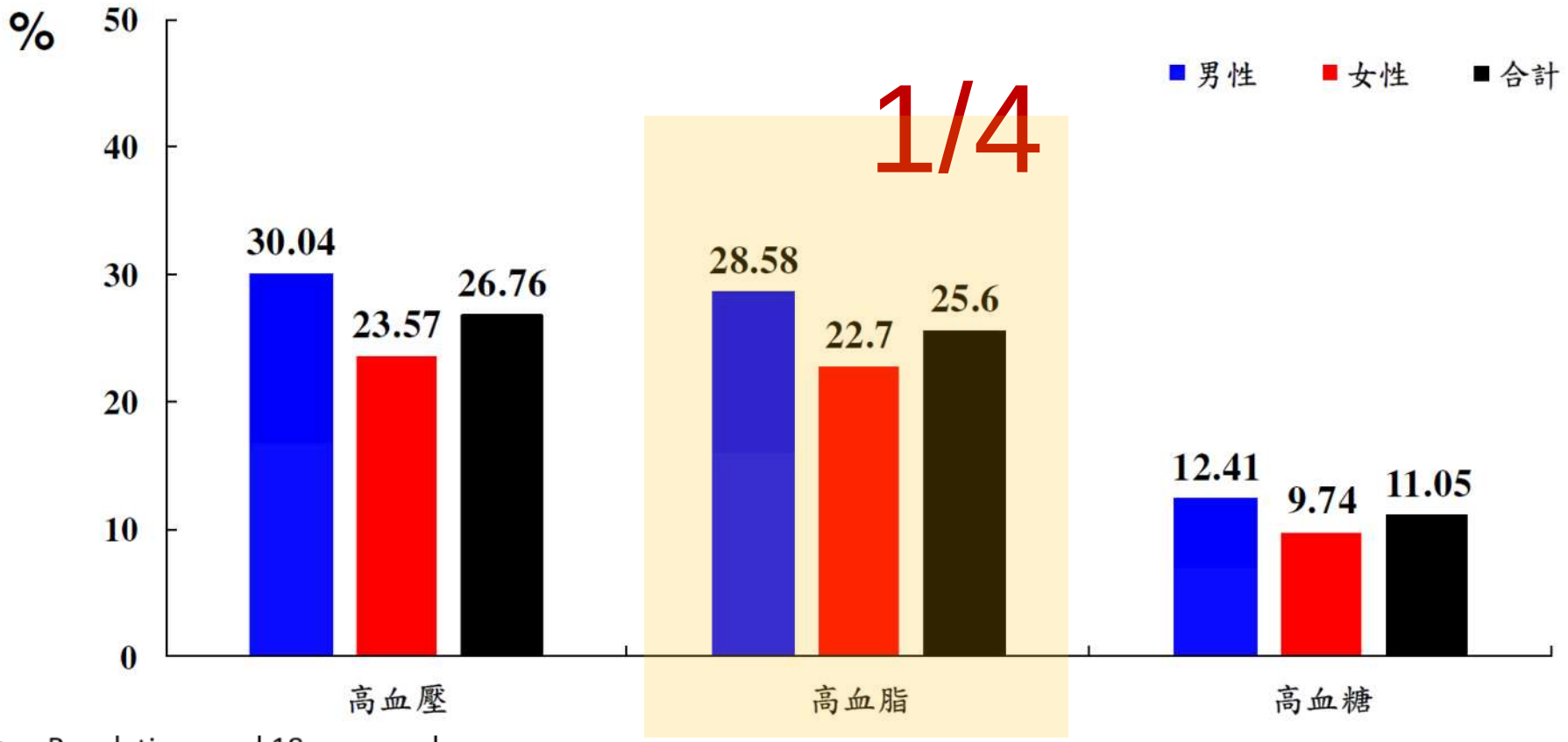
高風險病患混合型血脂治療首選

Guideline recommendations

Take home messages

台灣高膽固醇血症盛行率- 25.6% (2017-2020)

2017-2020 prevalence of hypertension, hyperlipidemia, and hyperglycemia

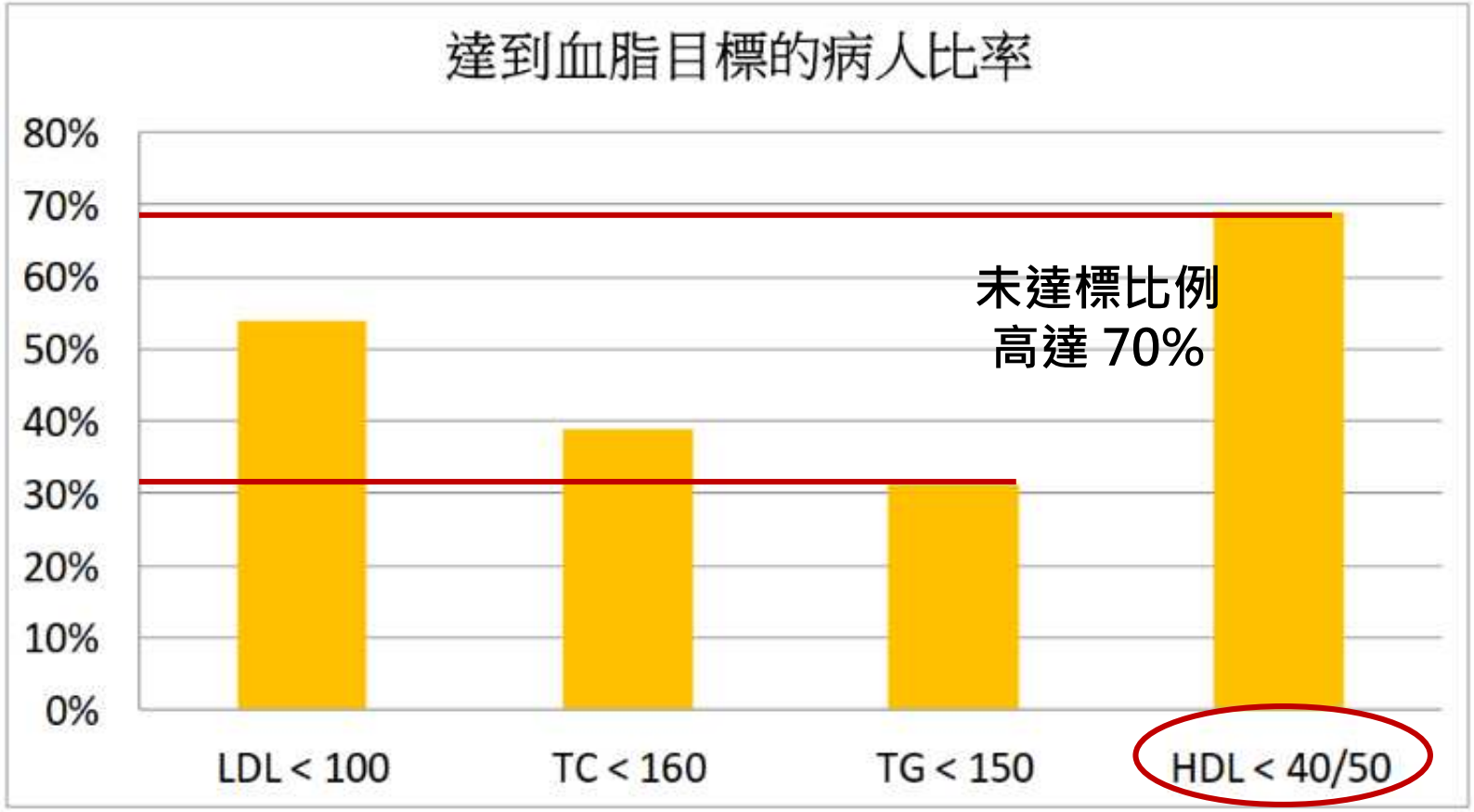


- Population aged 18 years and over
- Definition of hyperlipidemia: Total cholesterol ≥240 mg/dL, triglyceride ≥200 mg/dL or undergoing lipid lowering drugs

資料來源：2017-2020年國民營養健康狀況變遷調查。

https://www.hpa.gov.tw/Home/Index.aspx

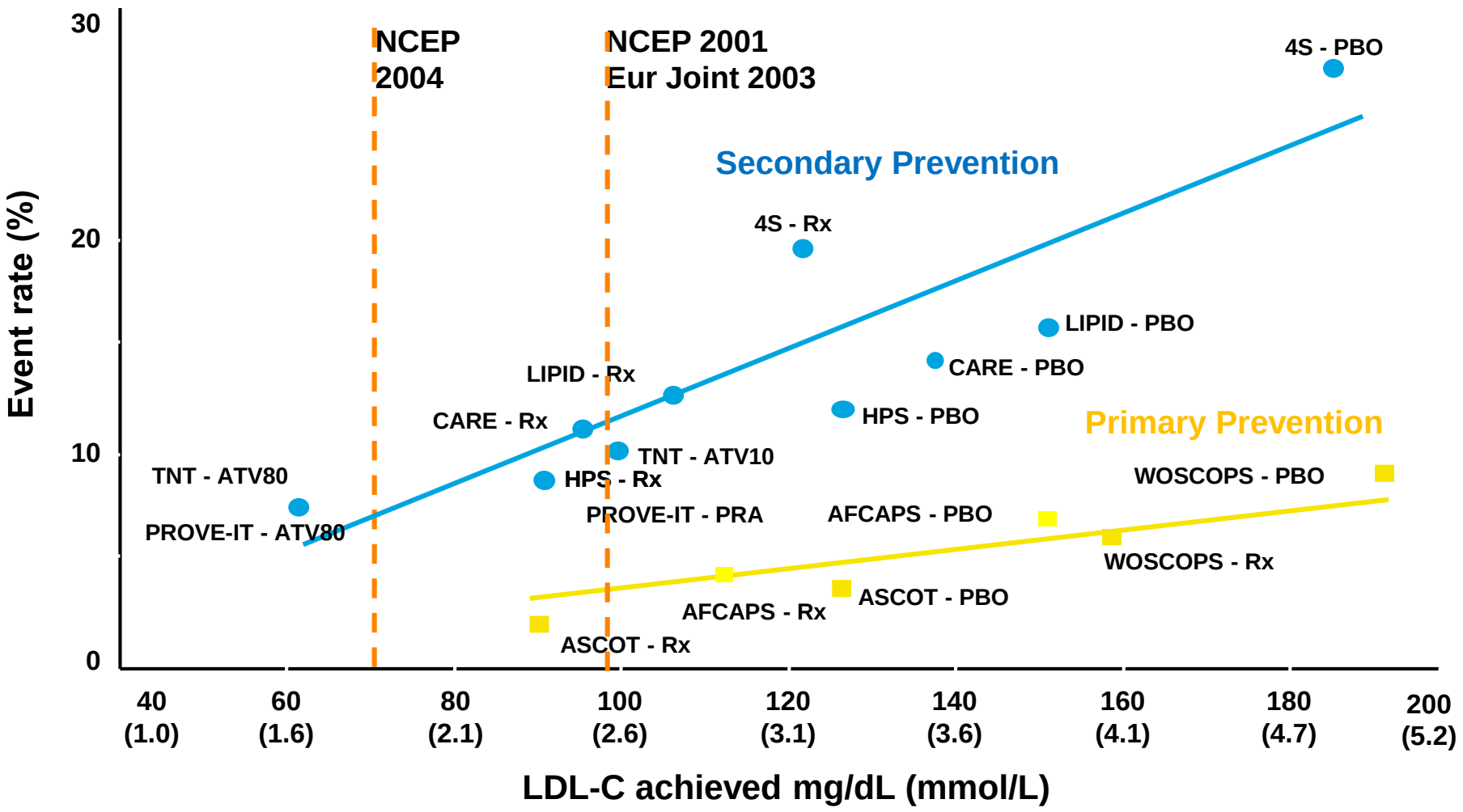
台灣血脂異常病人初級和次級預防之登錄研究計畫



最近對3,486位冠狀動脈疾病和腦血管疾病患者的調查中，只有54%的患者LDL-C 控制到100 mg/dL以下

PLoS One 2015 Mar 10; 10(3):e011651

LDL仍是降血脂首要目標



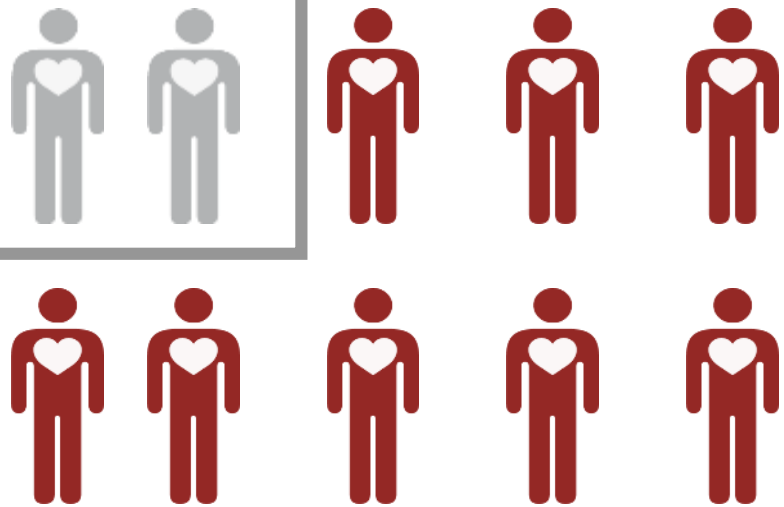
1. Rosensen, Exp Opin Emerg Drugs 2004;9:269;
2. LaRosa J et al, N Engl J Med, 2005;352:1425

While statins reduce CV risk, a substantial 80% residual risk remains

- A meta-analysis of 21 randomised clinical trials (N=129,526) revealed that statin treatment prevented approximately 2 out of 10 major vascular events (relative risk reduction 22%, p<0.0001)[1]

CTT Meta-analysis: Effect of statins on major vascular events[1]

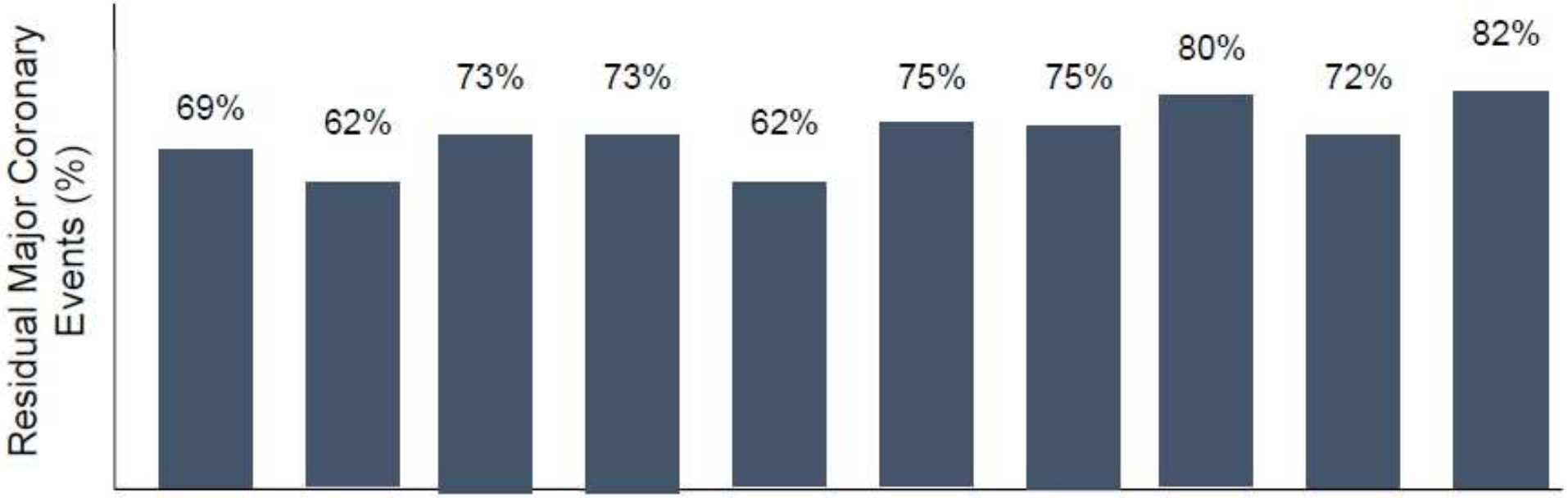
Statins prevent approximately 2 out of 10 events



Remaining residual risk may be due to other modifiable and unmodifiable risk factors, including other **lipid parameters, blood pressure, glycaemic control, weight and genetic predisposition**

Cholesterol Treatment Trialists' Collaborators. *Lancet*. 2010;376:1670-81.

服用Statin後仍有
6~7成 心血管殘餘風險

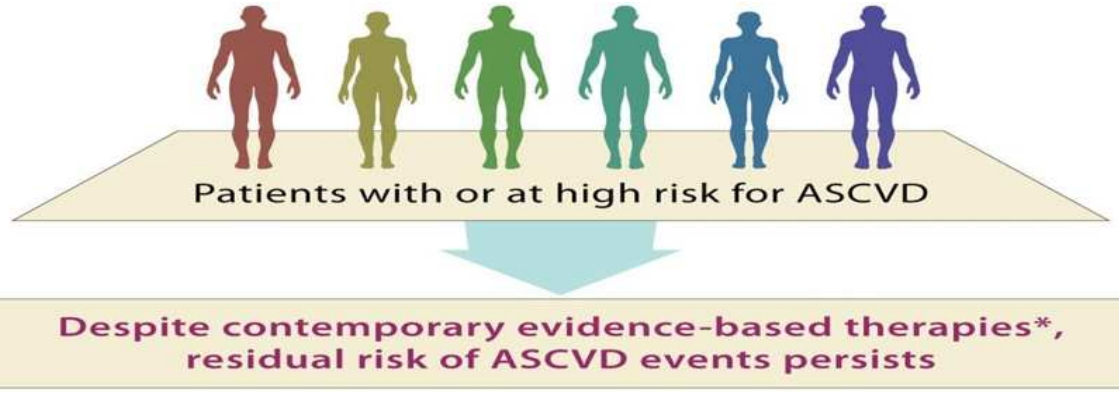


Trial	WOSCOPS	AFCAPS/ TexCAPS	HPS	ASPEN	4S	LIPID	CARE	TNT Total	TNT Met S	TNT Diabetes
N	6.595	6.505	20.536	2.410	4.444	9.014	4.159	10.001	5.584	1.501
Δ LDL-C	-26%	-27%	-29%	-29%	-36%	-25%	-28%	-21%	-24%	-20%

Adapted from Libby P, J Am Coll Cardiol 2005;46:1225-1228

Residual Risks as Unmet Clinical Needs

ESC European Society of Cardiology



Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

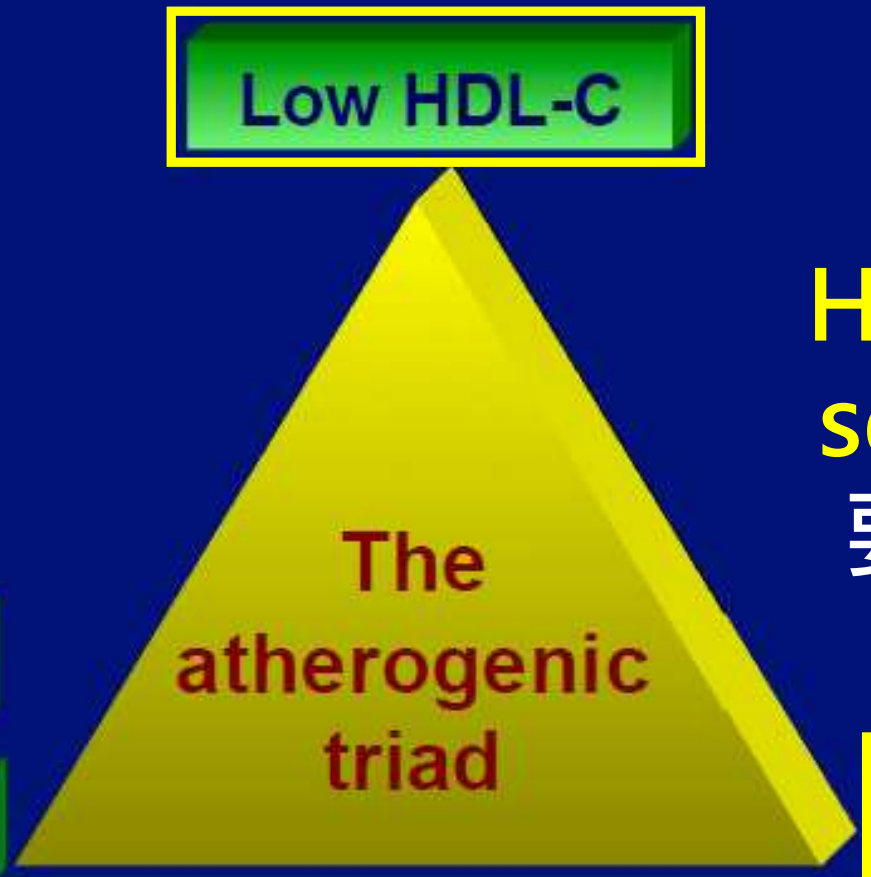
European Heart Journal (2021) 42, 1-4

Atherogenic dyslipidemia - The atherogenic triad

目前的治療偏重
LDL-C是否達標

High LDL-C

High sd LDL-C



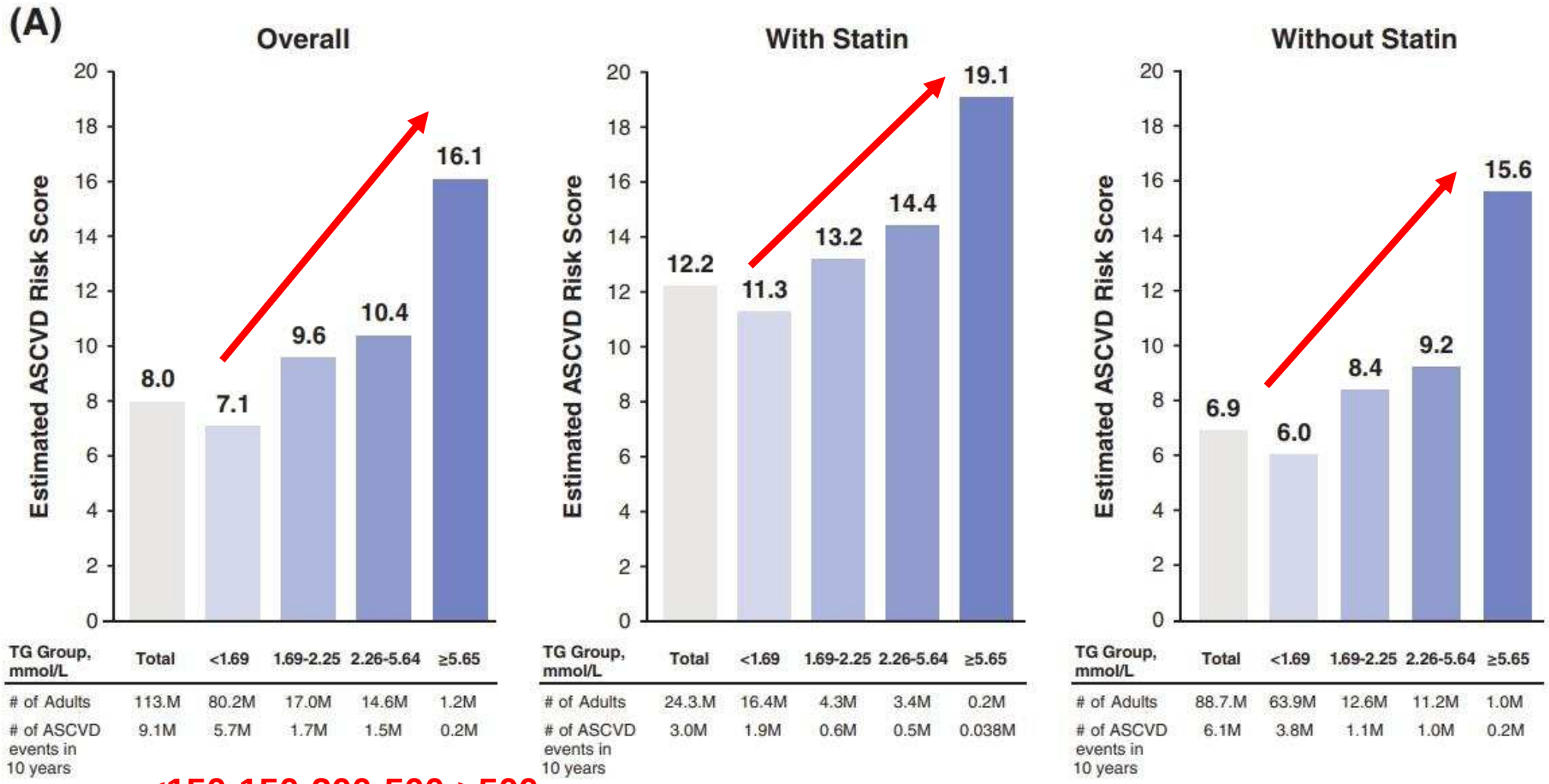
HDL-C 、TG、
sd LDL-C 的重
要性常被忽略

High TG

JAMA 2001;285:2486-2497

Risk of cardiovascular events in patients with hypertriglyceridaemia: A review of real-world evidence

