The role of Niacin ER and Lovastatin in mixed dyslipidemia

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Outlines

- Residual CV risk after statin treatment
- Unmet need of mixed dyslipidemia
- Niacin and statin combination
- Recommendation of clinical guidelines on Niacin
- TWN experiences of Linicor® (PMS data)

RESIDUAL CV RISK AFTER STATIN TREATMENT

In UKPDS

LDL-C Was the Strongest Predictor of CHD Risk in People with Diabetes

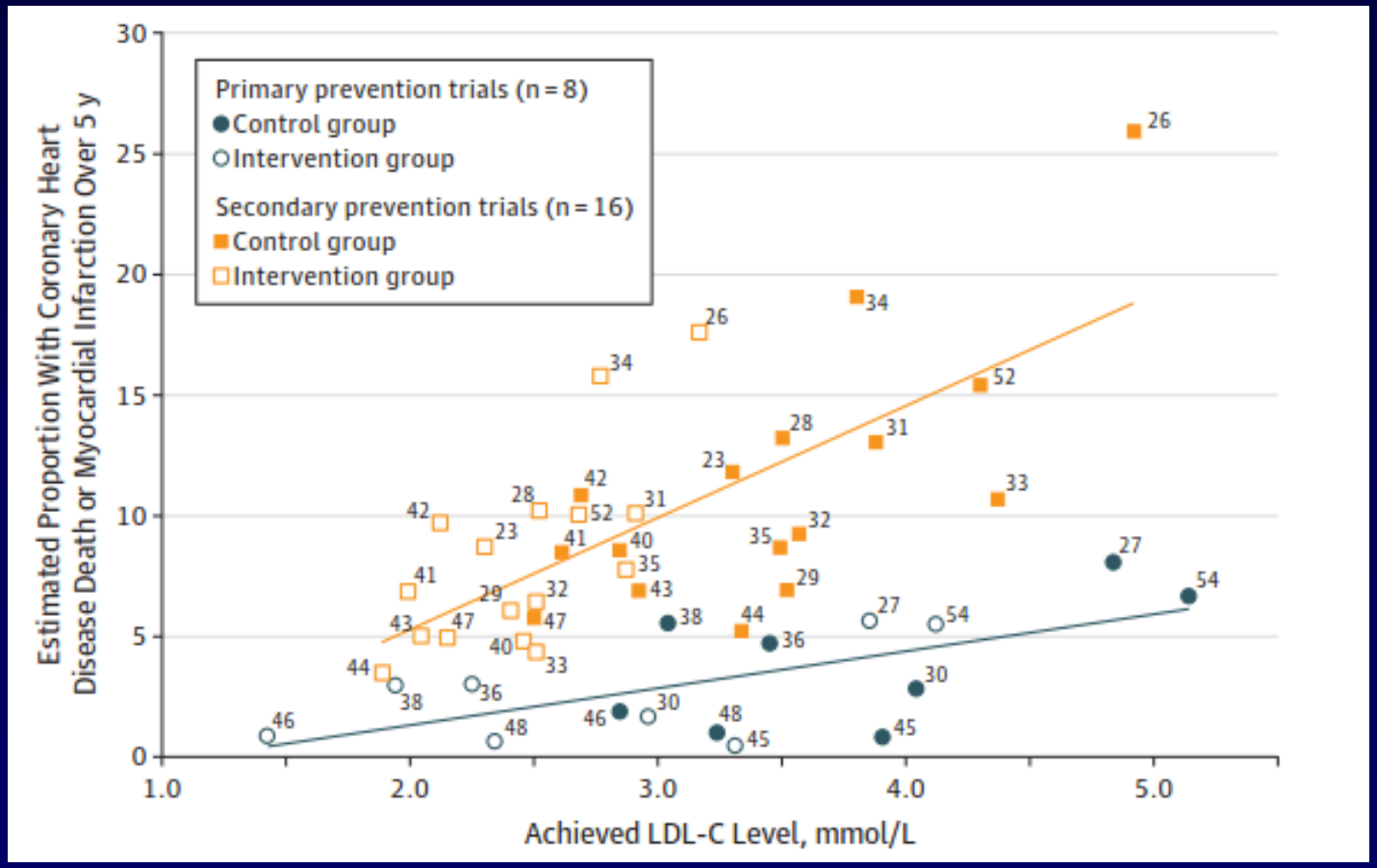
	% Increase in CHD risk
LDL-C of 1 mmol/L	**57**
HDL-C of 0.1 mmol/L	–15
Systolic blood pressure of 10 mmHg	15
HbA_{1c} level of 1%	11
Smoking was also a major contributor to CHD risk	

These data support the need for reducing LDL-C to lower CHD risk in people with diabetes mellitus. Glucose control is also important in reducing the risk of microvascular complications.

Adapted from Turner RC et al *BMJ* 1998;316:823-828.

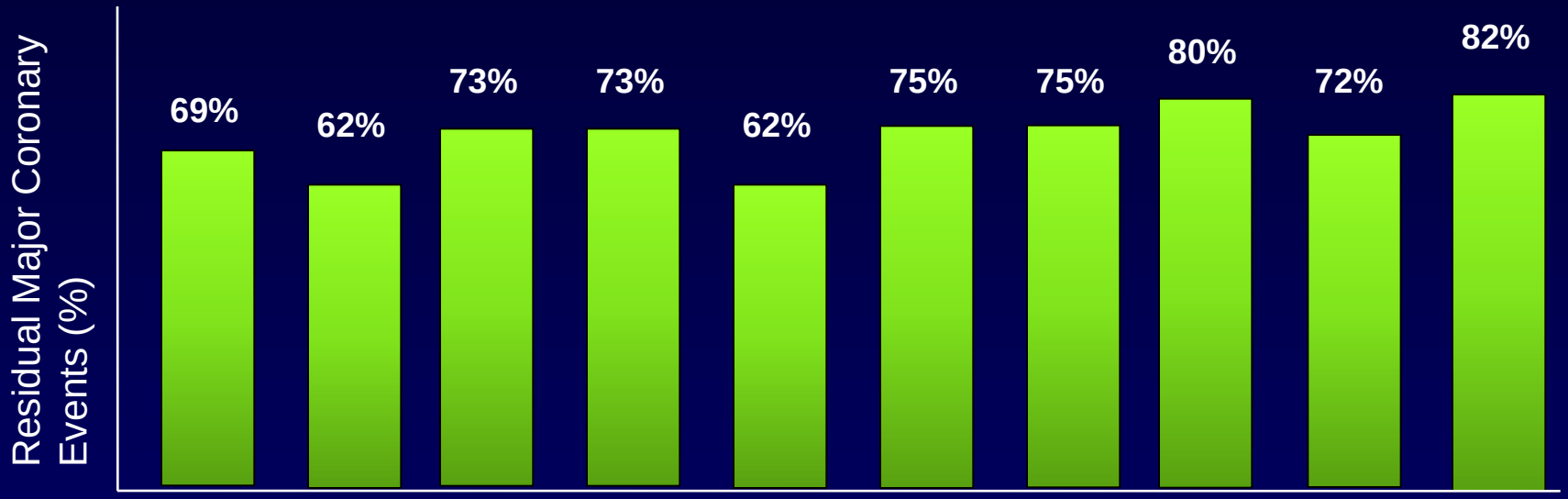
Effect of LDL-C Reduction on Major Coronary Event Rate