National Health and Nutrition Examination Survey (NHANES) database



<150-150-200-500->500

Diabetes Obes Metab. 2020 Mar;22(3):279-289

Adults with both high TG and low HDL-C have increased risks of incident CHD and stroke, especially in those with DM

High TG & Low HDL 增加CHD & Stroke風險

3216 participants composed of American Indians without CVD at baseline (median follow-up 17.7 years)

Strong Heart stroke study

	No DM (59%)				DM (41%)			
	Noncase, n (%)	Case, n (%)	Full model		Noncase, n (%)	Case, n (%)	Full model	
			HR	95% CI			HR	95% CI
CHD ($p_{interaction}$ = 0.003)								
TG (per SD increase)			1.07	0.92-1.24			1.47	1.08, 2.00
HDL-C (per SD increase)			0.87	0.75-1.01			0.95	0.83, 1.08
TG-HDL status								
Normal TG-HDL	681 (85)	122 (15)	1 (reference)		233 (69)	103 (30)	1 (reference)	
Normal TG, low HDL	435 (81)	103 (19)	1.26	0.94-1.69	306 (73)	111 (27)	0.92	0.67, 1.26
High TG, normal HDL	138 (82)	30 (18)	1.14	0.74-1.76	71 (62)	43 (38)	0.99	0.64, 1.54
High TG, low HDL	**251 (83)**	**50 (17)**	**0.88**	**0.60-1.29**	**258 (57)**	**192 (43)**	**1.54**	**1.15, 2.06**
Ischemic stroke ($p_{interaction}$ = 0.060)								
TG (per SD increase)			1.15	0.82-1.62			1.43	0.74, 2.73
HDL-C (per SD increase)			0.93	0.69-1.26			0.72	0.53, 0.97
TG-HDL status								
Normal TG-HDL	773 (96)	34 (4)	1 (reference)		326 (96)	13 (4)	1 (reference)	
Normal TG, low HDL	526 (98)	13 (2)	0.53	0.23-1.19	391 (93)	31 (7)	1.82	0.91, 3.66
High TG, normal HDL	164 (98)	4 (2)	0.53	0.15-1.81	112 (97)	4 (3)	0.77	0.21, 2.83
High TG, low HDL	**287 (94)**	**17 (6)**	**1.16**	**0.55-2.45**	**417 (91)**	**40 (9)**	**2.13**	**1.06, 4.29**

High TG: fasting TG≥150 mg/dl; low HDL <40 or <50 mg/dl (men or women)

Lee JS, et al. Diabetes Care. 2017;40:529-537.

CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation; TG, triglyceride.

Pattern and predictors of T2DM dyslipidemia

Lipid profile of the study subjects ($n = 366$).

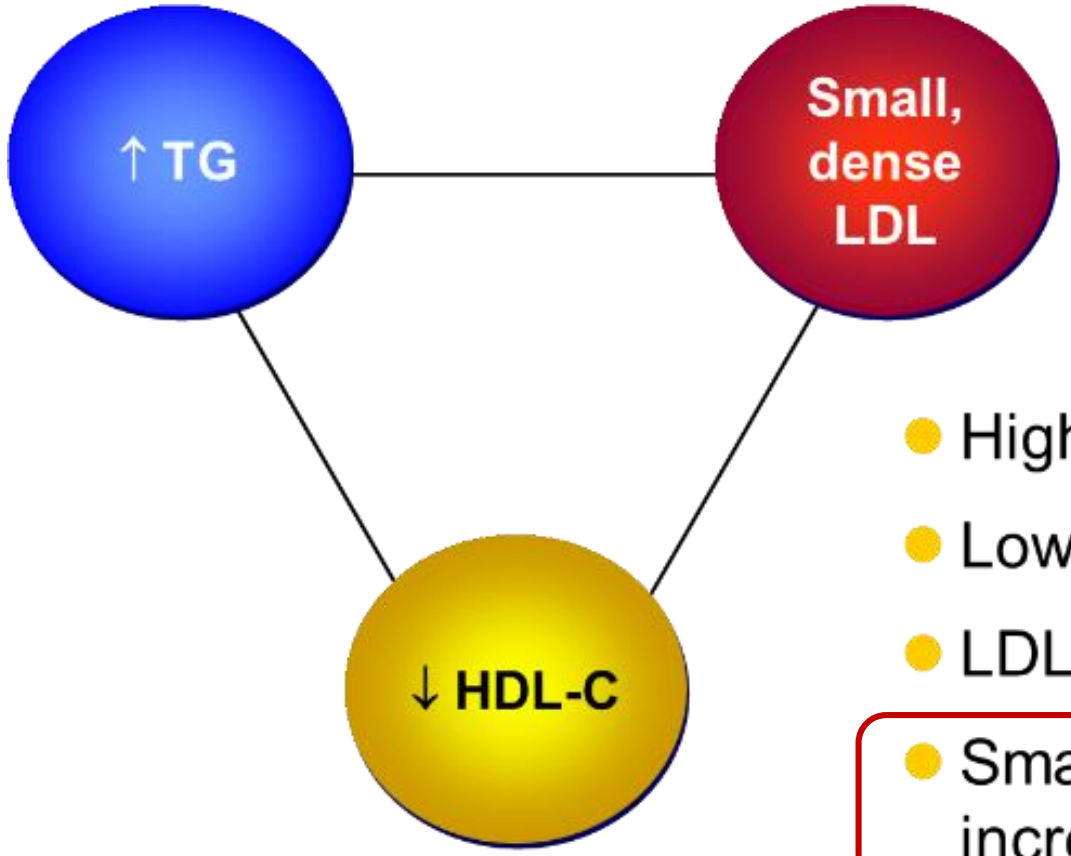
Variables	Sex		Total n (%)
	Male n (%)	Female n (%)	
TC			
<200 mg/dl	105 (76.6)	185 (80.8)	290 (79.2)
≥200 mg/dl	32 (23.4)	44 (19.2)	76 (20.8)
TG			
<150 mg/dl	58 (42.3)	121 (52.8)	179 (48.9)
≥150 mg/dl	79 (57.7)	108 (47.2)	187 (51.1)
HDL			
Low[a]	83 (60.6)	66 (28.8)	149 (40.7)
Normal	54 (39.4)	163 (71.2)	217 (59.3)
LDL			
<100 mg/dl	60 (43.8)	119 (52.0)	179 (48.9)
≥100 mg/dl	77 (56.2)	110 (48.0)	187 (51.1)
Dyslipidemia			
None	24 (17.5)	33 (14.4)	57 (15.6)
One	38 (27.7)	67 (29.3)	105 (28.7)
Two	32 (23.4)	51 (22.3)	83 (22.7)
Three	32 (23.4)	56 (24.5)	88 (24.0)
All four	11 (08.0)	22 (09.6)	33 (09.0)

[a] HDL < 40 mg/dl in male and <50 mg/dl in female. Results are expressed as number (percentage). TG, triglyceride; TC, total cholesterol; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol.

23~ 56%
混合型

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 7 (2013) 95–100

DM, 代謝症候群病患血脂異常的特點-混合型



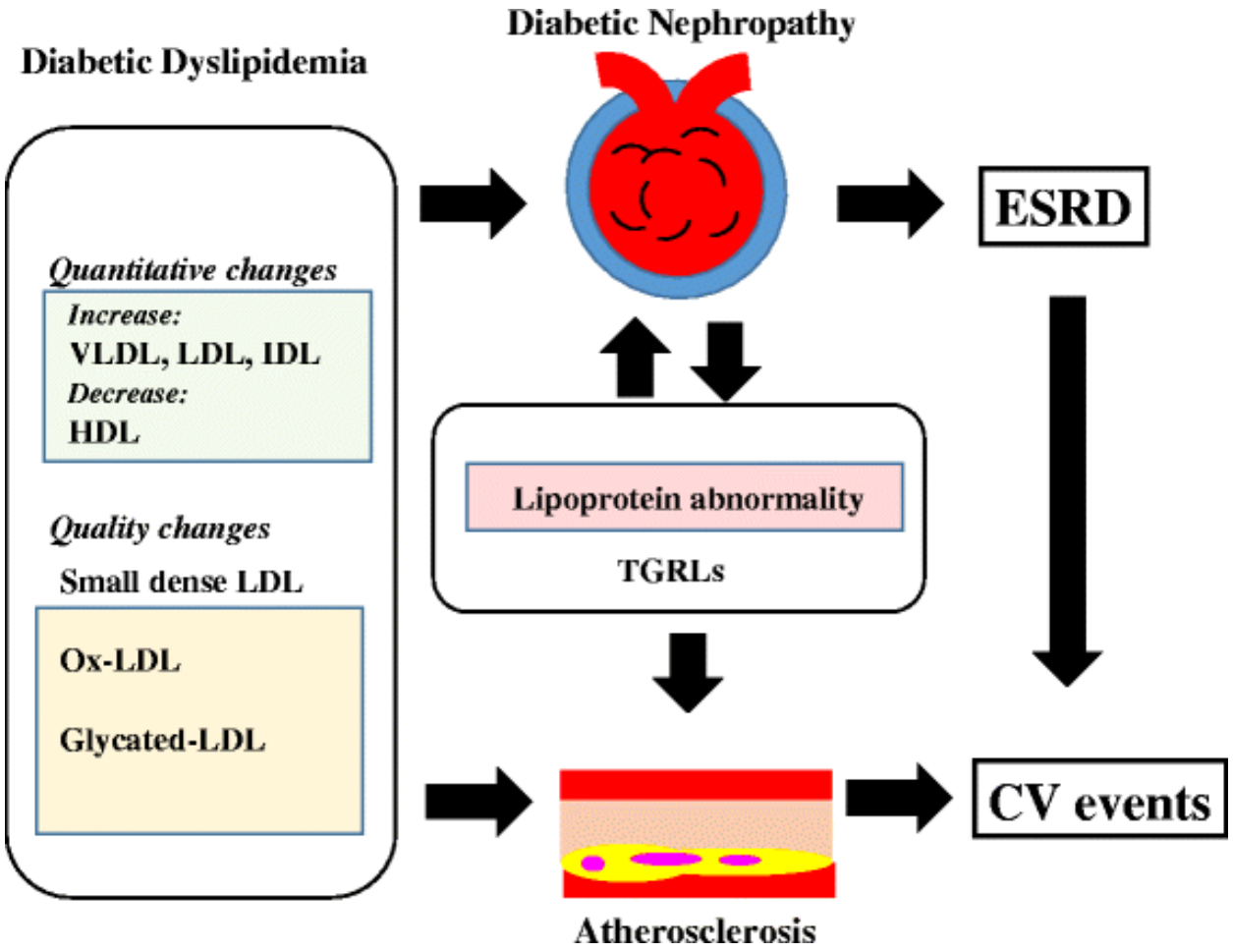
- High levels of triglycerides
- Low levels of HDL-C
- LDL-C not significantly increased
- Small, dense LDL-C particles increased

- **Patients with type 2 diabetes are at higher risk for ASCVD because high small dense-LDL-C level is more potentially atherogenic.**

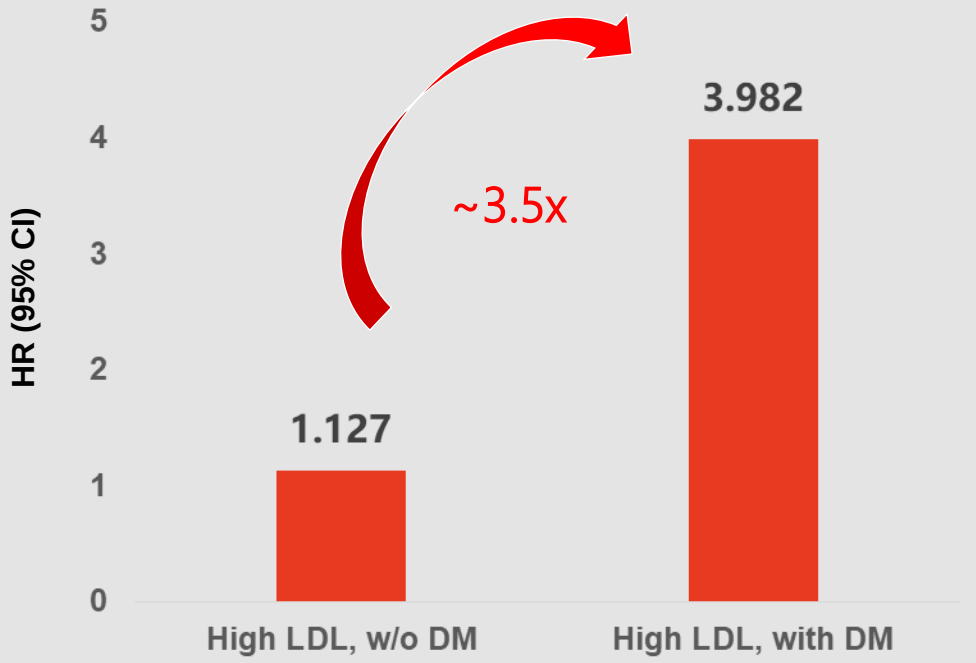
Bruno Vergès et al. *Diabetologia (2015) 58:886–899*

AACE/ACE Guidelines for the Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract. 2017;23(Suppl 2)*

糖尿病合併高血脂，增加CKD惡化風險



糖尿病合併高血脂，CKD惡化風險增加3.5倍



Analysis of factors affecting the CKD progression among patients with or without diabetes

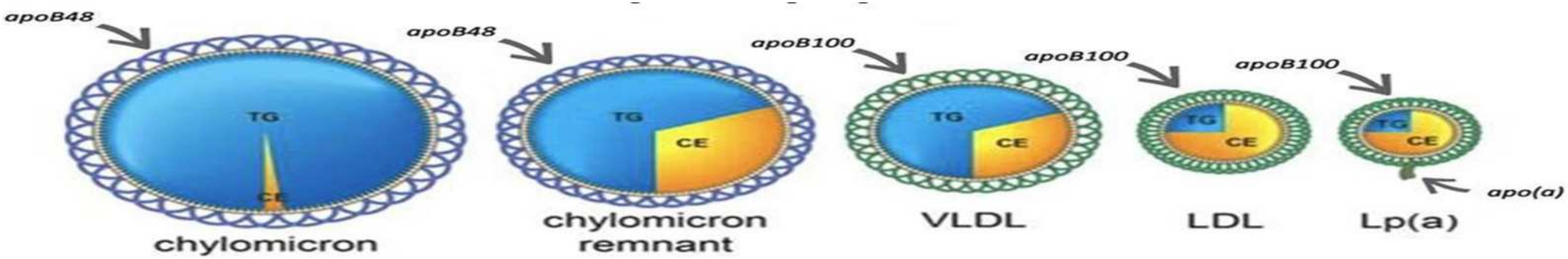
1.Dyslipidemia in diabetic nephropathy. *Ren Replace Ther* **2**, 16 (2016). https://doi.org/10.1186/s41100-016-0028-0
2. Journal of Diabetes Research, vol. 2022, Article ID 9613062, 12 pages, 2022. https://doi.org/10.1155/2022/9613062

Introduction to Cholesterol, TG, and Associated Lipoproteins

Class	Size (nm)	Major lipids	Major apolipoprotein
Chylomicrons	80 to 100	Triglycerides	ApoB-48
VLDL	30 to 80	Triglycerides	ApoB-100
IDL	25 to 30	Triglycerides, Cholesterol	ApoB-100
LDL	20 to 30	Cholesterol	ApoB-100
HDL	8 to 13	Cholesterol, phospholipids	Apo-A-1
Lp(a)	25 to 30	Cholesterol	Apo(a)

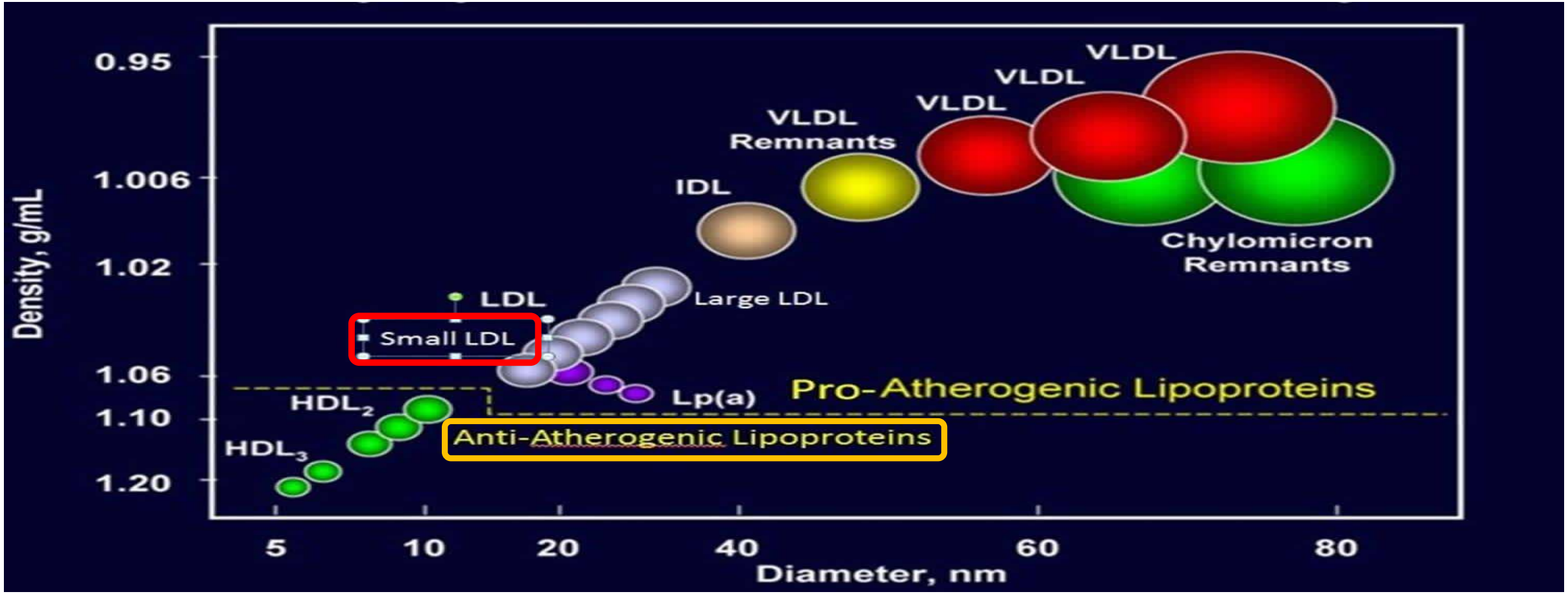
ApoB

Apo-A



1. Taiwan Diabetes Lipid Guideline 2023 2. Journal of the American Heart Association. 2022;11:e025858

Pro vs Anti-Atherogenic Lipoproteins



HDL-C

LDL-C

Remnant-C

Non-HDL-C

ApoA-1

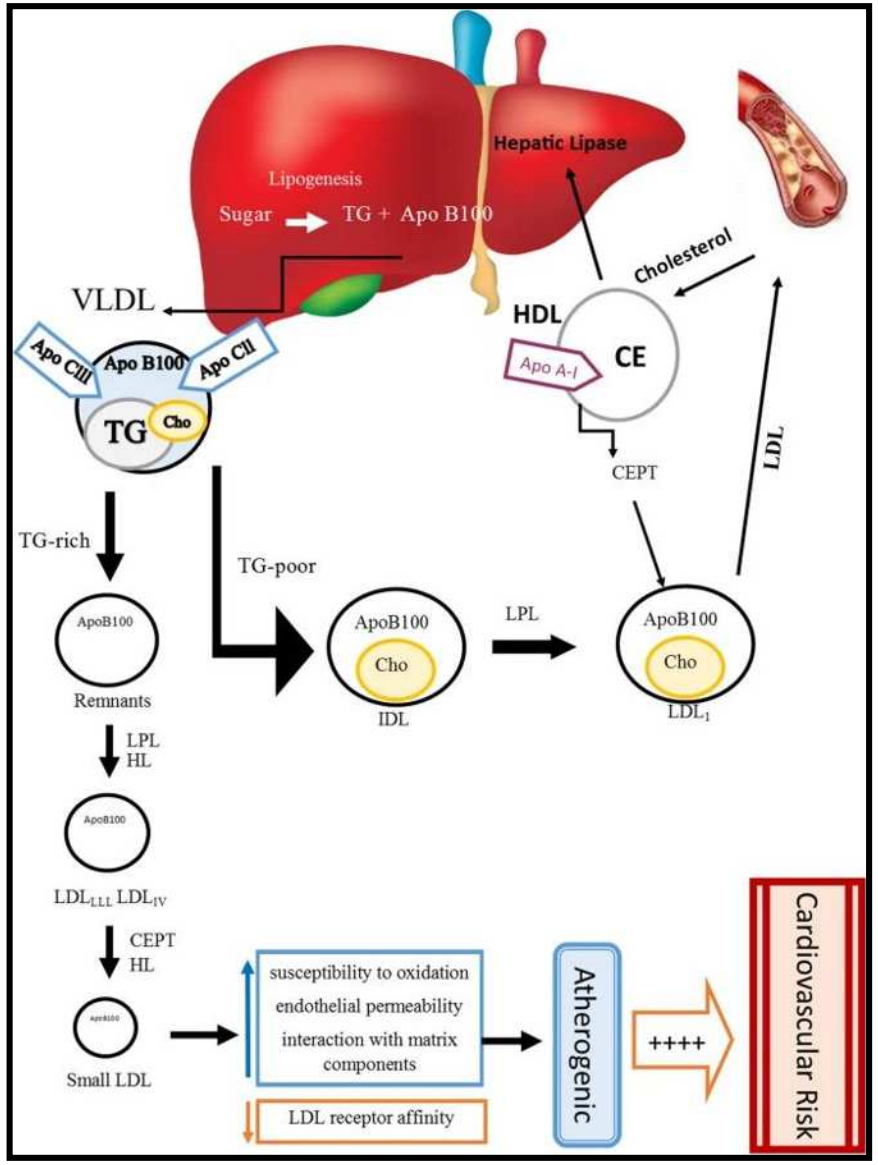
Apo-B

Total Cholesterol

https://www.ncbi.nlm.nih.gov/books/NBK305896/

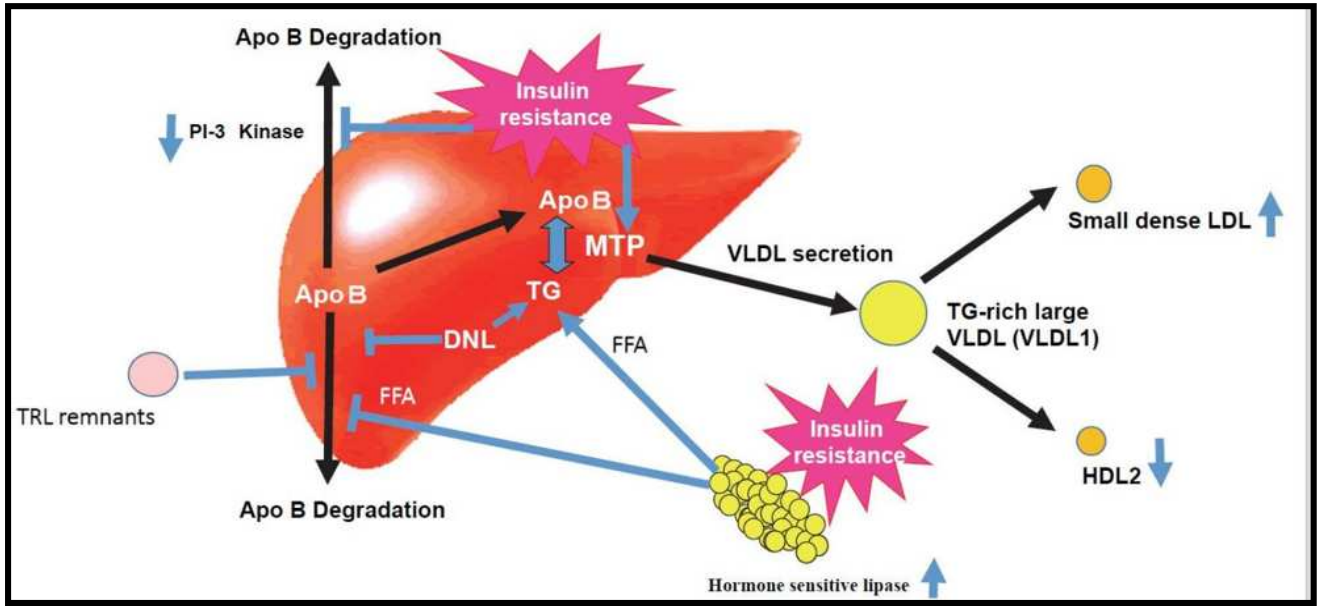
Why in T2D Pts: an appeared normal LDL-C level does not rule out risk of ASCVD?

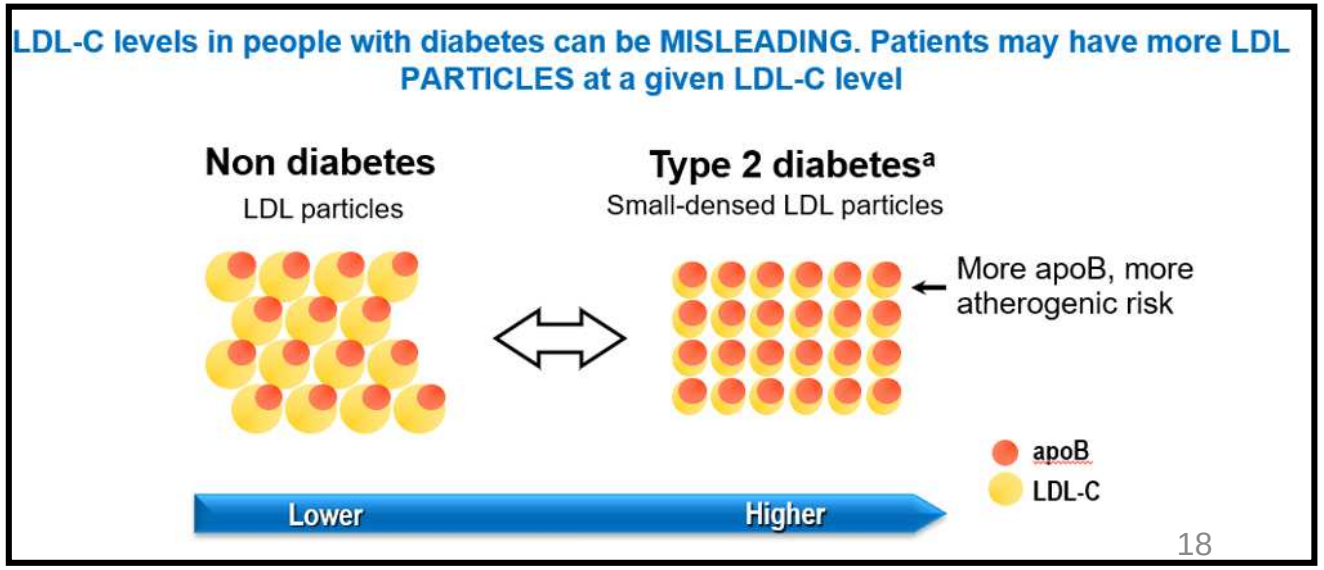
Normal physiological conditions



Talebi et al. Lipids in Health and Disease (2020) 19:66

Insulin resistance effect on lipoprotein metabolism

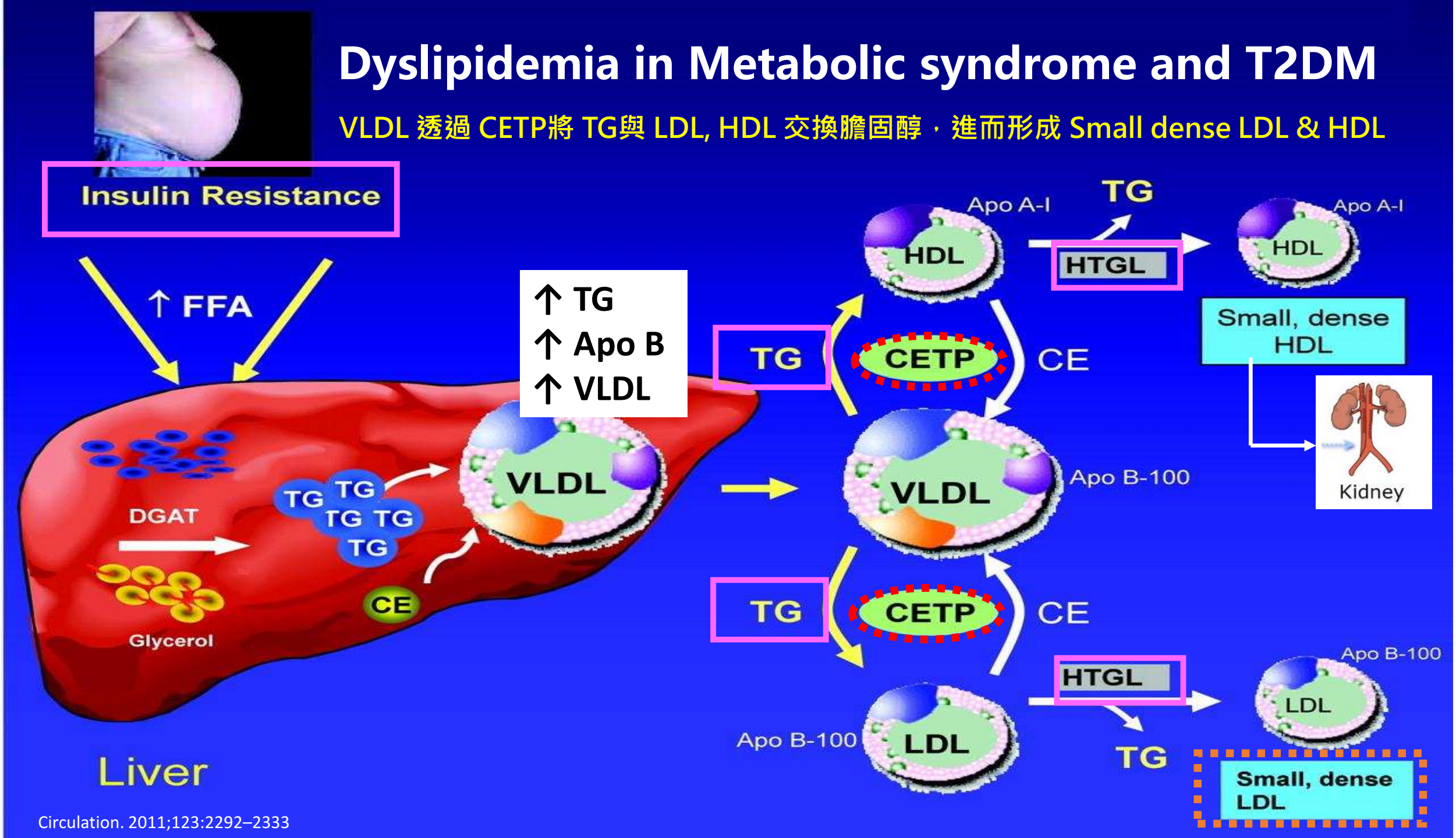




Tsutomu Hirano, J Atheroscler Thromb, 2018; 25: 771-782

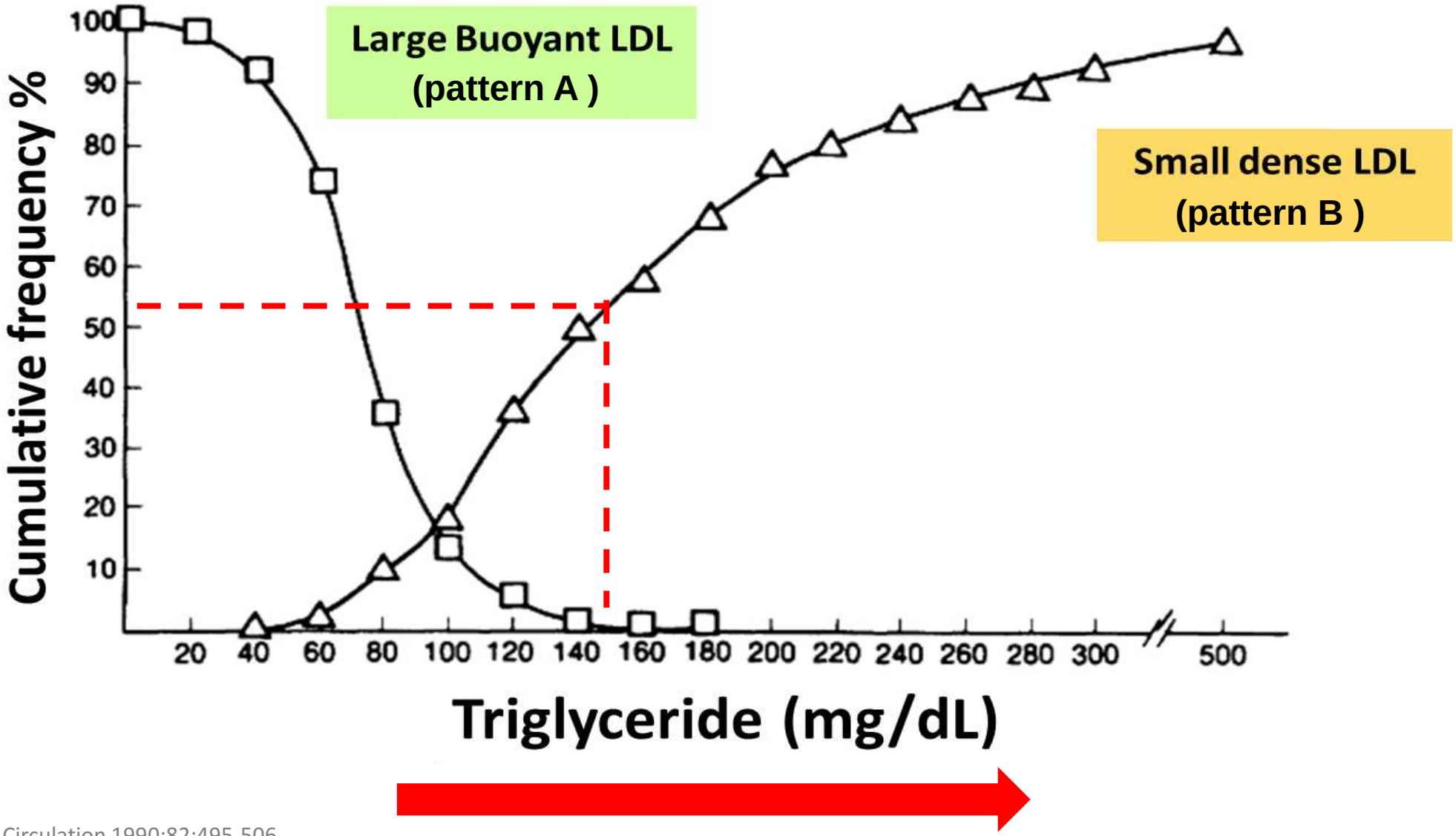
Dyslipidemia in Metabolic syndrome and T2DM

VLDL 透過 CETP將 TG與 LDL, HDL 交換膽固醇，進而形成 Small dense LDL & HDL



Circulation. 2011;123:2292–2333

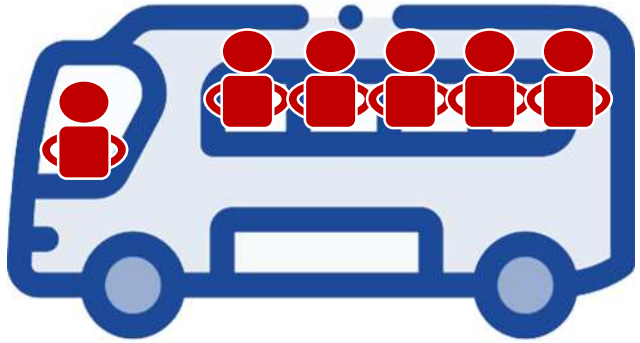
Relationship of Triglycerides and LDL particle size



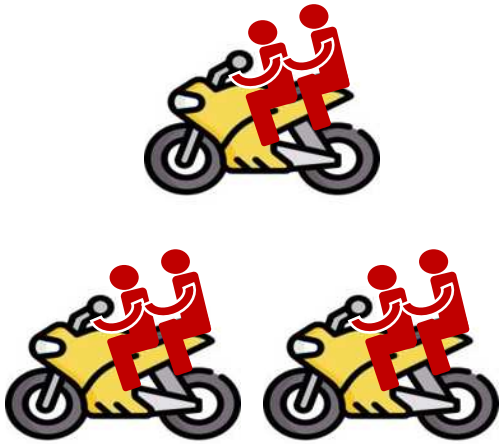
Austin M,et al.Circulation 1990;82:495-506

即使LDL-C濃度正常，sdLDL仍存在威脅

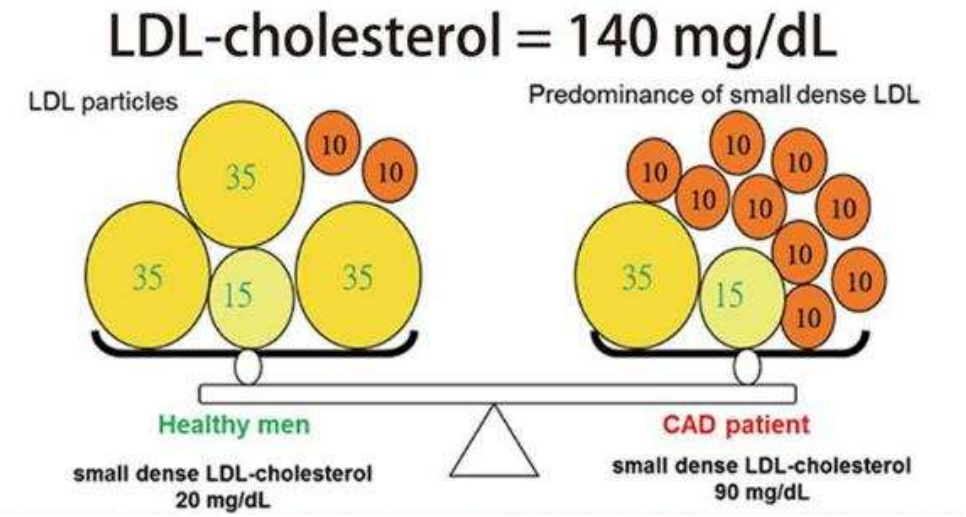
LDL膽固醇濃度一樣，但是...