- Association Between Achieved Low-Density Lipoprotein Cholesterol (LDL-C) and Major Coronary Event Rates From 24 Trials of Established Interventions That Lower LDL-C Predominantly Through Upregulation of LDL Receptor Expression



JAMA. 2016 Sep 27;316(12):1289-97

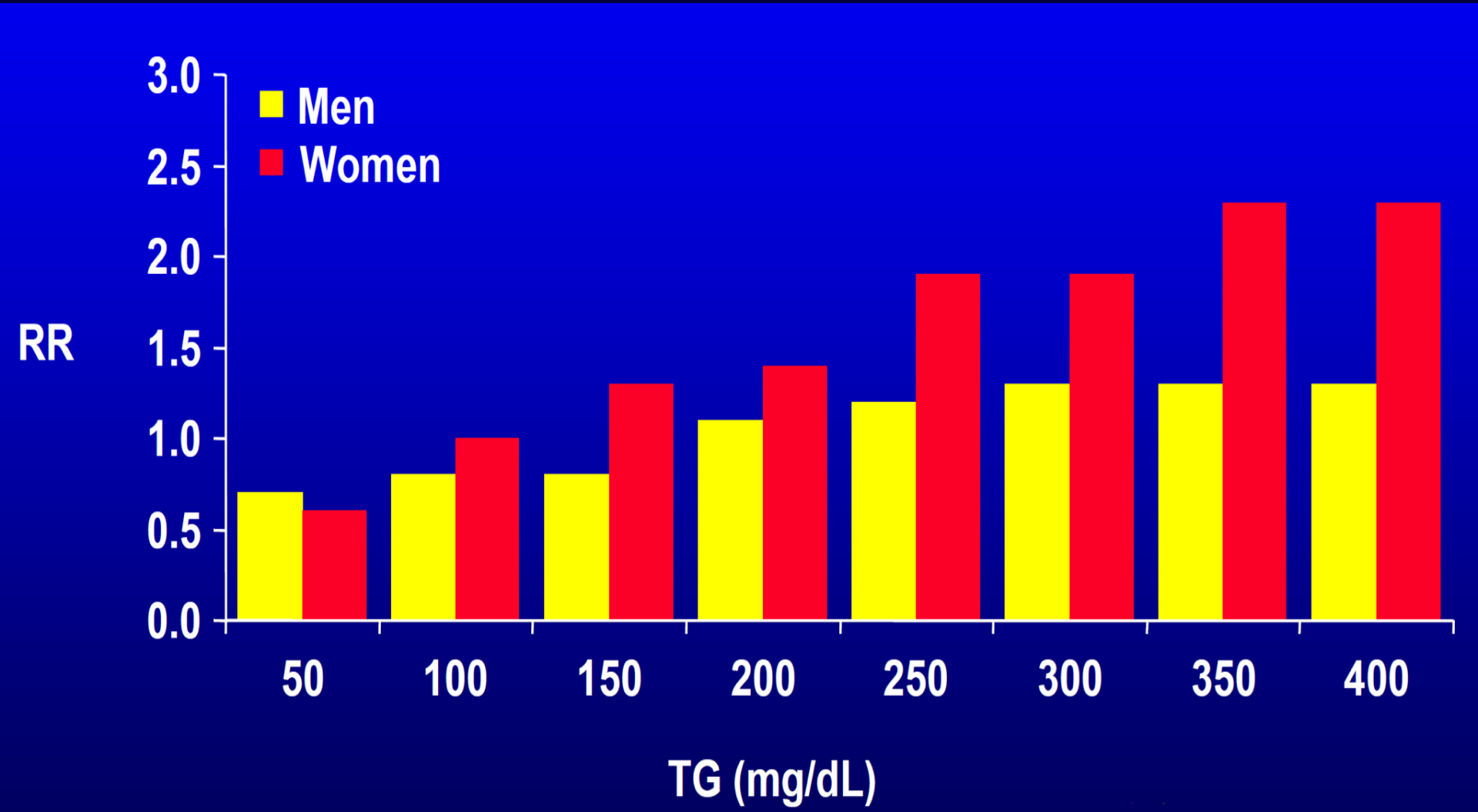
Statin outcome trials show the existence of significant residual cardiovascular risk



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
⊗LDL-C	-26%	-27%	-29%	-29%	-36%	-25%	-28%	-21%	-24%	-20%