大顆 LDL
(Large LDL pattern A)
威脅度稍低



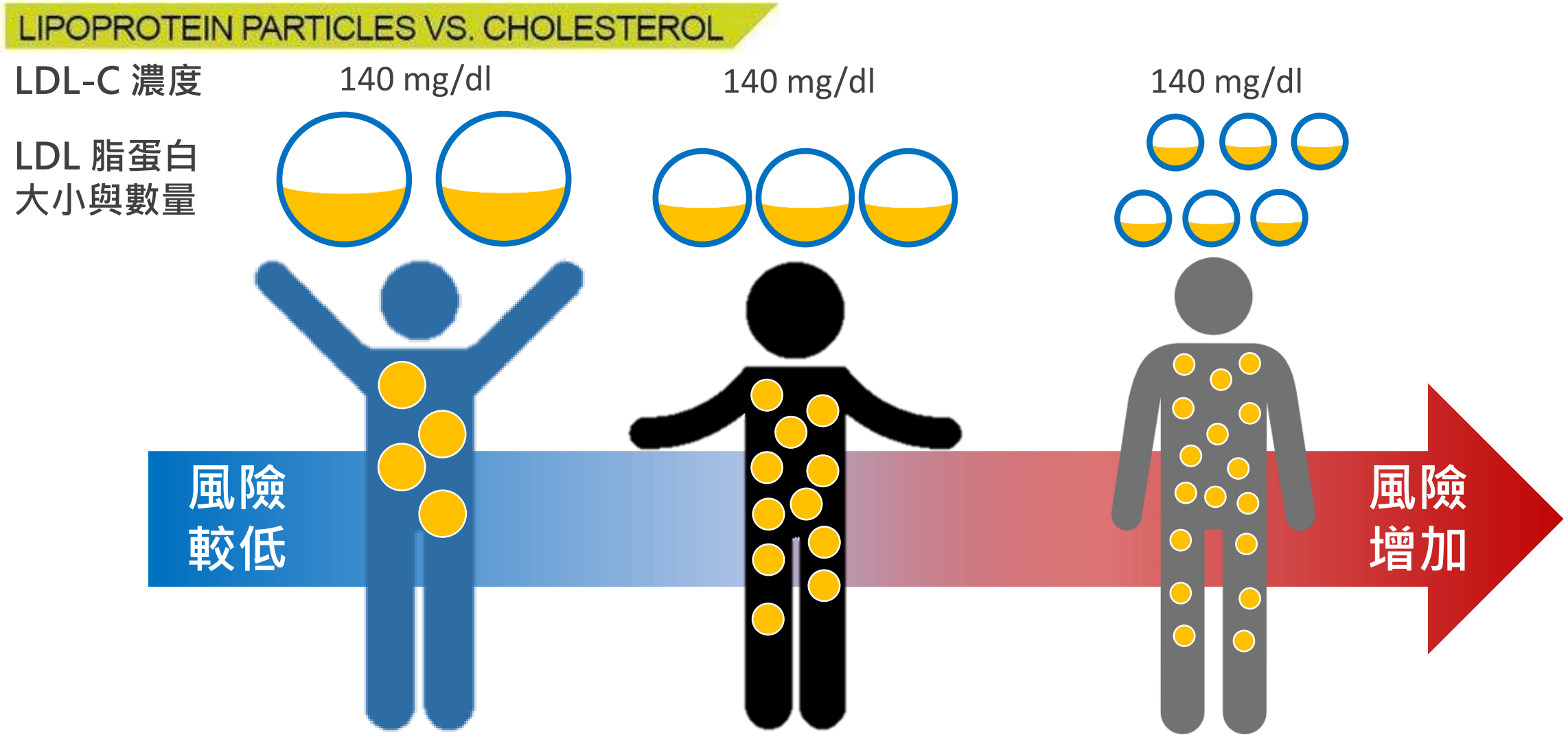
小顆 LDL
(Small LDL pattern B)
威脅度大



即使LDL-C濃度一樣
超壞低密度膽固醇濃度可能不同

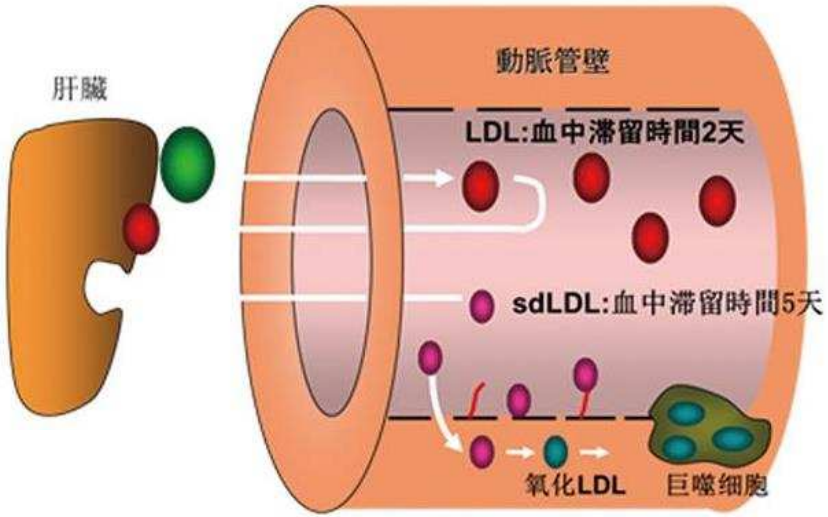
小顆粒 LDL-C越多，罹病風險越高

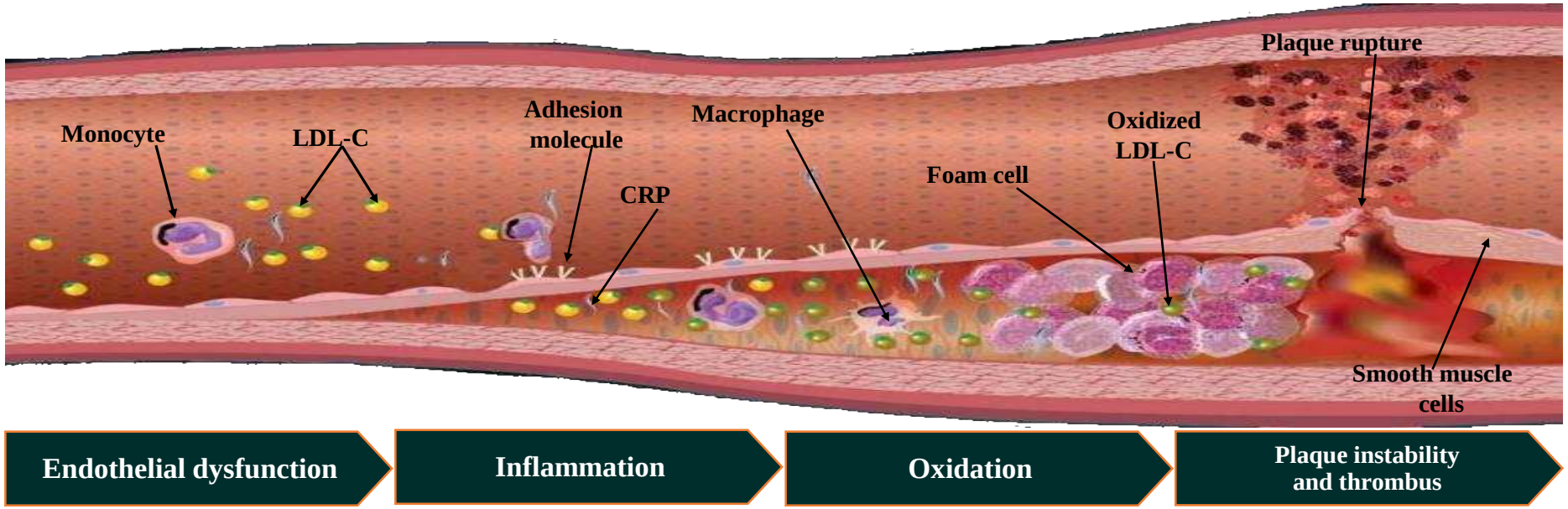
同樣LDL數值下，體內有較多Small, dense LDL的病患，罹病風險越高



Atherosclerosis: A Progressive Disease

- ◆ 雖LDL-C正常
  - Small dense LDL-C (sd-LDL) 可能超標
- ◆ Sd-LDL**不容易被代謝**:
  - LDL-C在血中滯留約**2天**
  - Sd-LDL滯留時間高達**5天**
- ◆ Sd-LDL**體積小**: 更易鑽進血管內皮細胞
- ◆ Sd-LDL**易氧化**: 更易被巨噬細胞吞食成為斑塊



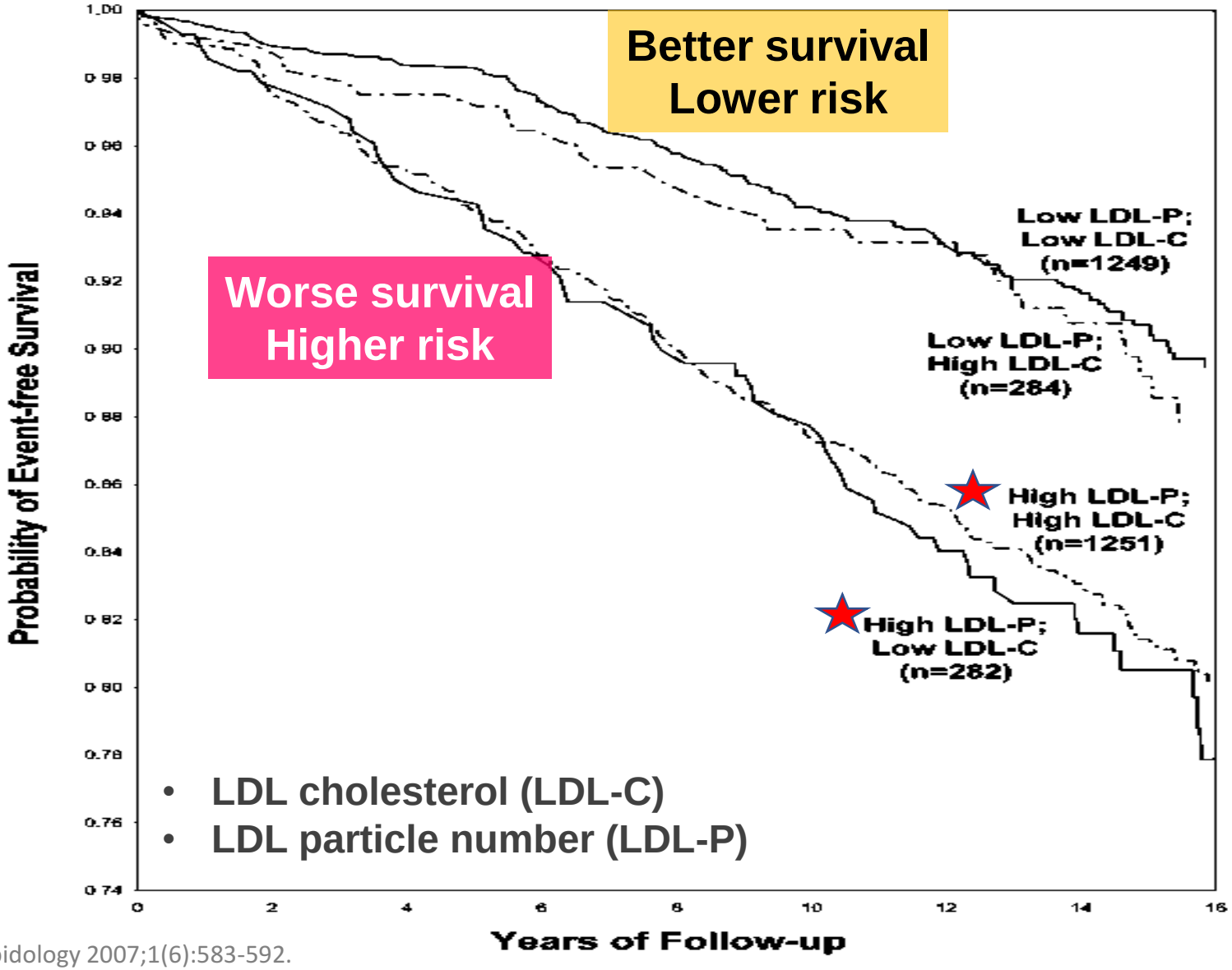


CRP=C-reactive protein; LDL-C=low-density lipoprotein cholesterol.

Libby P. *Circulation.* 2001;104:365-372; Ross R. *N Engl J Med.* 1999;340:115-126.

CHD Event Associations of LDL-P versus LDL-C

Framingham Offspring Study (n=3,066)

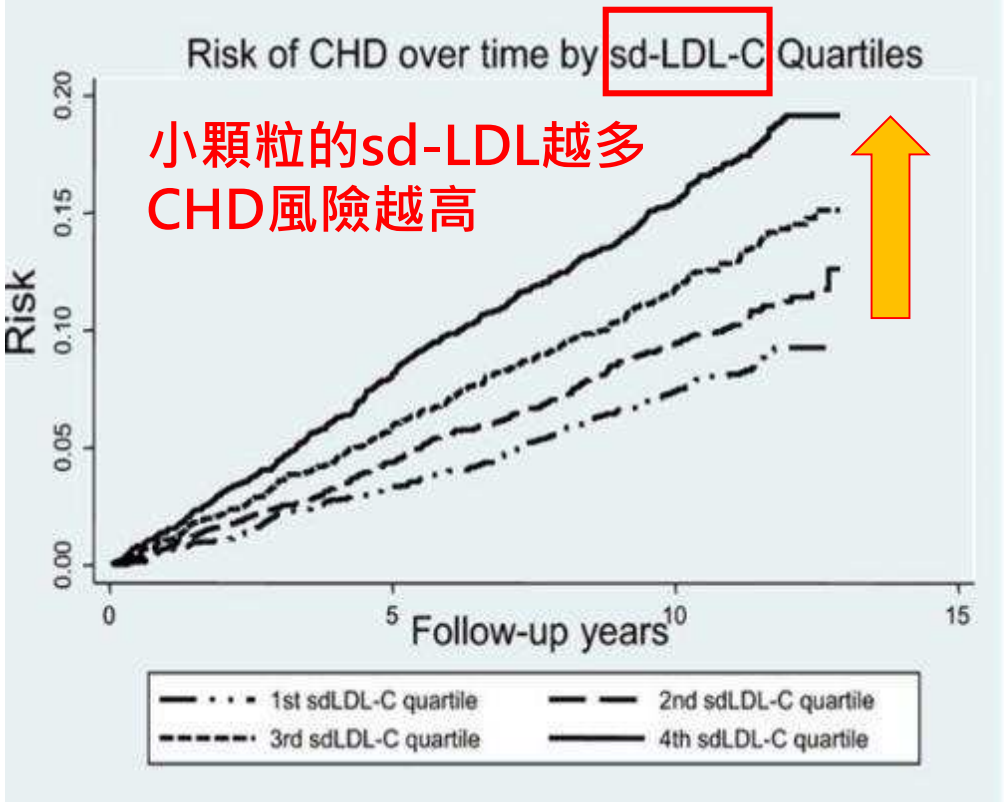


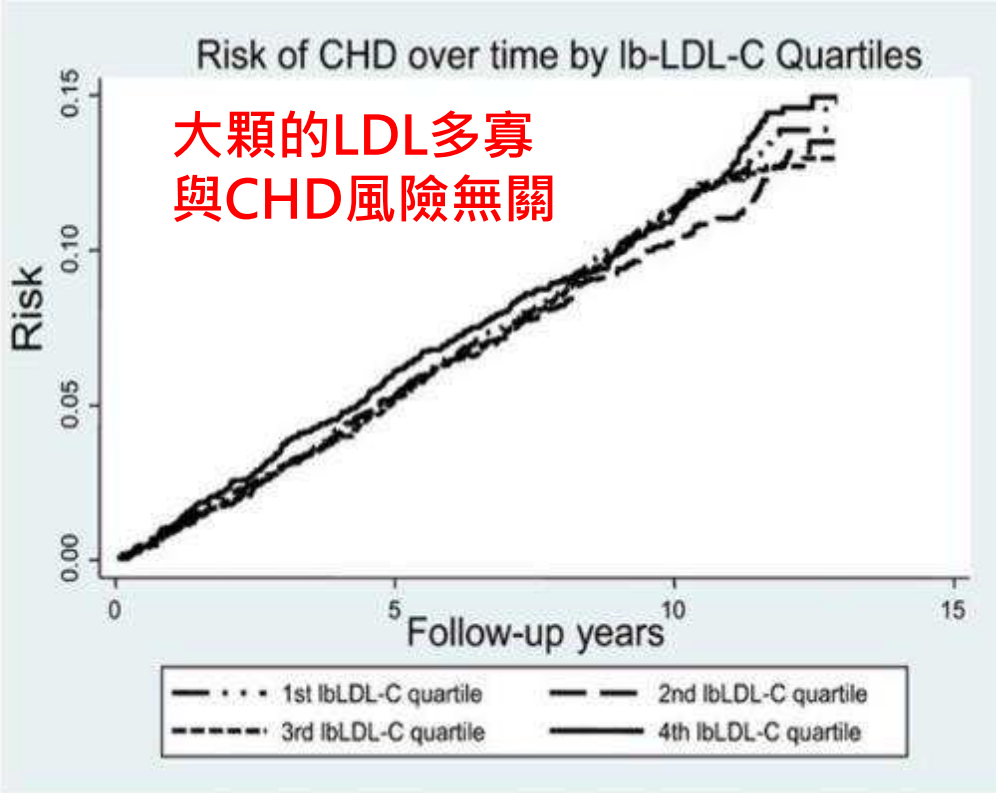
- LDL cholesterol (LDL-C)
- LDL particle number (LDL-P)

Cromwell WC et al. J Clin Lipidology 2007;1(6):583-592.

Small Dense Low-Density Lipoprotein-Cholesterol Concentrations Predict Risk for Coronary Heart Disease

Cumulative incidence curves for risk of coronary heart disease (CHD) by small dense low-density lipoprotein-cholesterol (sdLDL-C) and large buoyant LDL-C (lbLDL-C) quartiles, adjusted for age, race, and sex.



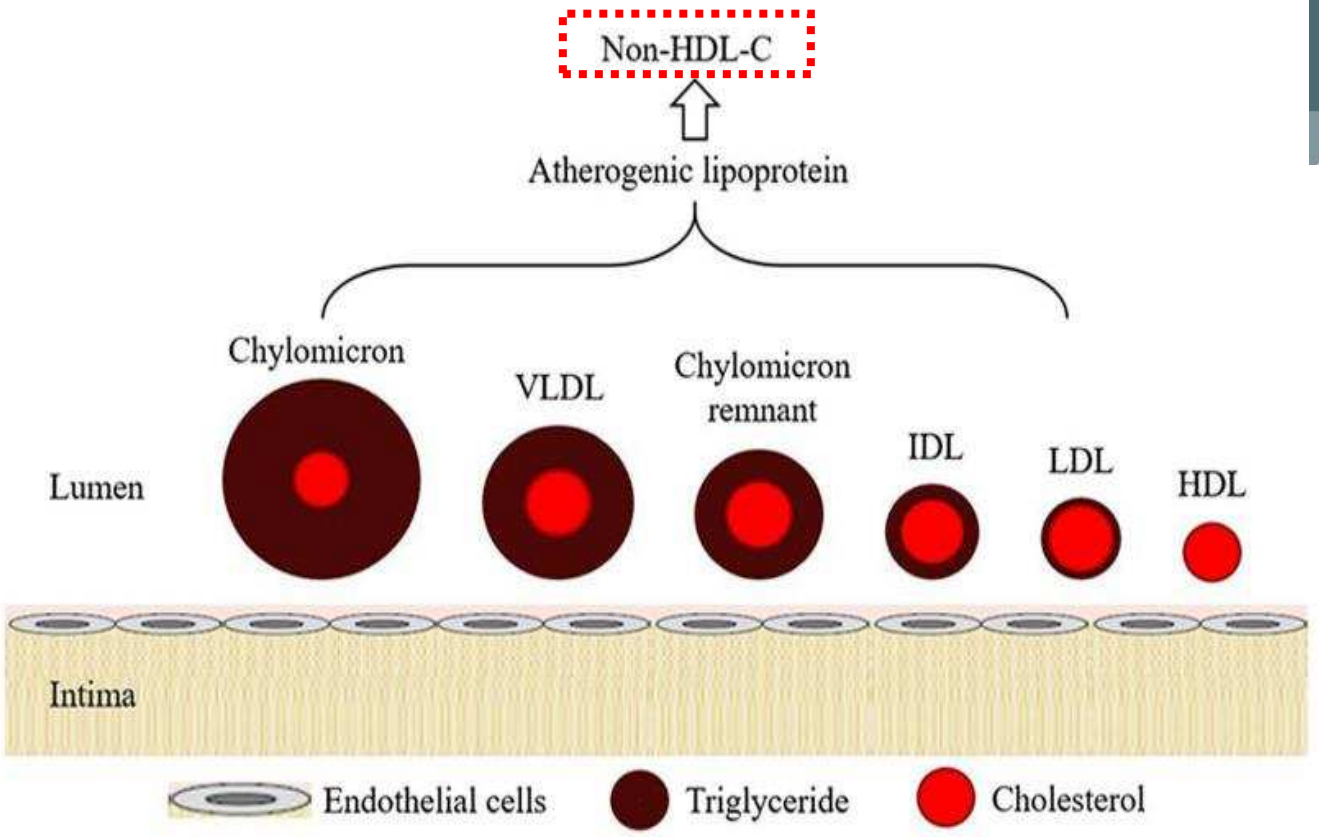


American Heart Association

Ron C. Hoogeveen et al. Arterioscler Thromb Vasc Biol. 2014;34:1069-1077

Non-HDL-C 濃度越高，CV risk 風險越高

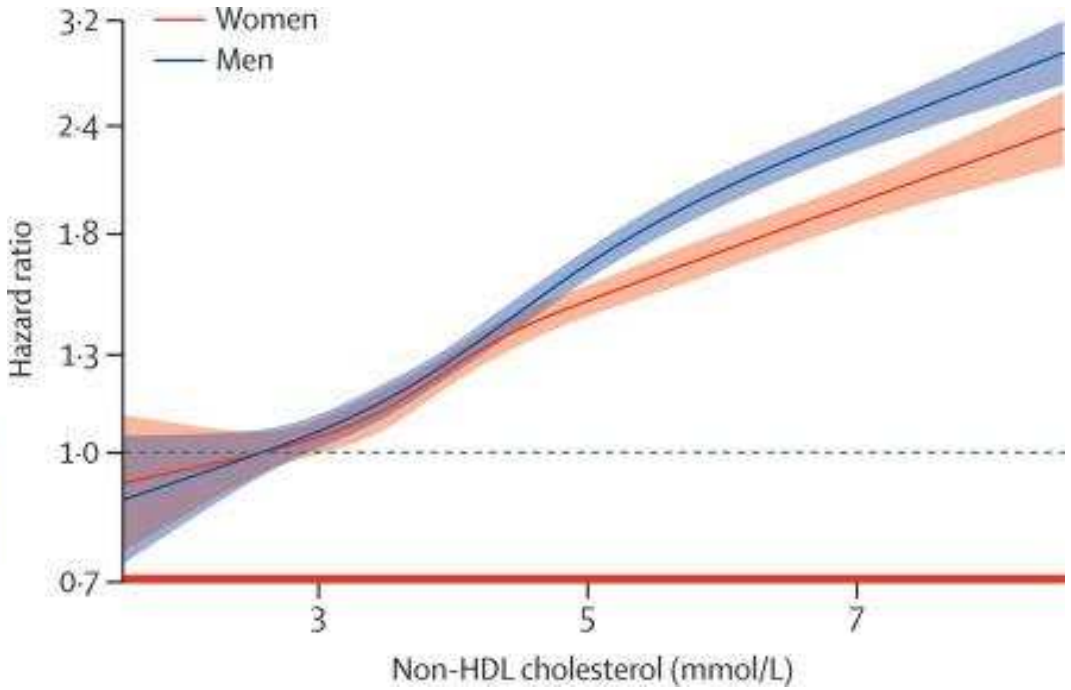
Non-HDL-C = TC – HDL-C



THE LANCET

ARTICLES | VOLUME 394, ISSUE 10215, P2173-2183, DECEMBER 14, 2019

Application of non-HDL cholesterol for population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium



116 193 270 (mg/dl)

Lipids Health Dis . 2019 Jun 7;18(1):134. doi: 10.1186/s12944-019-1080-x.

Lancet . 2019 Dec 14;394(10215):2173-2183.