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

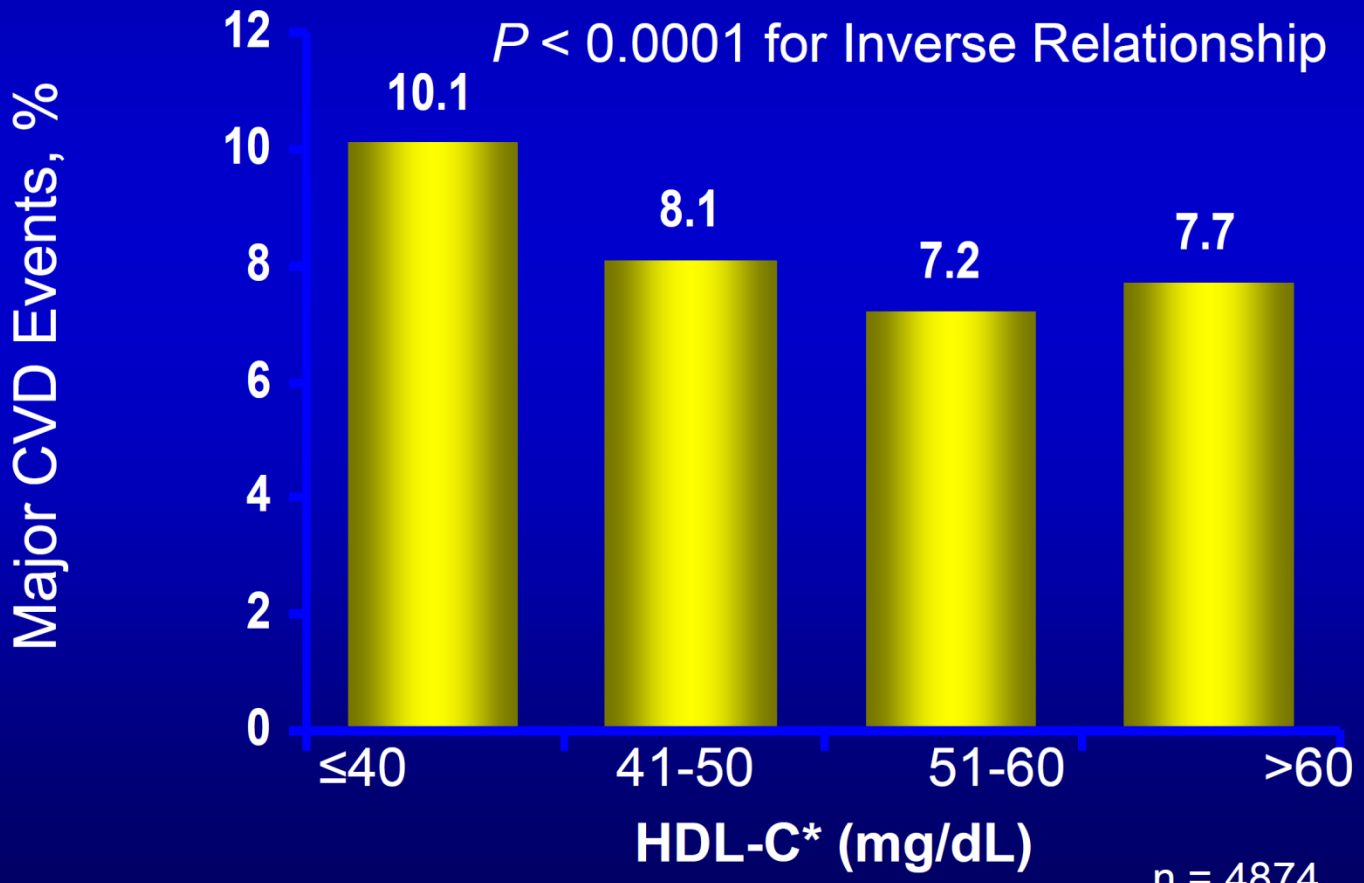
Triglycerides and CHD Risk: Framingham Heart Study



Low HDL-C Increases CVD Risk Even if LDL-C Levels Are Well-Controlled

Treating to New Targets (TNT) Study

Patients with LDL-C ≤80 mg/dL on Atorvastatin 80 mg



n = 4874

*On-treatment level (3 months)

Barter P, et al. NEJM.

HDL: A Major Risk Factor for CHD

- A low plasma HDL is an important risk factor for CHD in the general population
- A high level of HDL may confer cardioprotection
- Reverse cholesterol transport by HDL may be the principle cardioprotective mechanism

On average, a 10% decrease (RRR) in CHD risk occurs for each increase of 4 mg/dL in the HDL level.

The ILIB Lipid Handbook for Clinical Practice. 1995:26.

UNMET NEED OF MIXED DYSLIPIDEMIA

Diabetic Dyslipidemia pattern in Textbook

Table 1. Dyslipidemia in the Metabolic Syndrome and Type 2 Diabetes

Lipid	Metabolic Syndrome	Type 2 Diabetes
Triglycerides	↑	↑↑
HDL-C	↓	↓↓
LDL-C	↔	↔
sdLDL	↑	↑↑
apo B	↑	↑↑

apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; sdLDL = small, dense low-density lipoprotein particles.

Adapted from Lippincott Williams & Wilkins.[3]

Obesity: Mechanisms and Clinical Management. New York: Lippincott Williams & Wilkins, 2002:378–98

Pattern and predictors of T2DM dyslipidemia

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

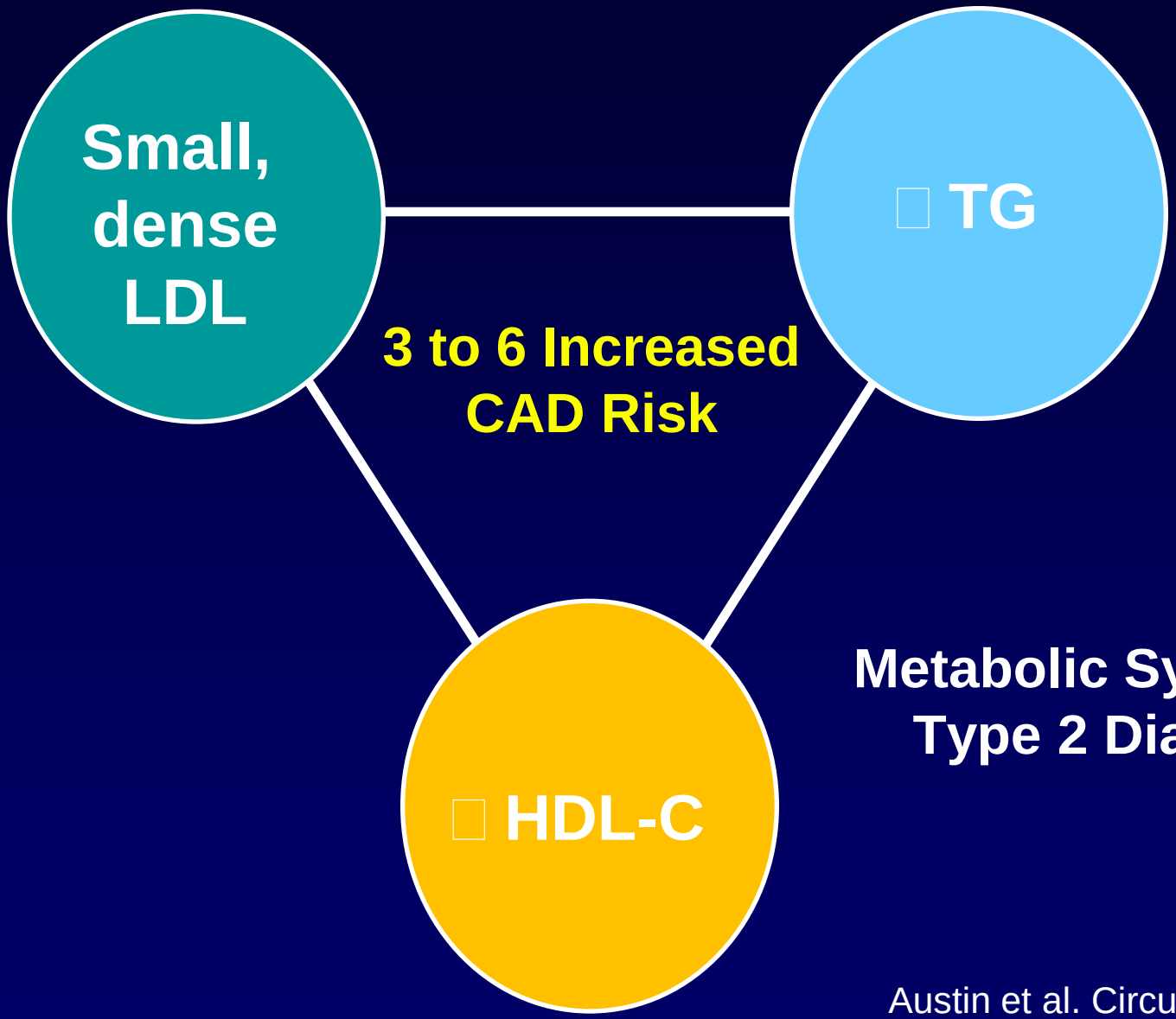
Variables	Sex		Total n (%)
	Male n (%)	Female n (%)	
TC			
<200 mg/dl	105 (76.6)	185 (80.8)	290 (79.2)
≥200 mg/dl	32 (23.4)	44 (19.2)	76 (20.8)
TG			
<150 mg/dl	58 (42.3)	121 (52.8)	179 (48.9)
≥150 mg/dl	79 (57.7)	108 (47.2)	187 (51.1)
HDL			
Low[a]	83 (60.6)	66 (28.8)	149 (40.7)
Normal	54 (39.4)	163 (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.