Outline

Unmet need in the treatment of dyslipidemia

Linicor- Niacin and Statin combination

高風險病患混合型血脂治療首選

Guideline recommendations

Take home messages

仿單

理脂膜衣錠500/20毫克
Linicor F.C.T. 500/20mg

GMP G-11579
衛署藥製字第057216號

【敘述】

維生素 B3

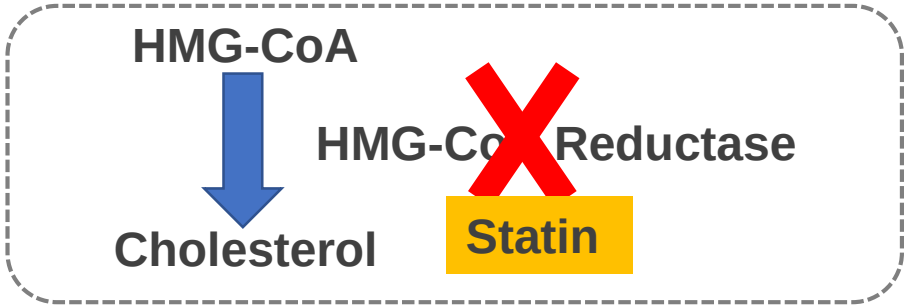
- 理脂膜衣錠500/20毫克包含緩釋劑型 niacin 和 lovastatin。
- Lovastatin是一種三氫氧基三甲基穀胱胺基輔酶A還原酶的抑制劑 (HMG-CoA reductase inhibitor) 。
- Niacin，亦稱菸鹼酸或3-吡啶羧酸。Niacin為白色非吸濕性結晶粉末，極易溶於水、沸騰的乙醇和丙二醇，不溶於乙醚。Niacin的實驗式為 C6H5NO2，分子量為123.11。
- 兩者均為血脂調節藥物

【適應症】

高血脂症，且適合同時使用 niacin 及 lovastatin 治療者。 患者在接受 Linicor 治療之前應採用標準之低膽固醇飲食療法，並且在 Linicor 治療期間仍應持續進行這種飲食療法。

Statin 強度比較表

2018 AHA/ACC Guideline



	High-intensity	Moderate-intensity	Low-intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Primary statin medications	Rosuvastatin 20 mg (40 mg*) Atorvastatin (40 mg‡) 80 mg*	Rosuvastatin (5 mg) 10 mg Atorvastatin 10 mg (20 mg) Simvastatin 20–40 mg§	Simvastatin 10 mg
Other statin medications	–	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

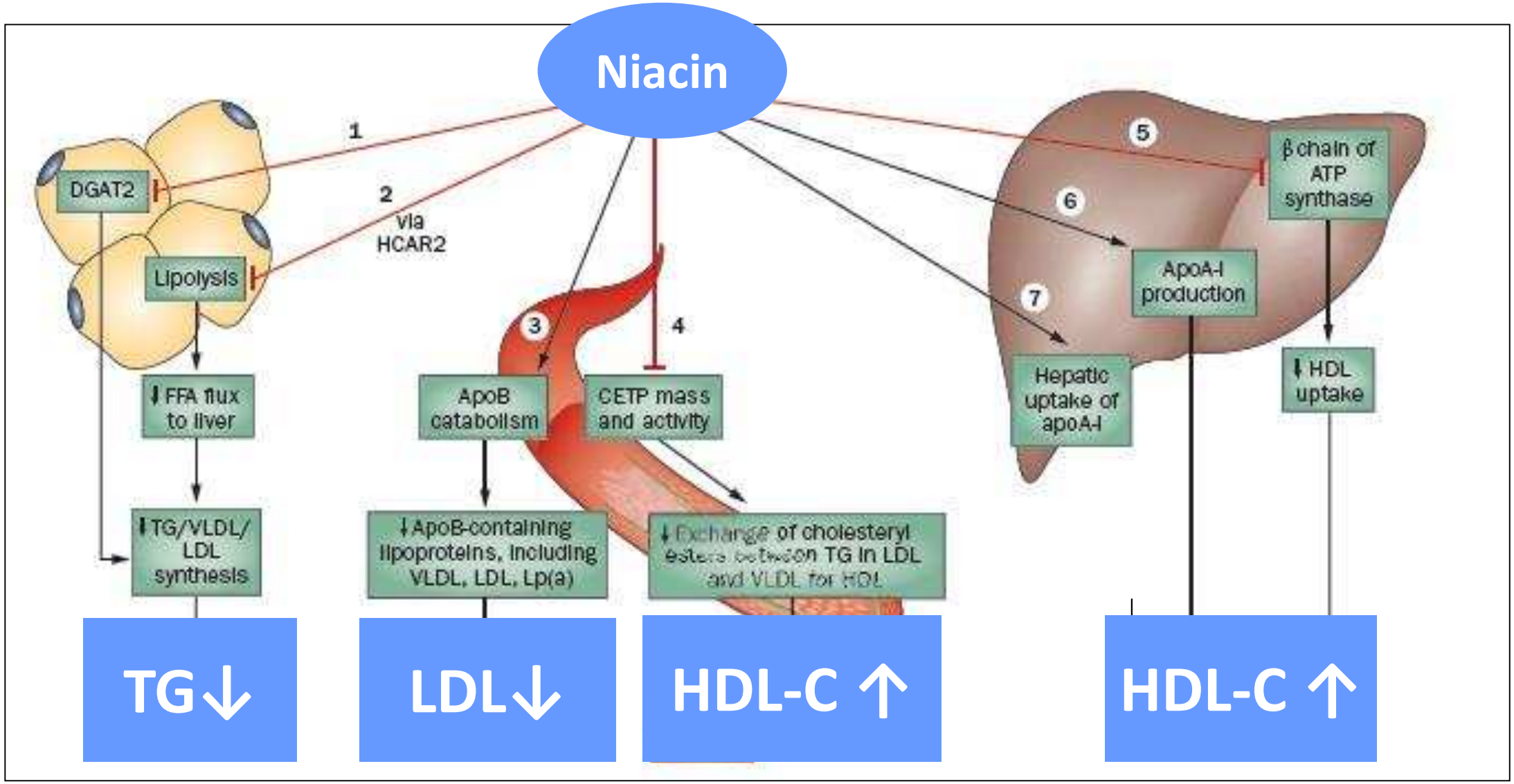
***Rosuvastatin 40 mg, atorvastatin 80 mg, pravastatin 80 mg, lovastatin 80 mg are not indicated in Taiwan.**

†LDL-C lowering that should occur with the dosage listed below each intensity. Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. ‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study. §Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

AHA/ACC, American Heart Association/American College of Cardiology; BID, twice daily; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial.

Grundy SM, et al. Circulation. 2019;139:e1046-e1081.

Niacin 多元作用機轉



Nat Rev Endocrinol. 2012 Sep;8(9):517-28

Statin + Niacin 併用功效互補
全方位控制血脂異常

- Linicor 單顆複方，方便、廣效、療效優異

血脂指標	Statins	Niacin	Fibrate
↓ LDL-C	+++	+	+
↓ TG	+	++	++
↑ HDL-C	+	+++	++
↓ VLDL-C	+/++	++/+++	+++
↓ LDL particle number	+++	+	+
↑ LDL particle size	+	+++	++

1. AM J Health-Syst Pharm-vol60 Jul1,2003 Suppl 2 S15-S21
2. Heart Disease 2002:4:124-137

Combination Niacin Extended-Release/ Lovastatin vs Monotherapy with Atorvastatin or Simvastatin

	Percent Change from Baseline			
	Week 8		Week 12	
	Linicor® Niacin ER + Lovastatin	A 10 mg	Linicor® Niacin ER + Lovastatin	S 20 mg
LDL-C	−39%*	−38%	−42%*	−35%
HDL-C	+20%**	+3%	+19%**	+8%
Triglyceride	−30%**	−20%	−36%**	−15%
Lipoprotein(a)	−16%**	+5%	−20%**	−1%

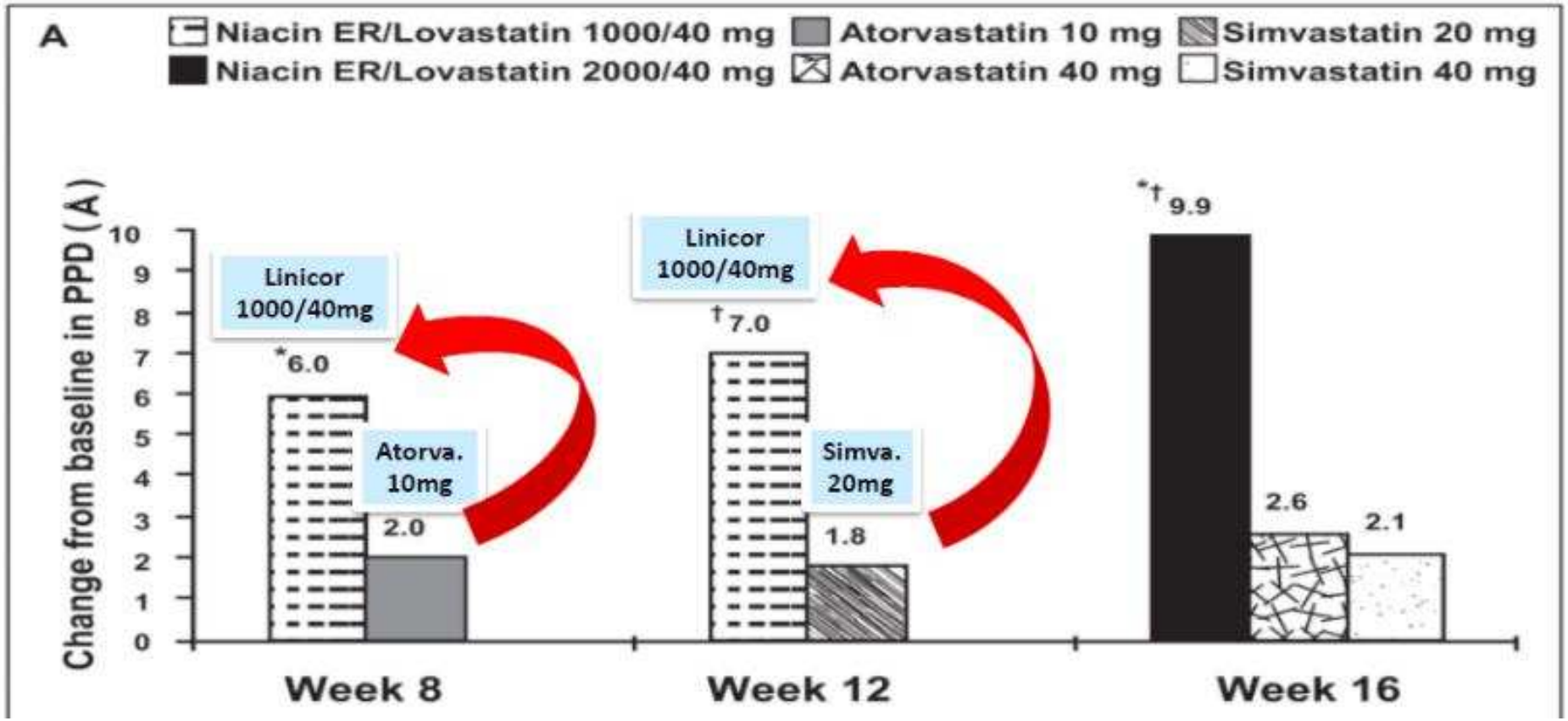
*P<0.01 versus simvastatin; **P<0.001 versus atorvastatin and simvastatin

Bays H et al. *Am J Cardiol* 2003;91:667-672.

ADVOCATE study 療效優異

1) Linicor 與atorvastatin及simvastatin比較

增加 LDL Particle Size



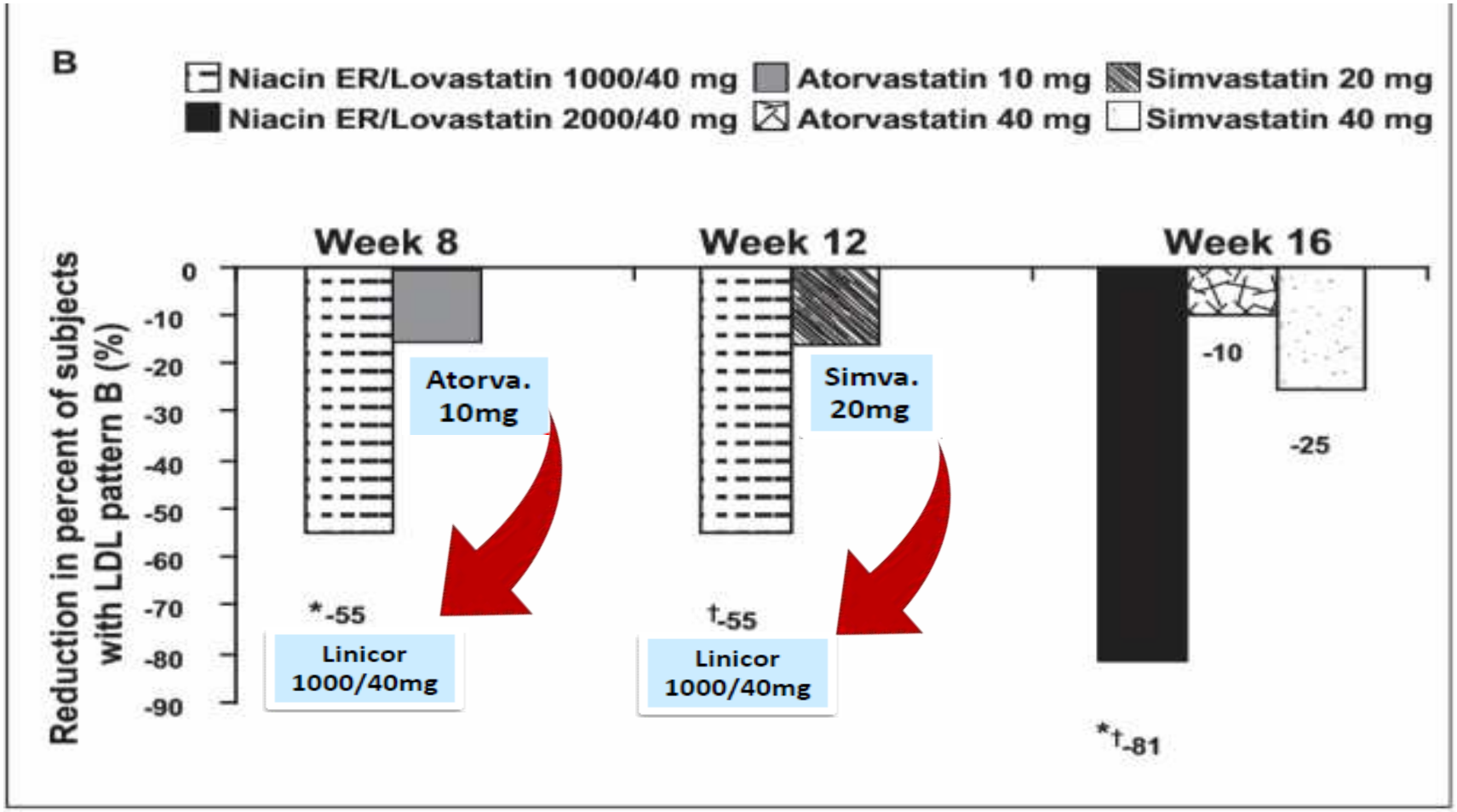
*PPD: peak particle diameter

Am J Cardiol 2003;91:667-672

ADVOCATE study 療效優異

2) Linicor 與atorvastatin及simvastatin比較

大幅減少sd-LDL濃度



Am J Cardiol 2003;91:667-672

Niacin: 有效提升糖尿病患者的 functional HDL-C

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

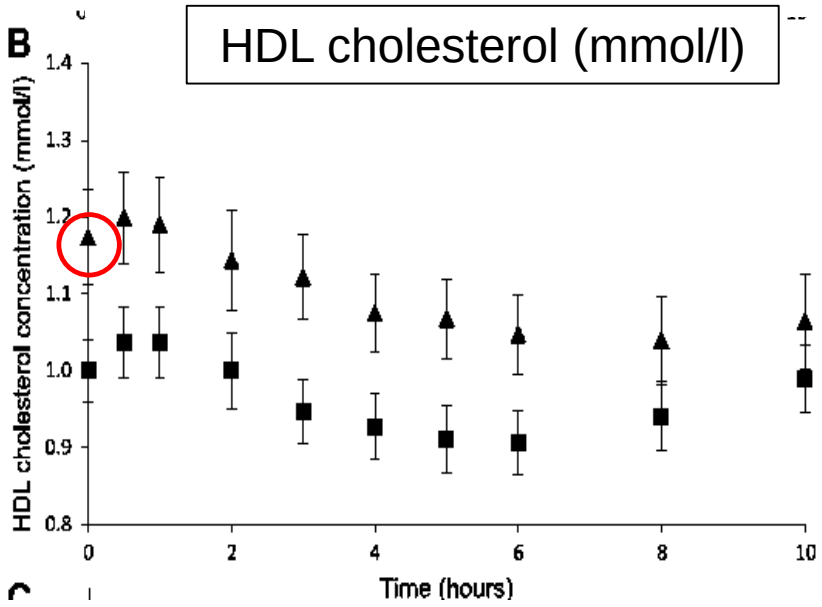
Effect of Niacin on High-Density Lipoprotein Apolipoprotein A-I Kinetics in Statin-Treated Patients With Type 2 Diabetes Mellitus

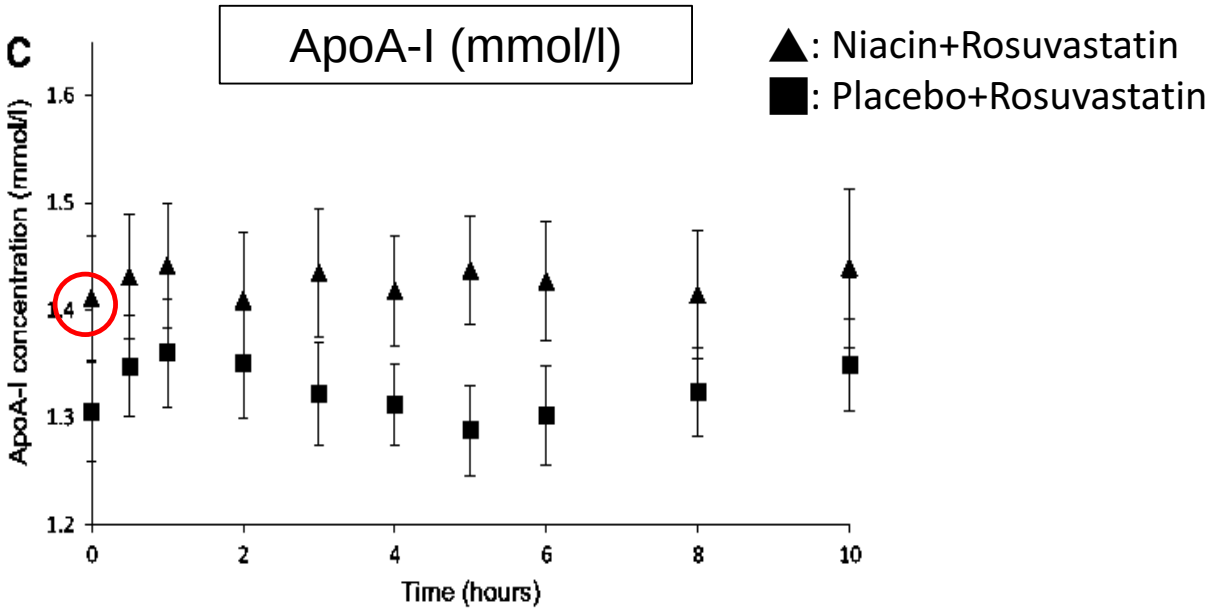
Jing Pang, Dick C. Chan, Sandra J. Hamilton, Vijay S. Tenneti, Gerald F. Watts and P. Hugh. R. Barrett

Conclusions—ER niacin increases HDL apoA-I concentration in statin-treated subjects with type 2 diabetes mellitus by lowering apoA-I fractional catabolic rate. The effect on HDL metabolism was independent of the reduction in plasma triglyceride with ER niacin treatment. Whether this finding applies to other dyslipidemic populations remains to be investigated. (***Arterioscler Thromb Vasc Biol.*** **2014;34:427-432.**)

Niacin: 有效提升糖尿病患者的 ApoA-1 與 functional HDL-C

- For T2DM men **(N=12)** under optimal rosuvastatin therapy, a randomization was performed for rosuvastatin alone or rosuvastatin plus niacin ER for 12 weeks.
- 與 rosuvastatin alone相比，add-on Niacin後，可**顯著提升**病患 **HDL-C** 和 **ApoA-1.**





***Rosuva. Plus Niacin* vs. *Rosuva.*:**

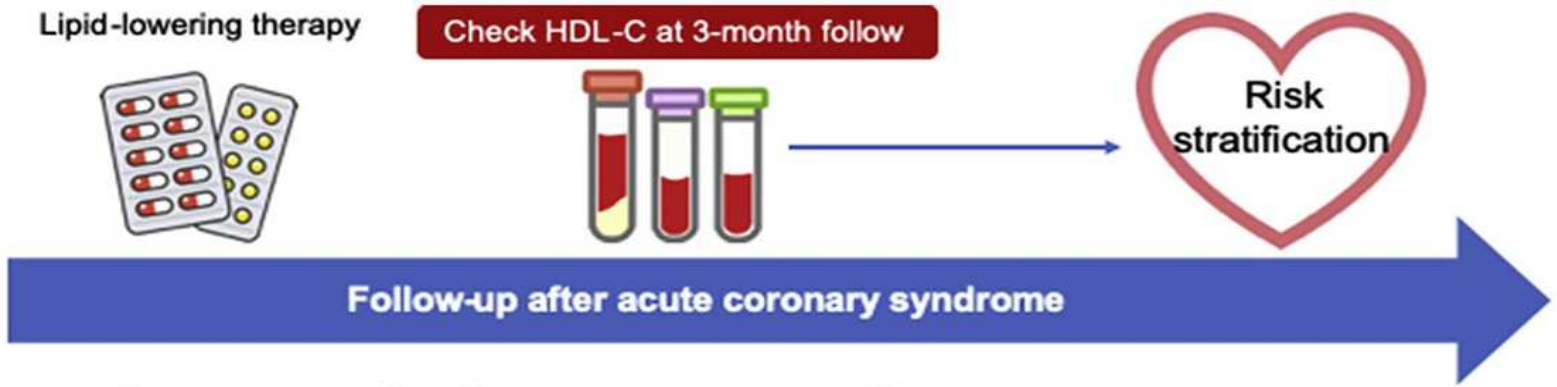
✓ HDL cholesterol (mmol/L): 1.17±0.06 vs. 1.00±0.04, p<0.001

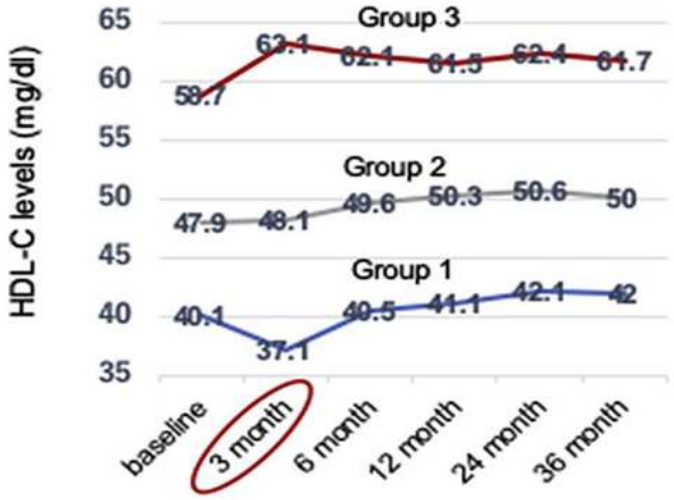
✓ ApoA-1(mmol/L): 1.41±0.06 vs. 1.31±0.05, p=0.020

10 subjects to 2g
1 subject to 1.5g
1 subject to 1g

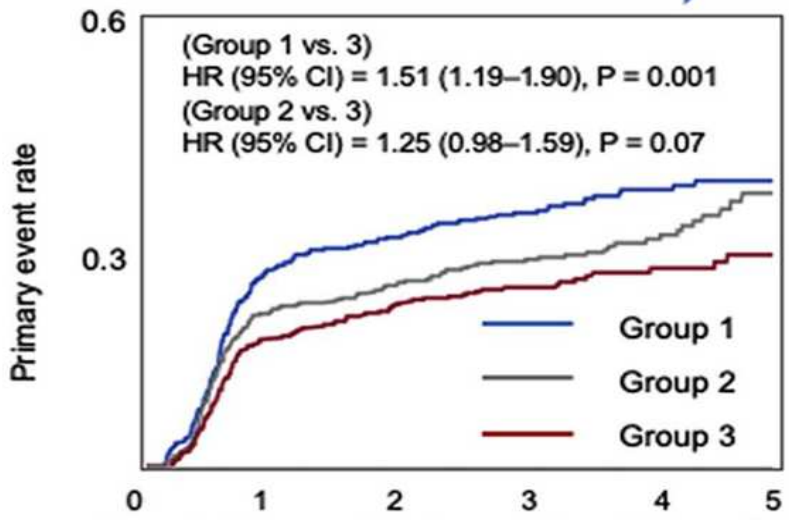
Arterioscler Thromb Vasc Biol. 2014 Feb;34(2):427-32