55.7%

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

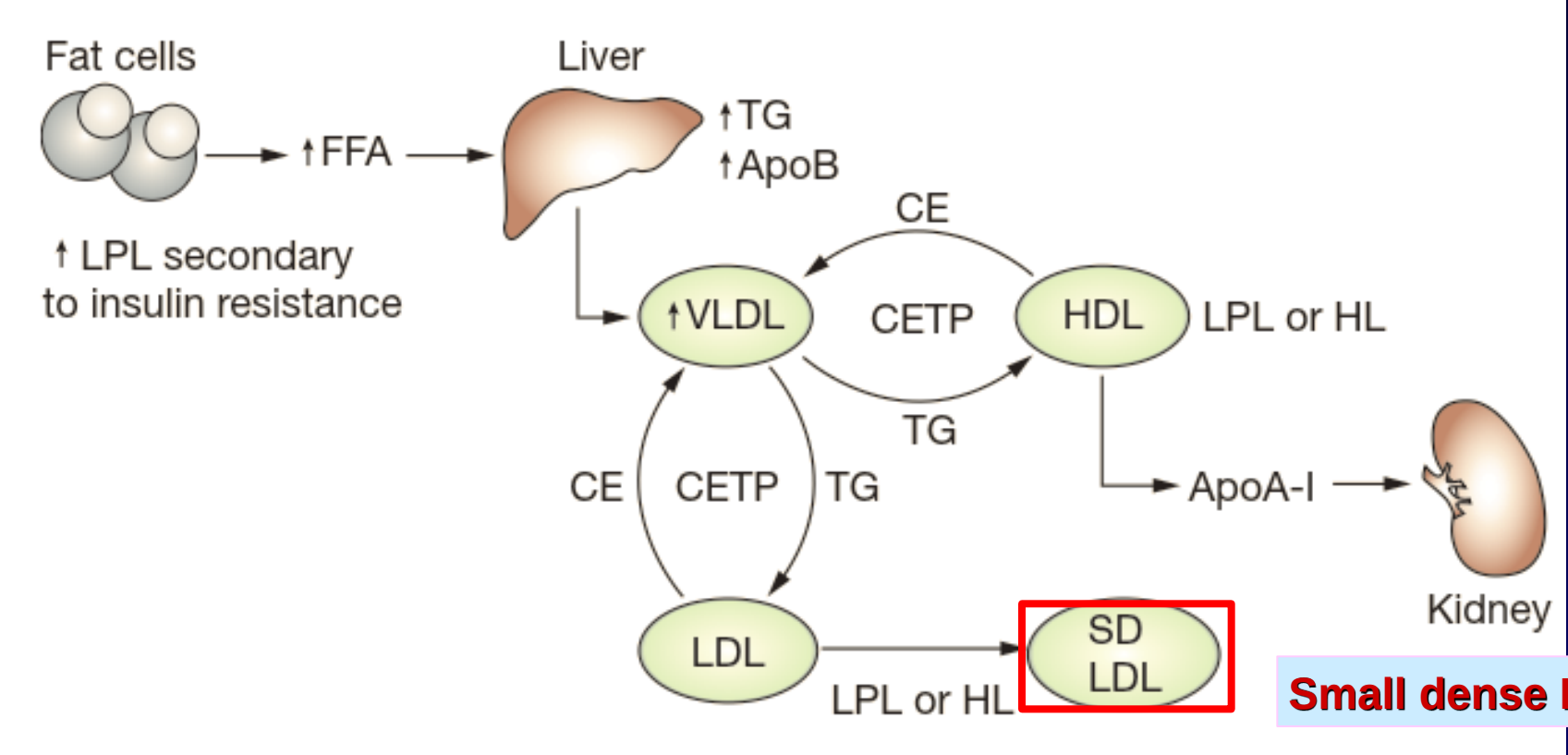
Atherogenic Lipoprotein Profile



Metabolic Syndrome
Type 2 Diabetes

Austin et al. Circulation 1990

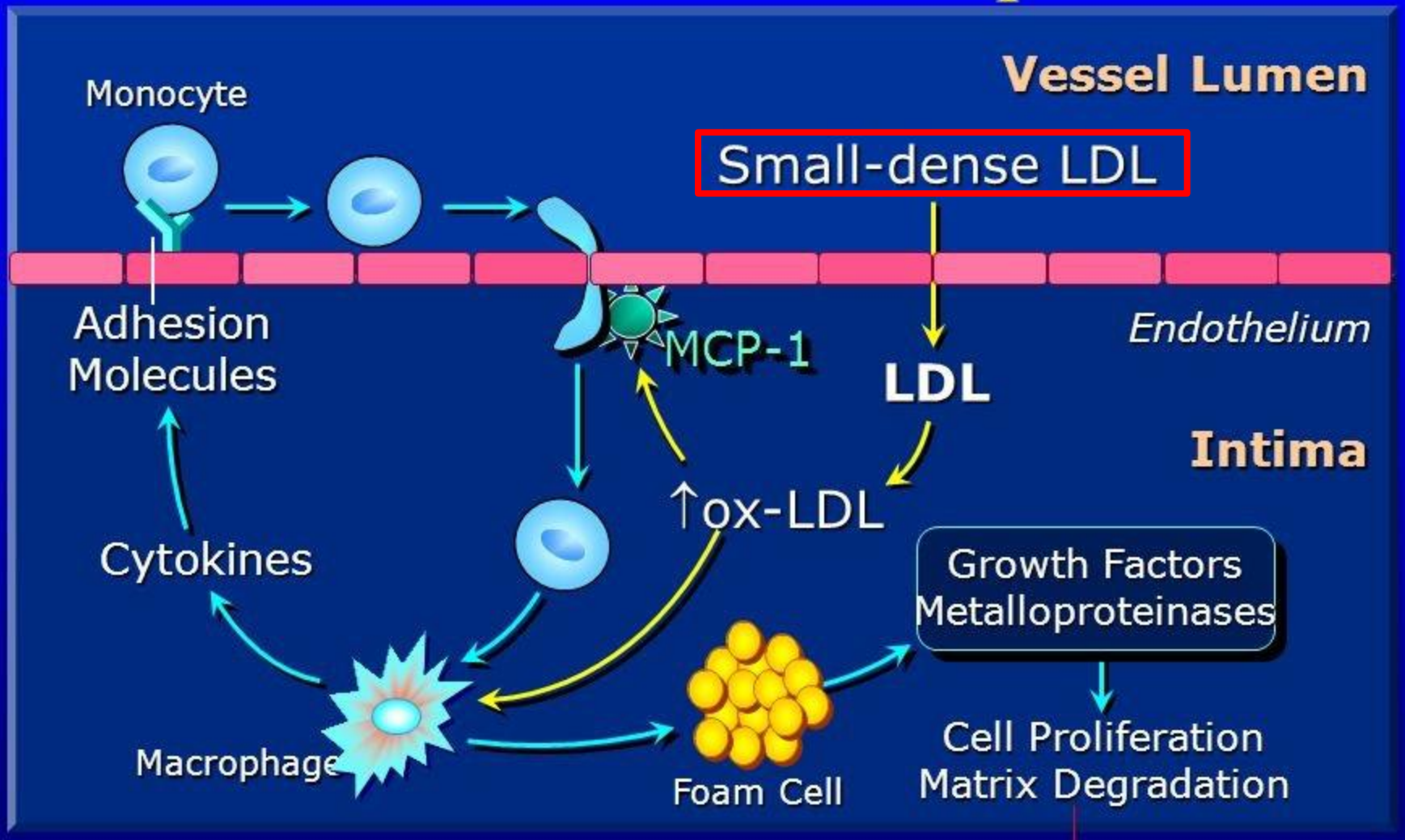
Effects of insulin resistance in diabetic dyslipidemia



Insulin resistance initiates the characteristic triad of high triglyceride level, low HDL cholesterol level and high small dense LDL level. If the concentration of VLDL transported triglyceride is high, CETP promotes the transfer of LDL cholesteryl ester or HDL cholesteryl ester in exchange for triglyceride. Triglyceride-rich HDL cholesterol or LDL cholesterol can undergo hydrolysis by hepatic lipase or lipoprotein lipase.

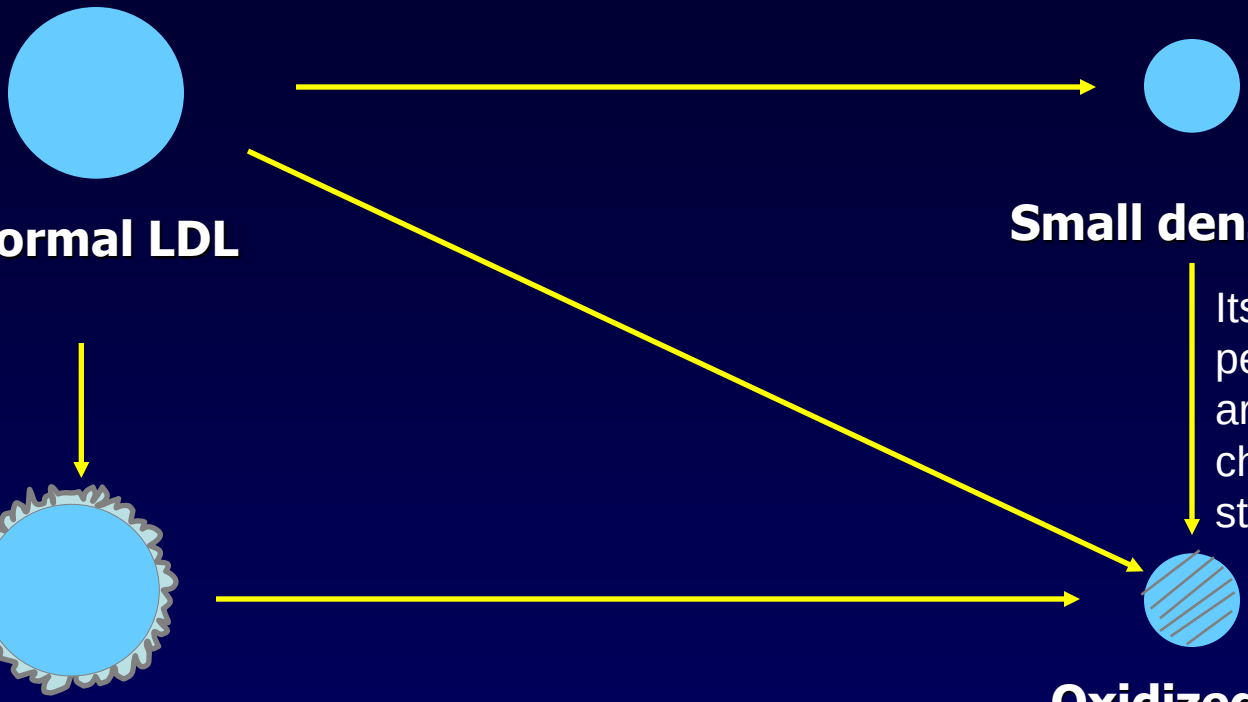
Nat Clin Pract Endocrinol Metab. 2009 Mar;5(3):150-9

Small dense LDL and Atherosclerotic Plaque



Ross R. *N Engl J Med* 1999;340:115-126.

Diabetes and Atherosclerosis
LDL Modifications



Normal LDL

Small dense LDL

Its small size favors penetration into arterial wall as cholesterol and lipid storage.

Desialylated LDL

Oxidized LDL

Oxidation induce immune response and inflammation

Increase the affinity of sdLDL particle to proteoglycans in the arterial wall and hence residence time is prolonged.

Monocytes -Macrophages

Lipid storage and atherosclerosis plaque development

Foam Cells

Oxid Med Cell Longev. 2017; 2017: 1273042.

Journal of Clinical Lipidology (2007) 1, 583–592

Journal of Clinical Lipidology

Original Contributions

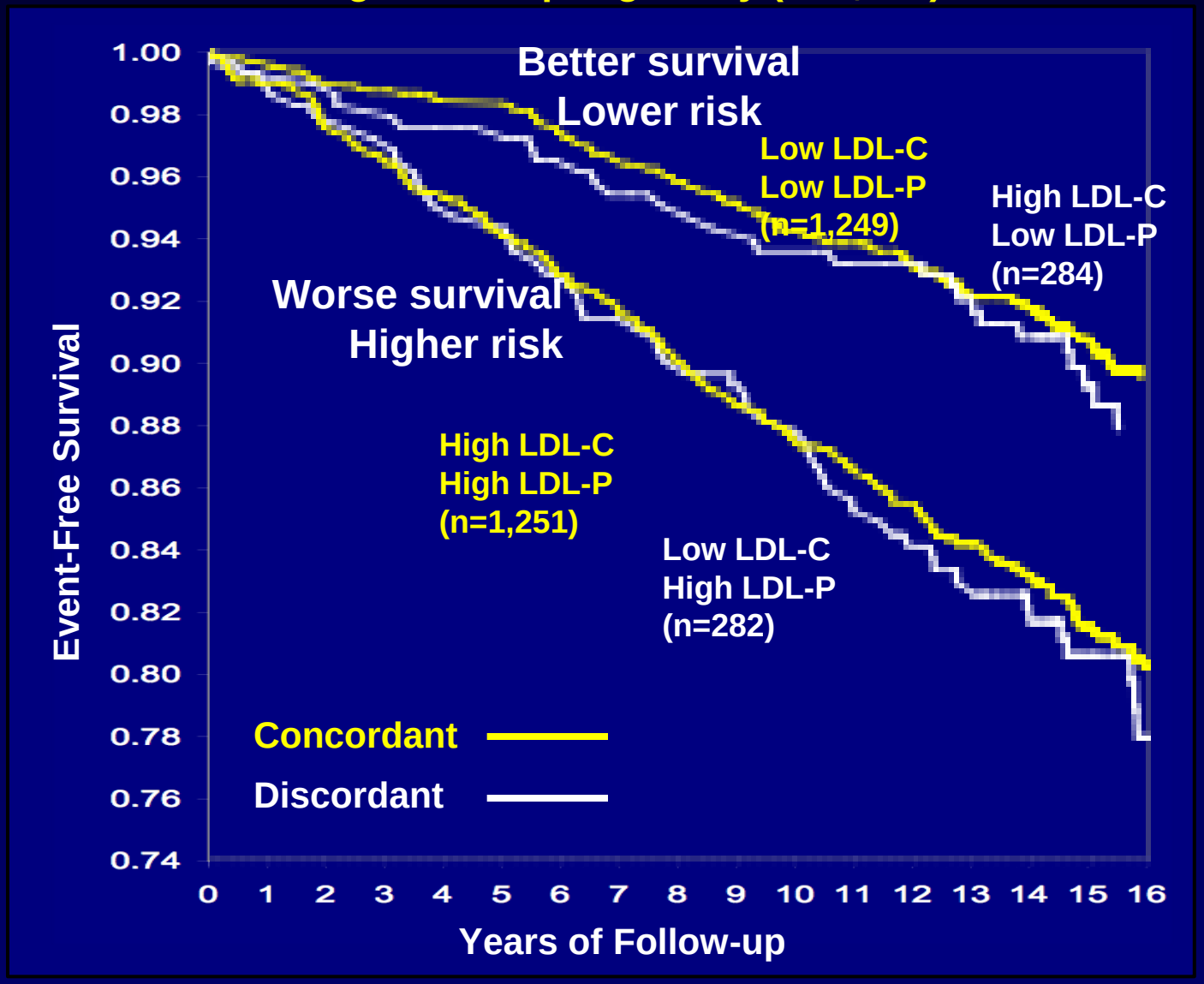
LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—Implications for LDL management

William C. Cromwell, MD,* James D. Otvos, PhD, Michelle J. Keyes, PhD, Michael J. Pencina, PhD, Lisa Sullivan, PhD, Ramachandran S. Vasan, MD, Peter W. F. Wilson, MD, Ralph B. D'Agostino, PhD

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

CHD Event Associations of LDL-P versus LDL-C

Framingham Offspring Study (n=3,066)