ACS 患者，HDL-C 過低 CV 風險顯著提升





HDL-C levels at 3-month follow-up: Group 1, HDL-C levels ≤ 43 mg/dL; Group 2, HDL-C levels>43, < 53.6 mg/dL; and Group 3, HDL-C levels ≥ 53.6 mg/dL



primary endpoint (a composite of all-cause death, non-fatal myocardial infarction, non-fatal stroke, unstable angina pectoris, or ischemia-driven revascularization

HDL ≦ 43 mg/dl

HDL 43 ~ 53.6 mg/dl

HDL ≧ 53.6 mg/dl

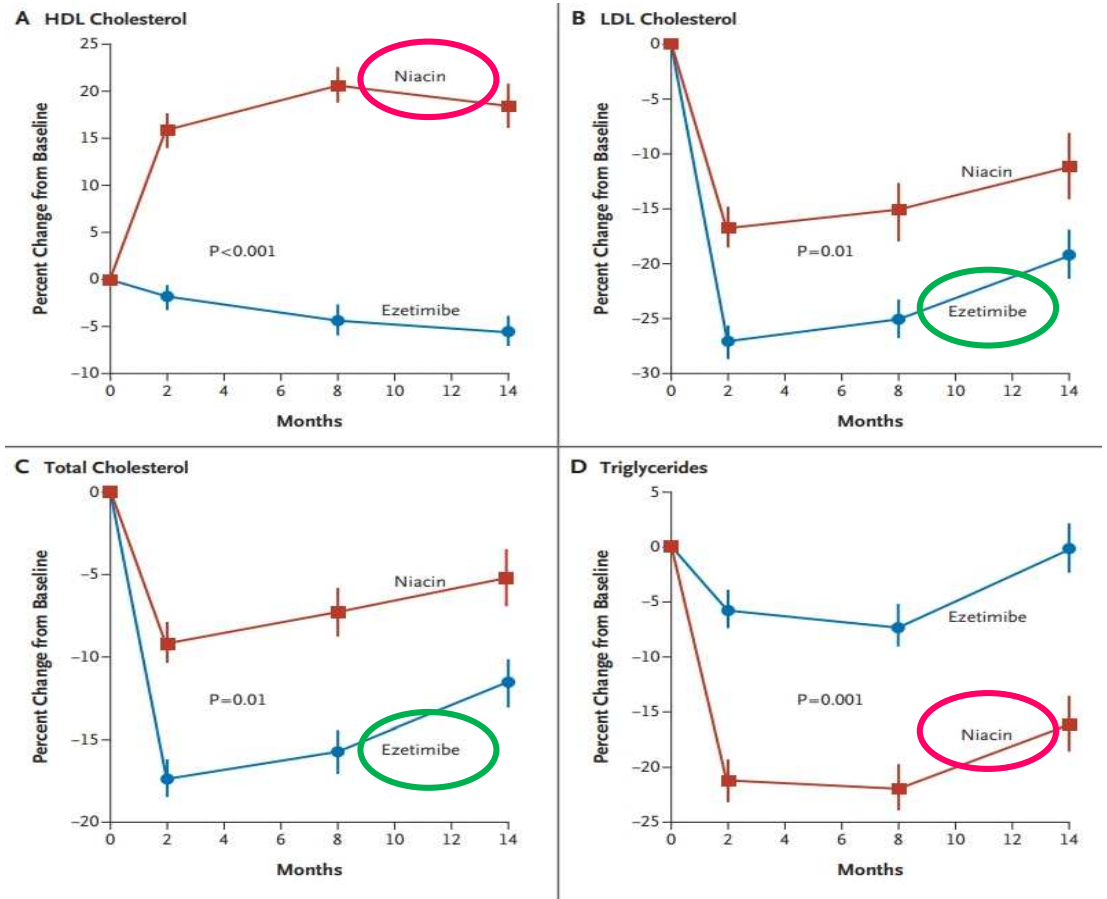
Conclusions

Lower levels of HDL-C at 3-month follow-up are independently associated with higher incidence of cardiovascular events in ACS patients receiving contemporary lipid-lowering therapy.

Nakazawa M, et al. Atherosclerosis. 2020. PMID: 32474302

ARBITER6: 併用 Statin+Niacin 能降低 CIMT Regression Atherosclerosis

- 針對冠心病患 (N=363)，使用statin使LDL-C達標後，併用niacin 在頸動脈壁厚度(CIMT)改善上顯著優於ezetamibe。
- 對於臨床上使用statin及ezetamibe使LDL-C達到65.5mg/dL，只能減緩動脈粥狀硬化病程，選用statin及niacin合併療法才具有改善(regression)動脈粥狀硬化好處。



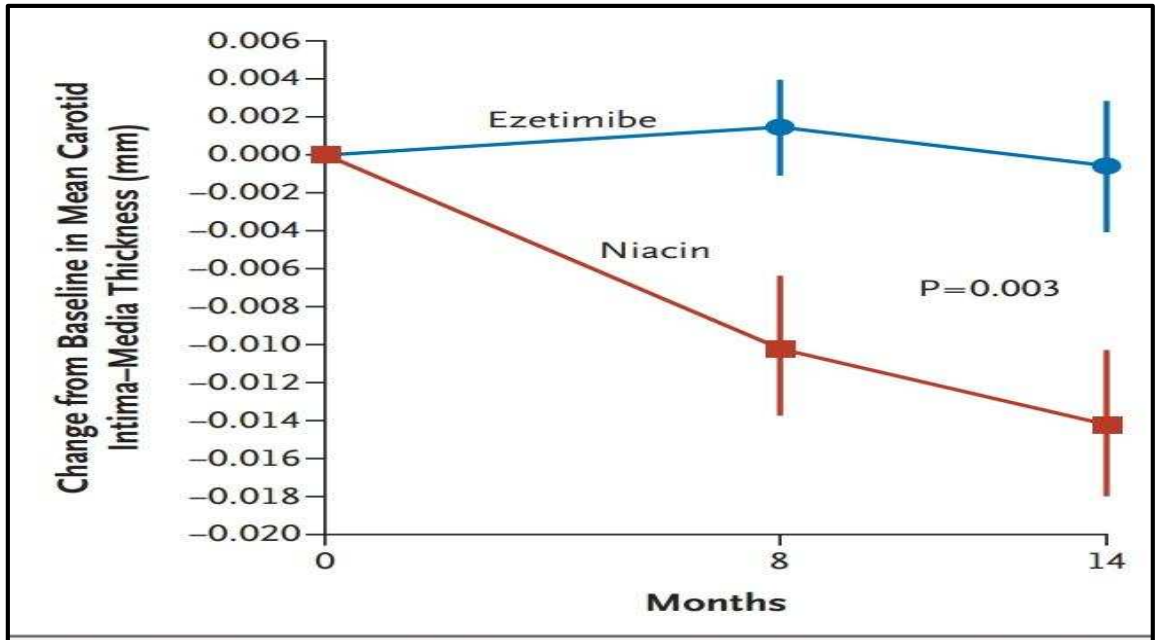
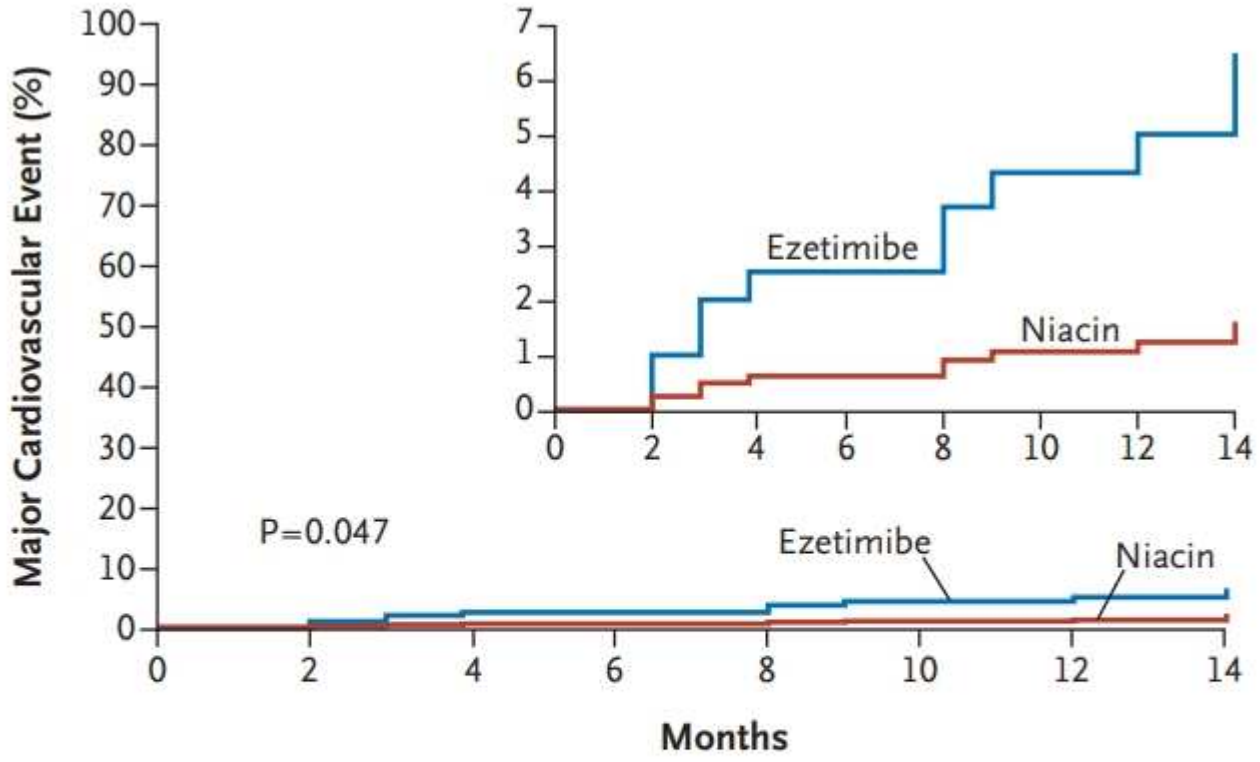


Figure 2. Changes in the Mean Carotid Intima–Media Thickness over the 14-Month Study Period, According to Treatment Group.

ER niacin (2000 mg/D)
Ezetimibe (10 mg/D)

2009, NEJM, Nov 26;361(22):2113-22

ARBITER6: 併用 Statin+Niacin 能降低 CIMT、減少心血管事件



No. at Risk

Ezetimibe	176	174	171	167	160	154	146	143	139	132	126	121	118	113	111
Niacin	187	185	171	163	160	152	138	132	130	116	106	104	101	97	97

Figure 3. Kaplan–Meier Estimates of the Incidence of a Major Cardiovascular Event among the 363 Study Patients, According to Treatment Group.

相較於Ezetimide和Statin併用，Niacin和Statin併用可顯著減少主要血管事件發生比例。

Major adverse CV events

- Myocardial infarction
- Myocardial revascularization
- Admission for an ACS
- Death from CHD)

2009, NEJM, Nov 26;361(22):2113-22

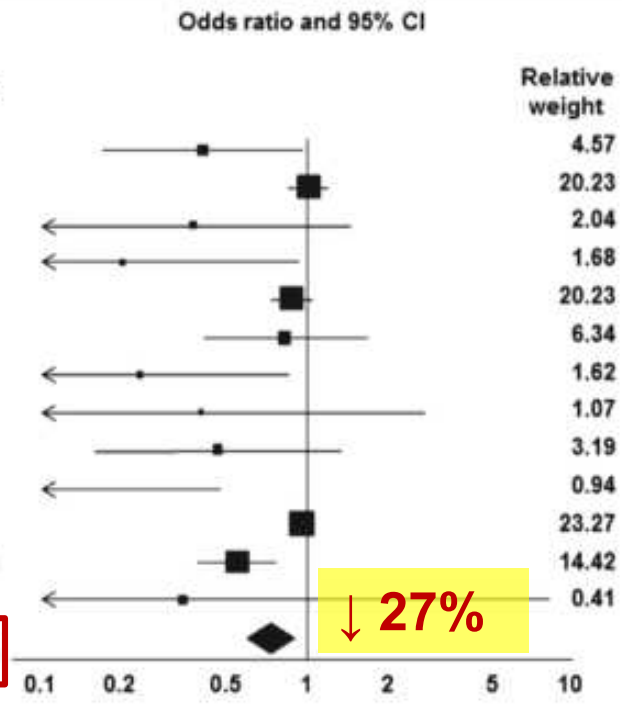
Niacin: 2016 meta-analysis (13 trials, N=35,723) reduces CVD events 27%

- Niacin therapy was associated with a significant reduction in
  - ✓ any cardiovascular event **(OR 0.73, p=0.003)**
  - ✓ major coronary events (**OR: 0.81; p= 0.04)**
  - ✓ any revascularization **(OR: 0.59; p= 0.006)**

Fig. 1 Summary effect of niacin on the occurrence of any cardiovascular event.

Random effects odds ratio, 95% confidence intervals (CI) and I^2statistic are shown.

Study name	Statistics for each study			Events / Total			Relative weight
	Odds ratio	Lower limit	Upper limit	Niacin	Control	p-Value	
AFREGS	0.40	0.17	0.97	9 / 71	19 / 72	0.04	4.57
AIM-HIGH	1.02	0.85	1.22	282 / 1,718	274 / 1,696	0.84	20.23
ARBITER-2	0.37	0.09	1.49	3 / 87	7 / 80	0.16	2.04
ARBITER-6	0.20	0.04	0.94	2 / 187	9 / 176	0.04	1.68
CDP	0.87	0.73	1.05	914 / 1,119	2,333 / 2,789	0.14	20.23
CLAS	0.82	0.41	1.67	18 / 94	21 / 94	0.59	6.34
FATS	0.18	0.04	0.88	2 / 48	10 / 52	0.03	1.62
Guyton et al.	0.40	0.06	2.86	2 / 676	2 / 272	0.36	1.07
HARP	0.46	0.16	1.36	6 / 44	12 / 47	0.16	3.19
HATS	0.06	0.01	0.48	1 / 38	12 / 38	0.01	0.94
HPS THRIVE	0.96	0.89	1.03	1,696 / 12,838	1,758 / 12,835	0.25	23.27
STOCKHOLM	0.54	0.38	0.77	90 / 279	129 / 276	0.001	14.42
UCSF_SCOR	0.33	0.01	8.39	0 / 48	1 / 49	0.50	0.41
TOTAL	0.73	0.59	0.90	3,025 / 17,247	4,587 / 18,476	0.003	



Test for overall effect: p = 0.003
Test for heterogeneity: p = 0.001, I^2 = 65%

Acta Cardiol 2016;71(4):463-472 doi:10.2143/AC.71.4.3159701

降三酸甘油脂藥物一覽

Niacin與現行降TG藥物療效差不多

Effect of Lipid-Lowering Therapies on Triglyceride Reduction

Drug	% Triglyceride Reduction	
Fibrates	30-50	降TG為主藥物
Immediate-release niacin	**20-50**	降TG為主藥物
Omega-3	20-50	降TG為主藥物
Extended-release niacin	**10-30**	降TG為主藥物
Statins	10-30	降LDL為主藥物
Ezetimibe	5-10	降LDL為主藥物

Circulation. 2011 May 24;123(20):2292-333

KDOQI治療指引建議

National Kidney Foundation
KDOQI

Medication Class and Agents	No CKD or stages 1-2	CKD stage 3	CKD stages 4-5
Statins (mg/day)			
Atorvastatin	10-80	10-80	10-80
Fluvastatin	20-80	20-80	10-80
Lovastatin	10-80	10-80	10-40
Pravastatin	10-40	10-40	10-20
Rosuvastatin	5-40	5-20	5-10
Simvastatin	5-40	5-40	5-20
Bile acid sequestrants (g/day)			
Cholestipol	5-30	5-30	5-30
Cholestyramine	4-16	4-16	4-16
Colesevelam	2.6-3.8	2.6-3.8	2.6-3.8
Fibric acid derivatives (mg/day)			
Bezafibrate*	400-600	200	Avoid
Clofibrate	1000-2000	500	500
Ciprofibrate*	200	Unknown	Avoid
Fenofibrate	96	48	Avoid
Gemfibrozil	1200	1200	600
Other (mg/day)			
Ezetimibe	10	10	10
Niacin	2000	2000	1000

2012, KDOQI guideline for diabetes and CKD

Linicor提供 CKD病患安全血脂用藥選擇
中文仿單：較不需調整劑量

- 針對LDL-C過高且TG過高的病患，如腎功能不全，可選擇**Linicor**
- 因**Fenofibrate須減量或禁用**，無法有效治療TG

腎功能不全	Linicor (Niacin ER 500mg及 Lovastatin 20mg)	Fenofibrate 160/200mg
輕微至中度 30<CCR<60	勝 劑量不變 (1000/40mg qd)	減量使用 (100mgor 67mg qd)
嚴重腎功能 CCR<30	勝 > 500/20mg 使用需注意	禁用

Fenofibrate 160/200mg中文仿單、Linicor 500/20mg中文仿單

Statin+ Fibrate 副作用比例提高

Gemfibrozil 與Statin 並用，橫紋肌溶解症顯著提升

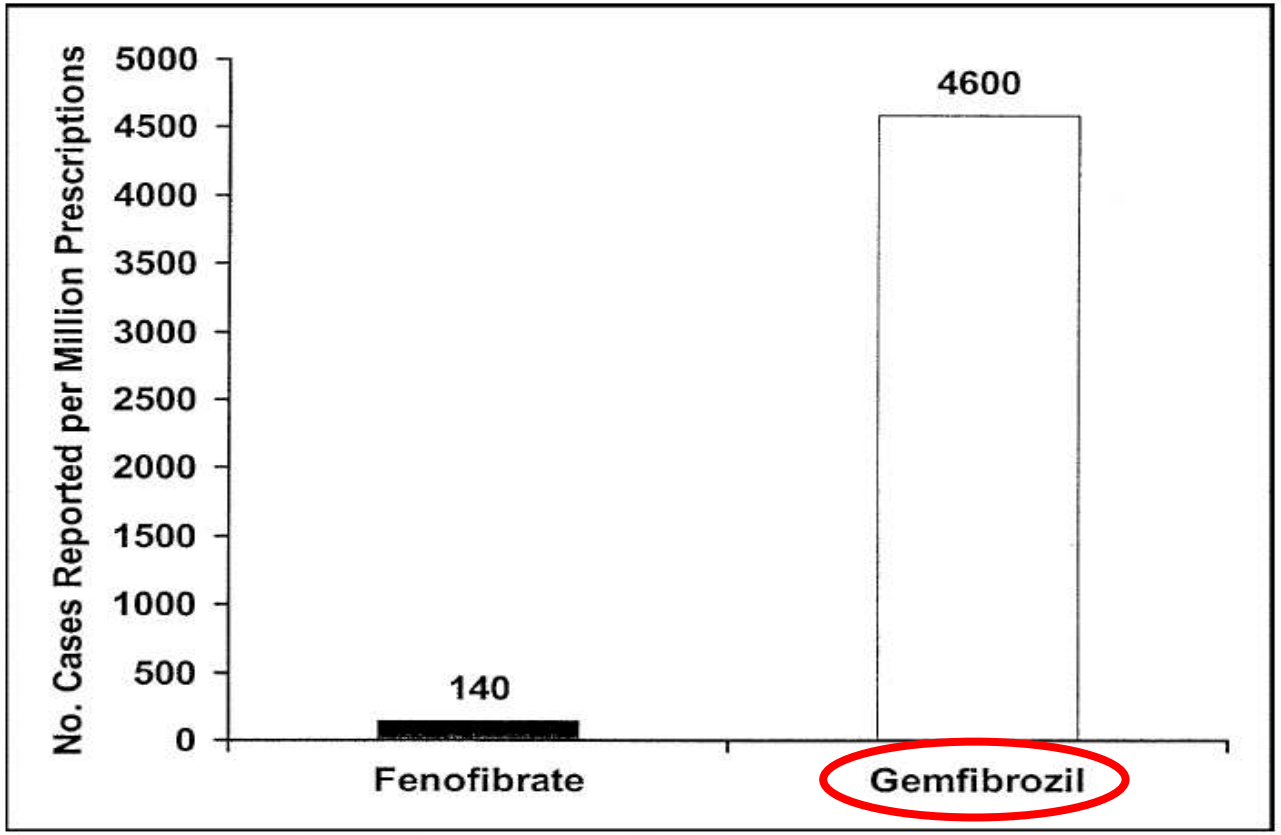


FIGURE 1. Number of cases of rhabdomyolysis reported per million prescriptions dispensed of cerivastatin in combination with fenofibrate or gemfibrozil. Fenofibrate resulted in a 33 times lower rhabdomyolysis reporting rate than did gemfibrozil.

Am J Cardiol. 2005 Jan 1;95(1):120-2.

TFDA 2022/6/28 針對fibrate及statin之公告

衛生福利部　公告

發文日期：中華民國111年6月28日
發文字號：衛授食字第1111404976號
附件：含choline fenofibrate及fenofibrate成分藥品之中文仿單修訂內容

主旨：公告fibrate類及statin類藥品之臨床效益及風險再評估結果相關事宜。

依據：藥事法第48條。

公告事項：

一、慮及使用fibrate類及/或statin類藥品可能具引起胰臟炎或肝臟相關不良反應之風險，本部為保障民眾用藥安全，依據藥事法第48條彙整國內外臨床文獻資料進行整體性評估，決定修訂藥品之中文仿單如下：

(一)含choline fenofibrate及fenofibrate成分藥品之中文仿單：

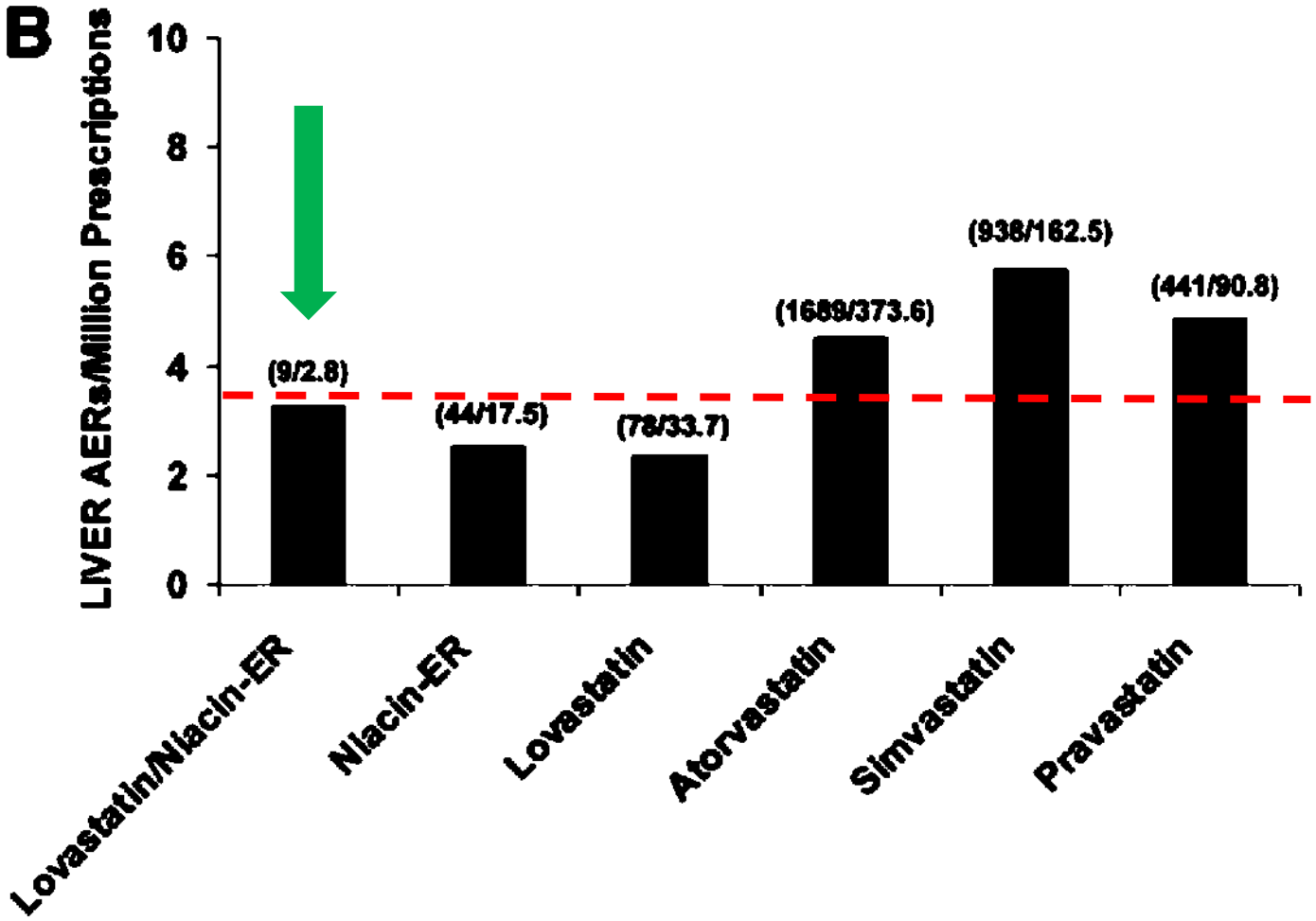
1、刪除禁忌症「患有膽囊疾病的病人」相關敘述，並修訂為「膽結石」。

2、刪除有關「AST及ALT上升超過正常範圍上限三倍必須停藥」相關敘述，並將禁忌症有關「肝功能不良」相關內容，修訂為「嚴重肝功能不良（包括不明原因的持續性肝功能異常）」，及於「警語及注意事項」段落加刊「若肝生化值 (AST、ALT、alkaline phosphatase) 上升超過正常範圍上限3倍或有黃疸發生時，宜考慮停藥」之內容。

3、於「警語及注意事項」段落加刊曾有胰臟炎之個案報告及可能導致胰臟炎之原因相關內容，其修訂內容詳如附件。

Niacin ER 與 Lovastatin合併，並無增加 hepatotoxicity

- The rate of combination lovastatin/niacin-ER associated liver AERs was similar to that observed with lovastatin or niacin-ER alone.

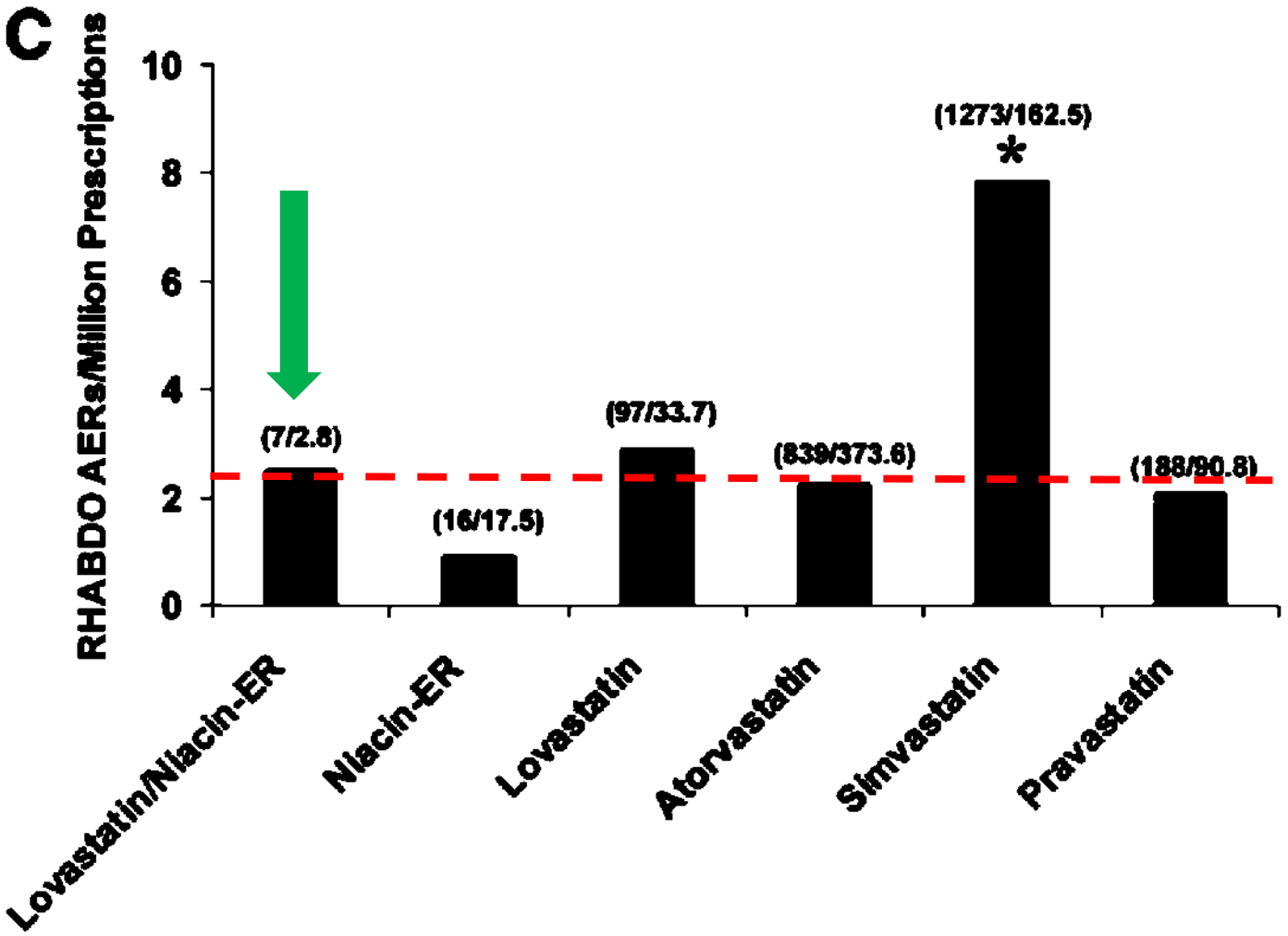


**Data above bars represent number of AERs/number of prescriptions in millions during study period.*

Am J Cardiol. 2007 Feb 1;99(3):379-81.

Niacin ER 與 Lovastatin合併，並無增加 rhabdomyolysis

- The rate of combination lovastatin/niacin-ER associated rhabdomyolysis AERs was similar to that observed with lovastatin or niacin-ER alone.



**Data above bars represent number of AERs/number of prescriptions in millions during study period.*

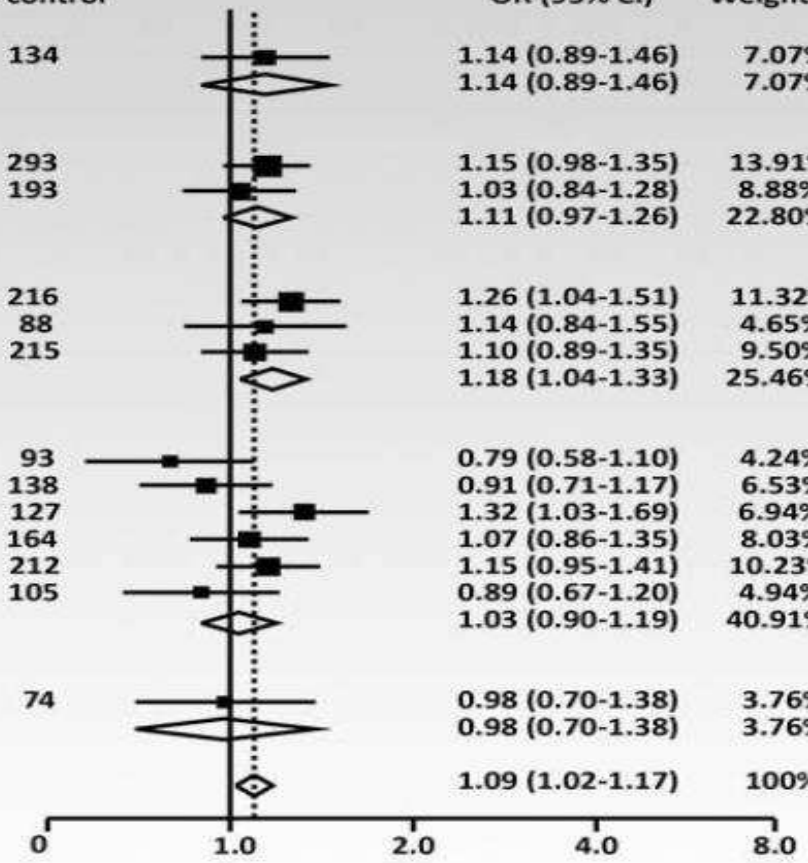
Am J Cardiol. 2007 Feb 1;99(3):379-81.

Why choose Lovastatin ?

Do Statins Increase New-Onset T2DM?

Yes: rosuva, simva, atorva; ***No***: prava, lova

	n	Statin	Placebo or control	OR (95% CI)	Weight (%)
Atorvastatin					
ASCOT-LLA	7773	154	134	1.14 (0.89-1.46)	7.07%
				1.14 (0.89-1.46)	7.07%
Simvastatin					
HPS	14573	335	293	1.15 (0.98-1.35)	13.91%
4S	4242	198	193	1.03 (0.84-1.28)	8.88%
Subtotal (I^2 = 0.0%, P = .445)				1.11 (0.97-1.26)	22.80%
Rosuvastatin					
JUPITER	17802	270	216	1.26 (1.04-1.51)	11.32%
CORONA	3534	100	88	1.14 (0.84-1.55)	4.65%
GISSI HF	3378	225	215	1.10 (0.89-1.35)	9.50%
Subtotal (I^2 = 0.0%, P = .607)				1.18 (1.04-1.33)	25.46%
Pravastatin					
WOSCOPS	5974	75	93	0.79 (0.58-1.10)	4.24%
LIPID	6997	126	138	0.91 (0.71-1.17)	6.53%
PROSPER	5023	165	127	1.32 (1.03-1.69)	6.94%
MEGA	6086	172	164	1.07 (0.86-1.35)	8.03%
ALLHAT-LLT	6087	238	212	1.15 (0.95-1.41)	10.23%
GISSI PREVENZIONE	3460	96	105	0.89 (0.67-1.20)	4.94%
Subtotal (I^2 = 47.5%, P = .090)				1.03 (0.90-1.19)	40.91%
Lovastatin					
AFCAPS/TexCAPS	6211	72	74	0.98 (0.70-1.38)	3.76%
				0.98 (0.70-1.38)	3.76%
Overall (I^2 = 11.2%)				1.09 (1.02-1.17)	100%



9%

T2DM = type 2 diabetes mellitus

Sattar N, et al. *Lancet*. 2010;375:735-742.

Outline

Unmet need in the treatment of dyslipidemia

Linicor- Niacin and Statin combination

高風險病患混合型血脂治療首選

Guideline recommendations

Take home messages

健保降膽固醇藥物給付規定 108年2月1日起

	非藥物治療	起始藥物治療血脂值 (控制目標為小於起始值)
• 有急性冠狀動脈症候群病史 • 曾接受心導管介入或 CABG 之冠狀動脈粥狀硬化患者	與藥物治療可並行	LDL-C ≧70 mg/dL
心血管疾病或糖尿病患者		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
1 個危險因子		TC ≧ 240mg/dL 或 LDL-C ≧ 160mg/dL
0 個危險因子		LDL-C ≧ 190mg/dL

●心血管疾病定義： (一) 冠狀動脈粥狀硬化包含：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 (二) 缺血型腦血管疾病包含： 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

2.6.1 全民健康保險降血脂藥物給付規定表

健保降三酸甘油酯藥物給付規定 108年2月1日起

	非藥物治療	起始藥物治療三酸甘油酯值
心血管疾病或糖尿病病人	與藥物治療可並行	TG ≧ 200mg/dL 且 (TC/HDL-C > 5 或 HDL-C < 40mg/dL)
無心血管疾病病人		TG ≧ 500mg/dL
無心血管疾病病人	給藥前應有 3-6 個月非藥物治療	TG ≧ 200mg/dL 且 (TC/HDL-C > 5 或 HDL-C < 40mg/dL)

●心血管疾病定義： (一) 冠狀動脈粥狀硬化包含：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 (二) 缺血型腦血管疾病包含： 1.腦梗塞。 2.暫時性腦缺血患者(TIA)。 3.有症狀之頸動脈狹窄。

2.6.1 全民健康保險降血脂藥物給付規定表

2022-台灣高風險病人血脂異常治療指引

Available online at www.sciencedirect.com

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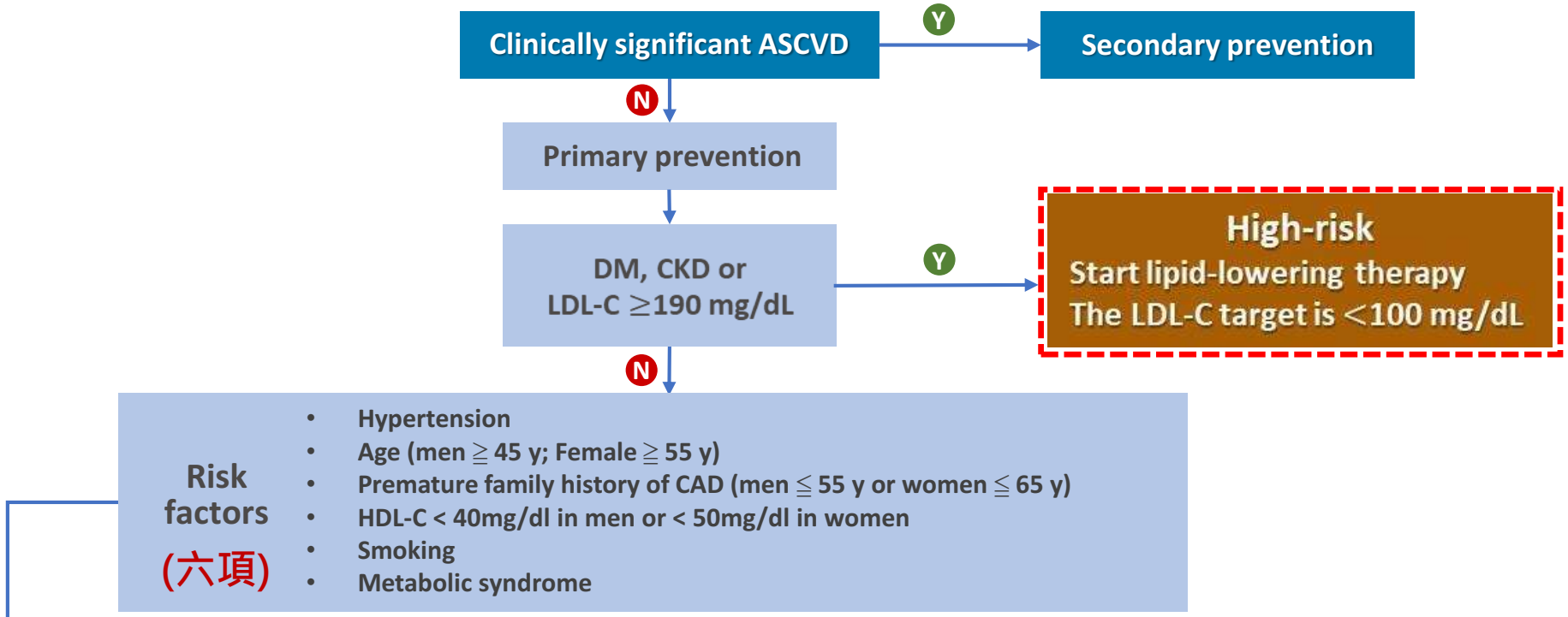
journal homepage: www.jfma-online.com

Clinical Practice

2022 Taiwan lipid guidelines for primary prevention

Po-Hsun Huang [a,b,1], Ya-Wen Lu [a,b,1], Yi-Lin Tsai [a,b,1], Yen-Wen Wu [c,d,e,1], Hung-Yuan Li [f,1], Hsin-Yun Chang [g,h,1], Chih-Hsing Wu [g,i,1], Chih-Yu Yang [j,k,1], Der-Cherng Tarng [j,l,1], Chin-Chou Huang [a,1], Li-Ting Ho [m,n,1], Chao-Feng Lin [o,p,1], Shih-Chieh Chien [p,q,r,1], Yih-Jer Wu [o,p,1], Hung-I Yeh [o,p,1], Wen-Harn Pan [s,1], Yi-Heng Li [t,*,1] on behalf of the expert committee for the Taiwan Lipid Guidelines for Primary Prevention

2022 Draft of Taiwan Lipid Guideline: New LDL-C targets in primary prevention of CVD



	LDL-C target
≥2 risk factors	<115 mg/dL
1 risk factor	<130 mg/dL
No risk factor	<160 mg/dL

If the LDL-C targets are not met, non-pharmacological therapy for 3 months followed by moderate intensity statin should be considered

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

2022 Draft of Taiwan Lipid Guideline.

High risk patients-心血管、腦血管疾病患者 LDL-C 治療目標下修

2022 指引更新 - 動脈硬化心血管疾病之 LDL-C 治療目標

指引更新內容

疾病類型	LDL-C 建議治療目標
急性冠心症 / 冠狀動脈疾病	< 70 mg/dL
急性冠心症 / 冠狀動脈疾病 併發： • 急性冠心病與糖尿病 或 • 12 個月內發生心肌梗塞 或 • 2 次心肌梗塞病史 或 • 多支血管病變之冠狀動脈疾病 或 • 伴隨周邊動脈疾病	考慮 < 55 mg/dL
周邊動脈疾病	< 70 mg/dL
• 周邊動脈疾病 併發 冠狀動脈疾病或頸動脈狹窄	考慮 < 55 mg/dL
缺血性中風 或 短暫性腦缺血發作併發腦部或頸部動脈粥狀硬化狹窄 或 已知冠狀動脈疾病	< 70 mg/dL

2017: <100 mg/dl

2017: <70 mg/dl

2022第2型糖尿病臨床照護指引

主要目標		說明
LDL	所有病人<100 mg/dl 已有心血管疾病 <70 mg/dl	建議使用中 / 強效 果 的 statins 為 第 一線藥物治療
HDL	男 > 40 mg/dl 女 > 50 mg/dl	生活型態介入治療 及血糖控制為優先
TG	< 150 mg/dl 血糖控制及生活型態 介入治療為優先	但三酸甘油酯 ≥500 mg/dl，需給 fibrates
次要目標		
Non-HDL	所有病人<130 mg/dl 已有心血管疾病 <100 mg/dl	當主要目標達成 時，再評估次要目 標

2022第2型糖尿病臨床照護指引- 中華民國糖尿病學會 & 糖尿病衛教學會

2023 糖尿病血脂異常治療指引

ASCVD risk categories of patients with diabetes, and treatment goals

	Categories	Chararcteristic	LDL-C	Non-HDL-C	TG	Apo-B
Primary prevention	High risk	DM aged 40 to 75 years	< 100 mg/dl or decrease of 30~ 40%	< 130 mg/dl	< 150 mg/dl	< 90 mg/dl
	Very high risk	* DM with ≥ 2 ASCVD RFs * DM with specific comorbidites	< 70 md/dl or decrease of 50%	< 100 mg/dl	< 150 mg/dl	< 80 mg/dl
Secondary prevention	Extremely high risk	DM with ASCVD	< 55 mg/dl and decrease of 50%	< 85 mg/dl	< 150 mg/dl	< 65 mg/dl

1. ASCVD: CHD, cerebrovascular disease, symptomatic PAD, aortic atherosclerotic disease.
2. ASCVD risk factors: age (men ≥ 45, women ≥ 55), a Fhx of premature ASCVD, HTN, smoking, and HDL-C level ≤40 mg/dL.
3. Specific comorbidities (predictors of ASCVD): albuminuria, CKD (eGFR ≤60 mL/min/1.73 m2), retinopathy, neuropathy, and ABI <0.9

Taiwan Diabetes Lipid Guideline 2023- 中華民國糖尿病學會 & 糖尿病衛教學會

Linicor-高風險病患混合型血脂治療首選

Linicor ®
Niacin ER + Lovastatin

✓ 目前治療偏重 LDL-C是否達標，HDL-C 、TG、sd LDL-C 的重要性常被忽略

- LDL-C the lower the better ?
  - LDL-C contribute 20~30 % CV risk reduction

✓ Linicor 是台灣目前唯一的 Niacin+ Statin SPC單顆複方降血脂藥

- Mixed type dyslipidemia:
  - LDL-C, TG 同時高, HDL低
  - 併用易被核刪，還要考慮藥物併用安全性
  - 輪流開？ 數值忽高忽低，病患易流失!