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

NIACIN AND STATIN COMBINATION

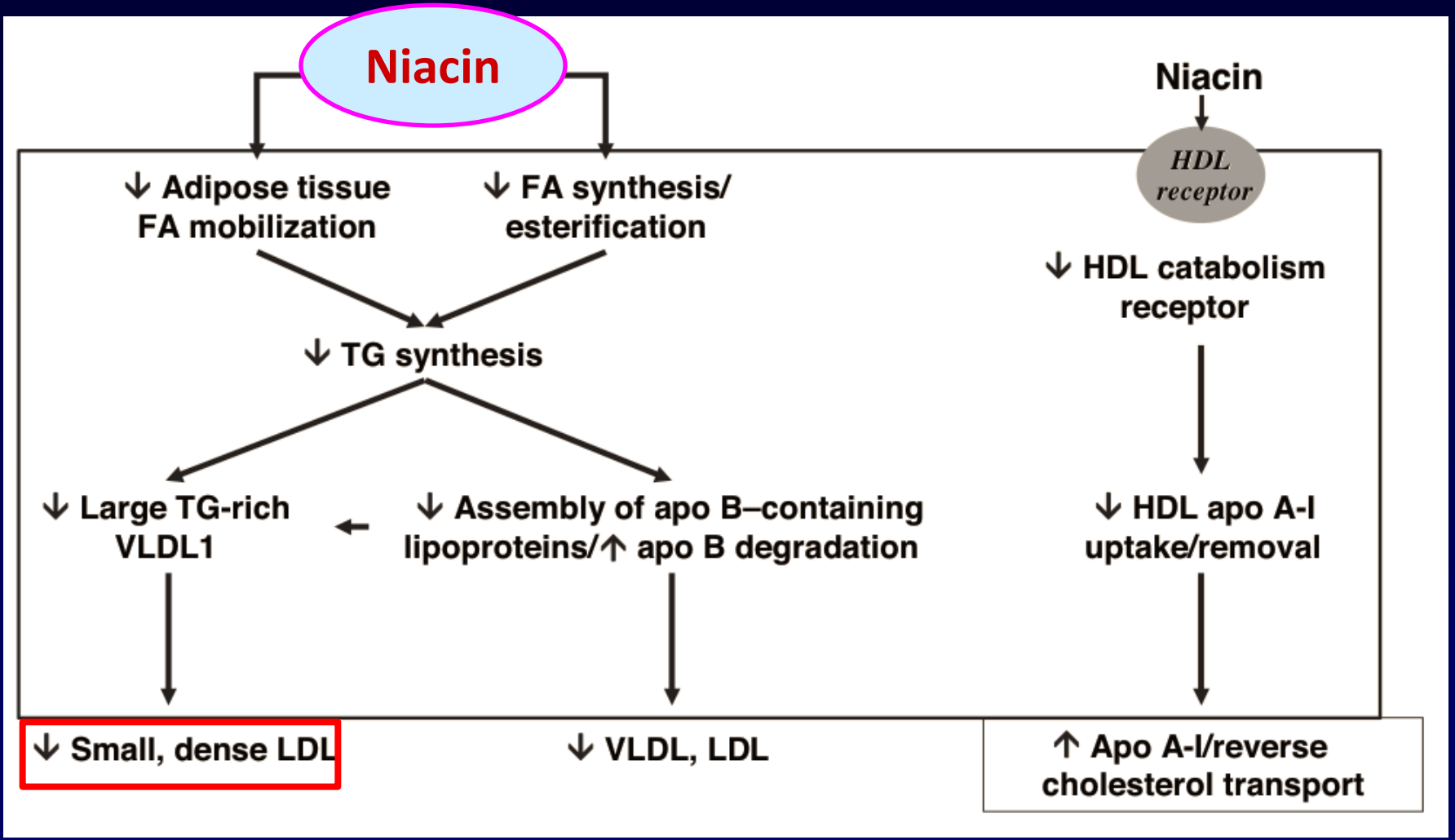
Linicor: single bill combination improve multiple lipid abnormalities

Convenience, Global lipid improvement, Better performance

	Statins	Niacin	Fibrate
↓ LDL-C	+++	+	+-
↓ TG	+	++	++
↑ HDL-C	+	+++	++
↓ VLDL-C	+/++	++/+++	+++
↑ LDL particle size	+	+++	++

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

Niacin's mechanism on LDL particle



Prev Cardiol. 2004 Fall;7(4):182-7

Linicor improve multiple lipid levels

- Linicor offers the **better convenience and cost-effectiveness** option, which replace the traditionally triple therapy as **statin, fenofibrate and acipimox**

Linicor (NiacinER/Lovastatin)	HDL-C	LDL-C	TG
500/20mg	+6.6%	-29.4%	-9.4%
1000/40mg	+20.7%	-37.8%	-28.9%

*劑量: 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

Linicor has global improvements (ADVOCATE study)

Compared with Atorvastatin and Simvastatin, Linicor can improve multiple lipid levels.

TABLE 3 Percent Change From Baseline

	Niacin ER/Lovastatin		Atorvastatin	Simvastatin
Week 8	1,000/40 mg	1,000/40 mg	10 mg	10 mg
LDL cholesterol	−38%†	−40%†	−38%†	−28%
HDL cholesterol	+20%†‡	+20%†‡	+3%	+7%‡
Triglycerides	−30%†‡	−35%†‡	−20%	−18%
Lipoprotein(a)	−16%†‡	−14%‡	+8%	0%‡
Week 12*	1,000/40 mg	1,500/40 mg	20 mg	20 mg
LDL cholesterol	−42%†	−42%†	−45%†	−35%
HDL cholesterol	+19%†‡	+24%†‡	+4%	+8%‡
Triglycerides	−36%†‡	−42%†‡	−30%†	−15%
Lipoprotein(a)	−20%†‡	−17%†‡	+2%	−1%
Week 16*	1,000/40 mg	2,000/40 mg	40 mg	40 mg
LDL cholesterol	−39%	−42%	−49%†§	−39%
HDL cholesterol	+17%†‡	+32%†‡	+6%	+7%
Triglycerides	−29%†	−49%†	−31%†	−19%
Lipoprotein(a)	−19%†‡	−21%†‡	0%	−2%

LDL and HDL cholesterol are expressed as mean values, and triglycerides and Lp(a) are expressed as median values.