Linicor®臨床處方族群

糖尿病或肥胖病患可能有多重血脂指標異常

臨床上控制LDL-C後，TG反而升高，很多病患可能合併HDL-C偏低問題

混合性血脂異常

- LDL-C輕微至中度異常 **TG過高**
- LDL-C輕微至中度異常 **TG過高、HDL-C過低**
- LDL-C輕微至中度異常 **HDL-C過低**

翹翹板問題

- LDL-C過高，治療後LDL-C達標，變成TG過高
- TG過高，治療後TG達標，變成LDL-C過高

降TG新機轉

- Fibrate 效果不佳
- Fibrate 耐受不良

Linicor與Fibrate併用

- Linicor成份包含Niacin，可與Fenofibrate併用治療，機轉不同且效果加成
- Linicor成份包含Statin，與Gemfibrozil併用治療為用藥禁忌

Linicor®臨床處方族群

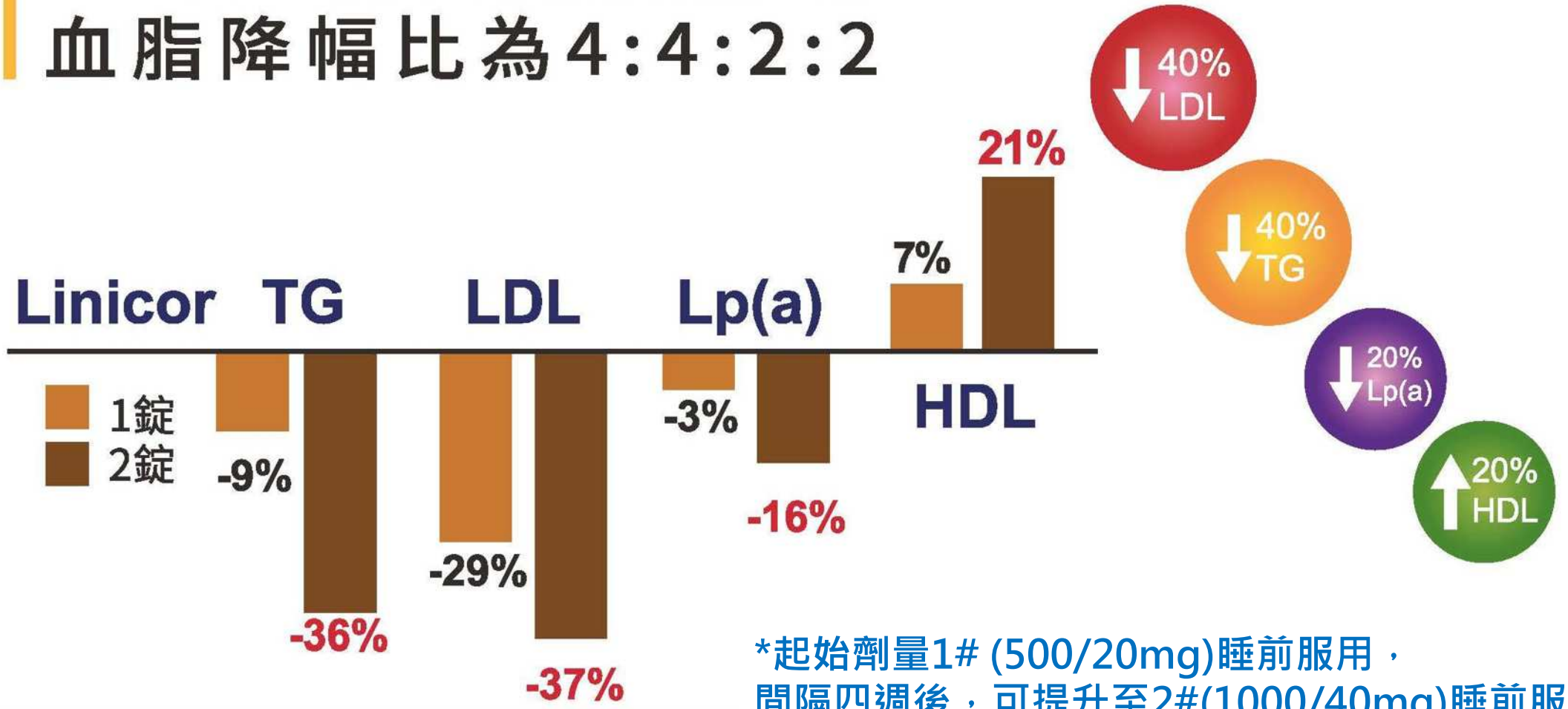
- 適應症：高血脂症
- 健保給付：符合降血脂給付規範
  可做為一線用藥(treatment-naive) 或 二線用藥(switched)

Hyperlipidemia

Treatment - Naïve	Statins switched to Linicor	Fibrates switched to Linicor	Statin/ Fibrate switched to Linicor

Linicor 使用 2顆 發揮最佳效果

Linicor 標準治療劑量2顆
血脂降幅比為4:4:2:2



*起始劑量1# (500/20mg)睡前服用，
間隔四週後，可提升至2#(1000/40mg)睡前服用

Arch Intern Med. 2004;164:1121-1127

仿單

理脂膜衣錠500/20毫克
Linicor F.C.T. 500/20mg

GMP G-11579
衛署藥製字第057216號

【適應症】

高血脂症，且適合同時使用 niacin 及 lovastatin 治療者。 患者在接受 Linicor 治療之前應採用標準之低膽固醇飲食療法，並且在 Linicor 治療期間仍應持續進行這種飲食療法。

【劑量和用法】

應於睡前服用與低脂點心併服。需整片服用，不可弄破、壓碎或咀嚼。原先並未服用緩釋劑型 niacin 製劑的患者，必須由最低起始劑量開始使用，即每天睡前服用一錠 500mg/20 mg 錠劑。緩釋劑型 niacin/lovastatin 複方錠劑的劑量每 4 週不可調高超過每天 500 mg（根據緩釋劑型 niacin 成份）。應依據患者個人的膽固醇與三酸甘油酯控制目標與患者反應調整複方錠劑劑量。緩釋劑型 niacin/lovastatin 複 方錠劑的劑量建議每天不可超過 1000 mg/40 mg。長時間（> 7 天）停用緩釋劑型 niacin / lovastatin 複方錠劑後 ， 重新開始 治療時應由最低劑量用起 。

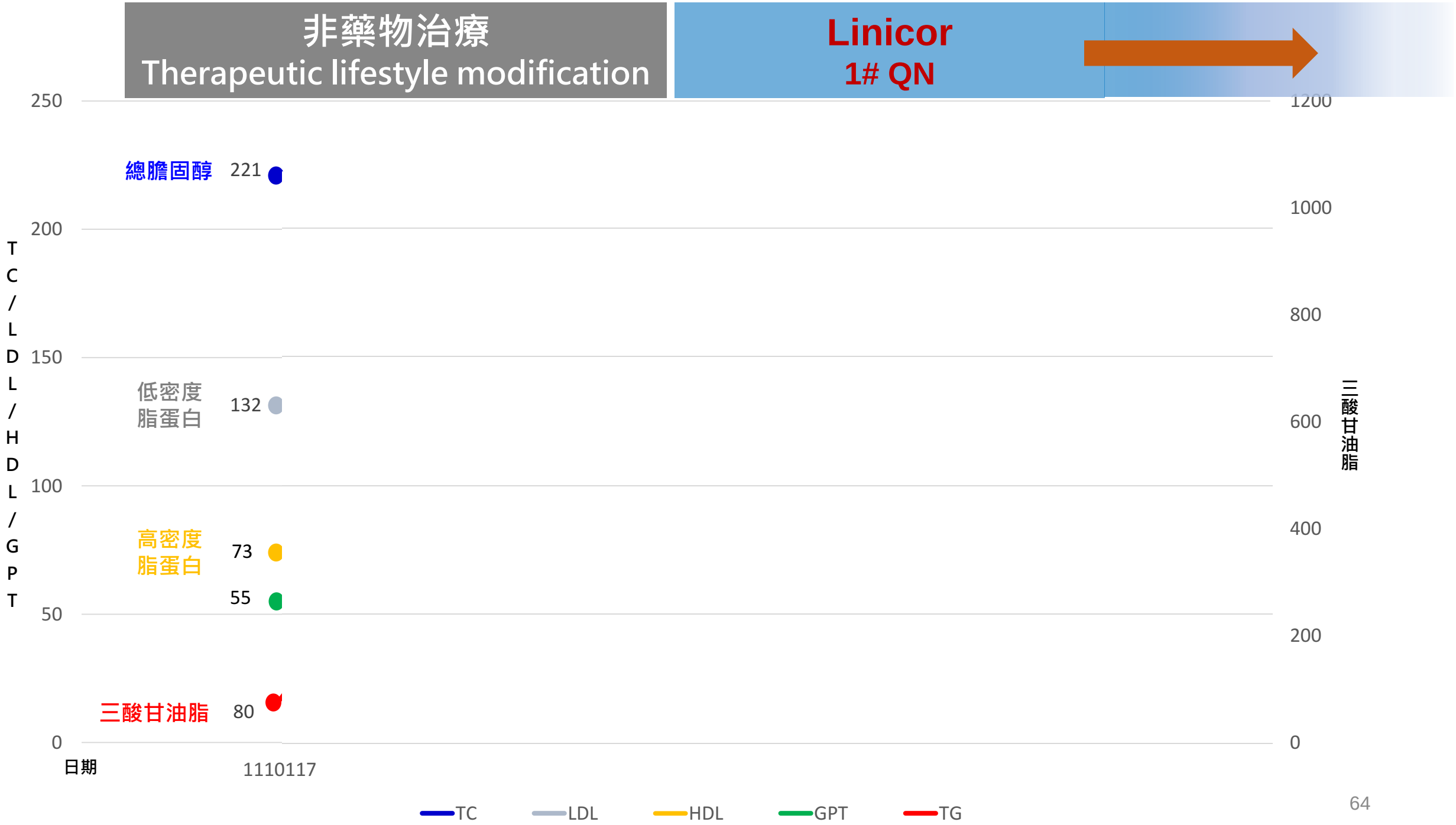
*起始劑量1# (500/20mg)睡前服用，間隔四週後，可提升至2#(1000/40mg)睡前服用

Case Sharing

基本資料

王先生 39歲

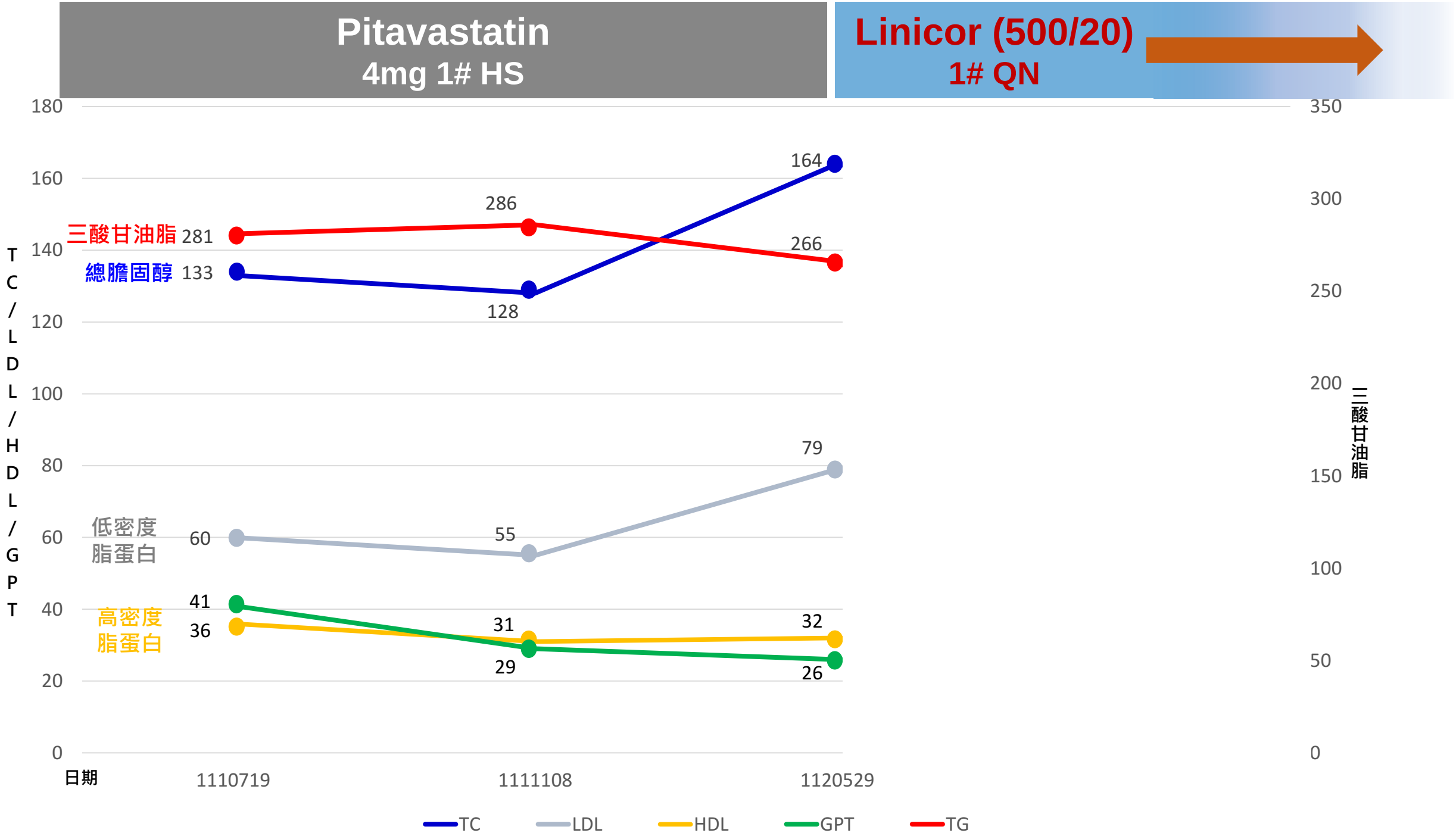
- **Occupation**
  - 業務
  - BW: 94.2 kg; BH: 175 cm; BMI: **30.8**
- **History**
  - IFS (Impaired fasting glucose)
  - Hypertension
  - Dyslipidemia
  - Moderate fatty liver
- **Lifestyle**
  - Smoke: **socially**
  - Alcohol: **frequent**
  - Betel nuts chewing: -
- **Family history:**
  - T2DM & ESRD, s/p H/D & CAD- mother
- **Medication** (降血脂藥外)
  - Olmetec 20mg 1# QD
  - Silymarin 1# BID


非藥物治療
Therapeutic lifestyle modification
Linicor
1# QN
250
200
150
100
50
0
1200
1000
800
600
400
200
0
TC/LDL/HDL/GPT
三酸甘油脂
總膽固醇 221
低密度脂蛋白 132
高密度脂蛋白 73
55
三酸甘油脂 80
日期
1110117
TC
LDL
HDL
GPT
TG

基本資料

王先生
68歲

- **Occupation**
  - 大陸經商
  - BW: 88.5 kg; BH: 180 cm; BMI: **27.3**
- **History**
  - Type II DM
  - Fatty liver
  - Dyslipidemia
- **Lifestyle**
  - Smoke: **socially**
  - Alcohol: **socially**
  - Betel nuts chewing: -
- **Family history:**
  - T2DM- mother
- **Medication** (降血脂藥外)
  - Xigduo 10/1000 1# QD
  - Metformin 500mg 1# BID
  - Tresiba 8U HS


Pitavastatin
4mg 1# HS
Linicor (500/20)
1# QN
TC/LDL/HDL/GPT
三酸甘油脂
180
160
140
120
100
80
60
40
20
0
350
300
250
200
150
100
50
0
三酸甘油脂 281
286
266
總膽固醇 133
128
164
低密度脂蛋白 60
55
79
高密度脂蛋白 41
36
31
29
32
26
日期
1110719
1111108
1120529
TC
LDL
HDL
GPT
TG

基本資料

吳先生 36歲

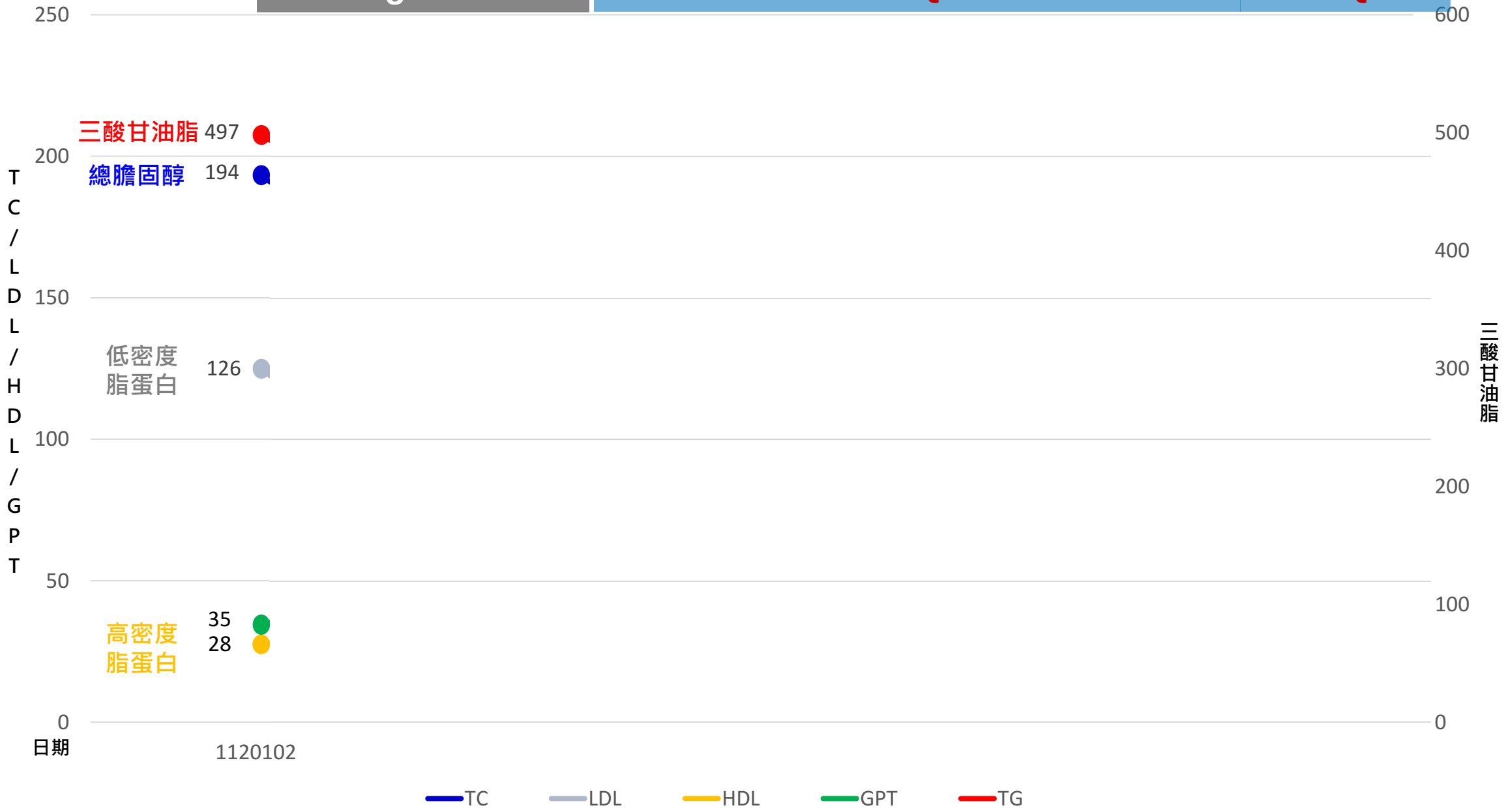
- **Occupation**
  - 上班族
  - BW: 81.1kg; BH: 168.6cm; BMI:**28.7**
- **History**
  - Type II diabetes
  - Dyslipidemia
  - Reflux esophagitis
- **Lifestyle**
  - Smoke: -
  - Alcohol: -
  - Betel nuts chewing: -
- **Family history:**
  - Heart disease & CVA & HTN & DM- father
  - T2DM-mother
- **Medication** (降血脂藥外)
  - Metformin 1000mg 1# QD
  - Ozempic 1mg QW
  - Diamicron MR 30mg 0.5# QD

新診斷
DM & HL

Pitavastatin
4mg 1# HS

Linicor (500/20)
1# QN

Linicor
2# QN

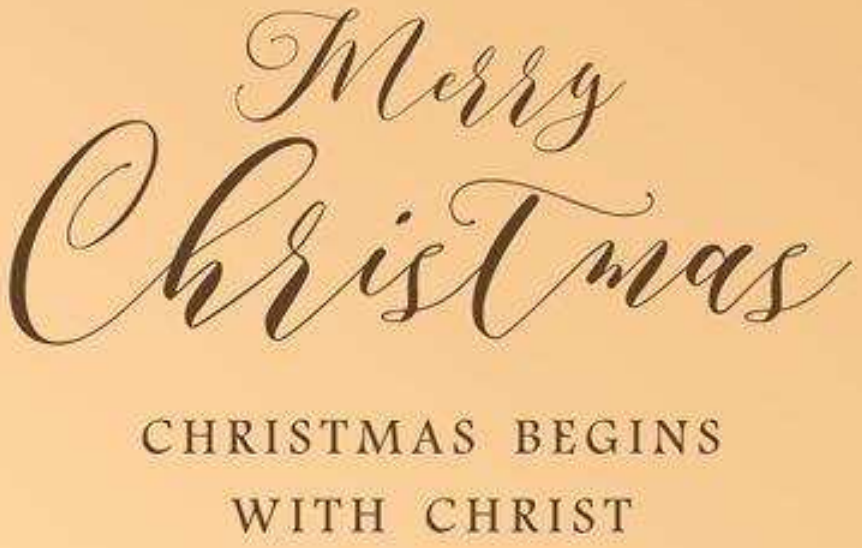


Linicor 六降二升 全方位控制血脂

Linicor ®
Niacin ER + Lovastatin

- 針對混和型、蹺蹺板型血脂異常
  - ✓ 能同時降低 sd-LDL、TG，LDL，提高 HDL
- 針對 DM、曾發生 MI、CVD等高風險病患
  - ✓ 能降低 CIMT，逆轉心血管疾病
- 降低 Lp(a)、Apo-B、LDL-P，增加 Apo-A1
  - ✓ 降低心血管事件，減少診所病患流失
- 不影響血糖控制

Thank you for your attention!



因今天在大衛的城裡，為你們生了救主，就是主基督。路加福音2:11

ICD10 code

ICD10		TC	TG	HDL	LDL	VLDL
E780	Pure hypercholesterolemia (Familial hypercholesterolemia)	+/-	-	-	+	+
E781	Pure hyperglyceridemia	+/-	++	-	-	+
E782	Mixed hyperlipidemia	+/-	+	+/-	+	+
E783	Hyperchylomicronemia		++ chylomicrons			
E784	Other hyperlipidemia	+/-	+/-	+/-	+/-	+/-
E785	Hyperlipidemia, unspecified	+/-	+/-	+/-	+/-	+/-