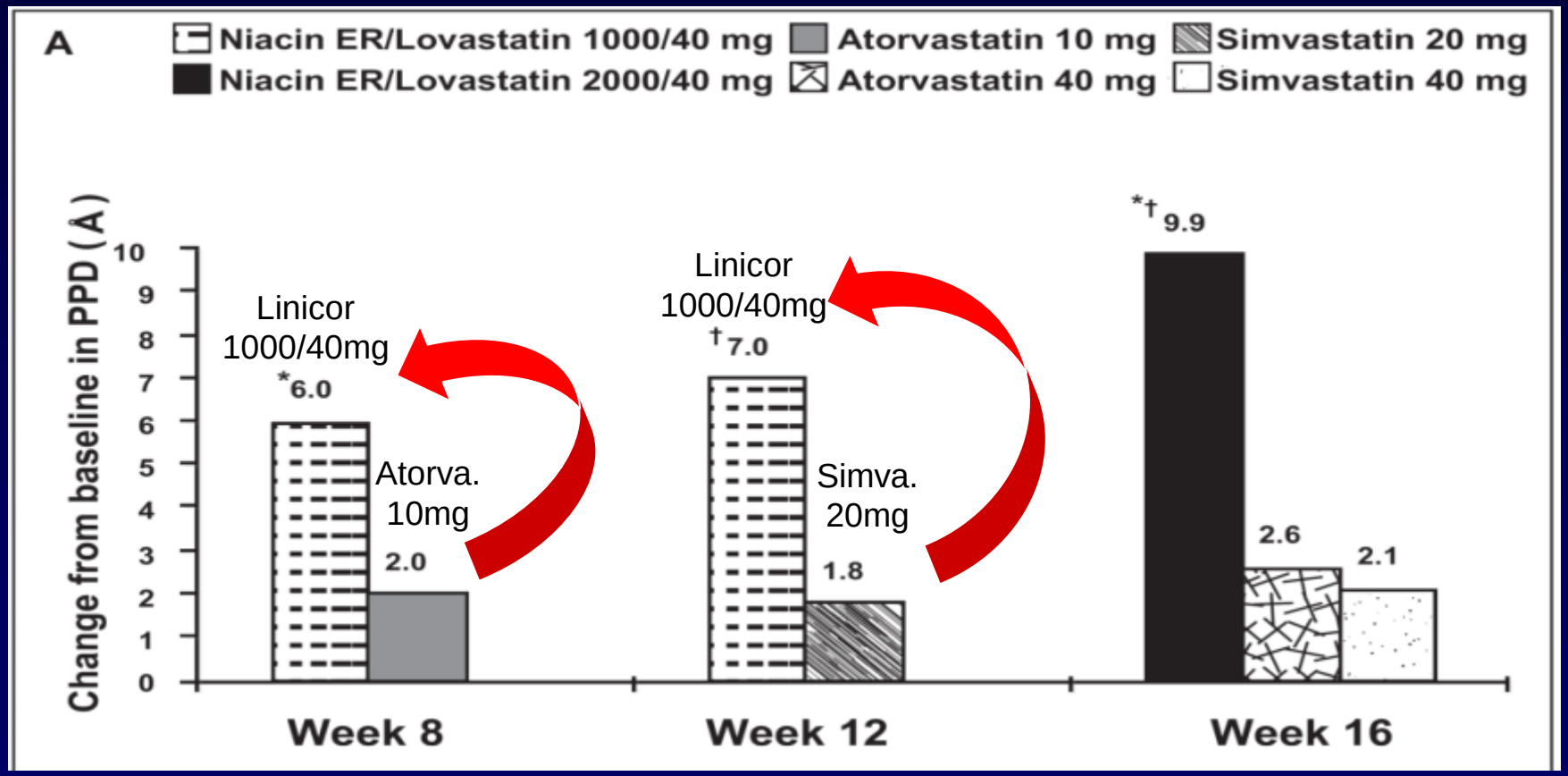
*Dosage is milligrams per day.

†$p \leq 0.05$ versus simvastatin; ‡$p \leq 0.05$ versus atorvastatin; §$p \leq 0.05$ versus niacin ER/lovastatin 1,000/40 and 2,000/40 mg.

Am J Cardiol 2003;91:667-672

NiacinER can increase LDL particle size (ADVOCATE study)

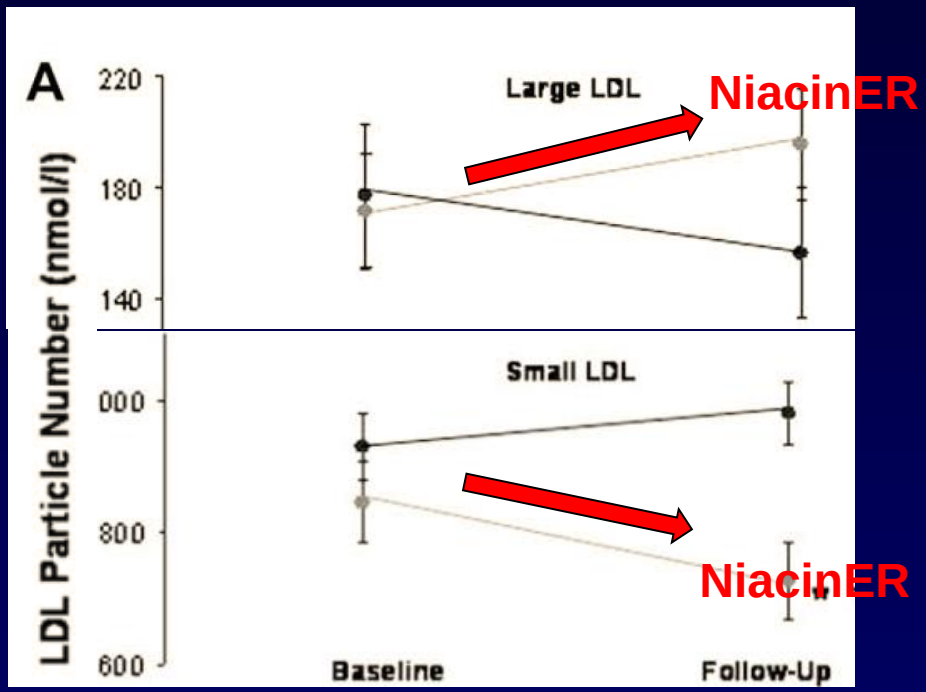
Compared with Atorvastatin and Simvastatin, Linicor not only improve lipid levels but also increase LDL-C particle size.

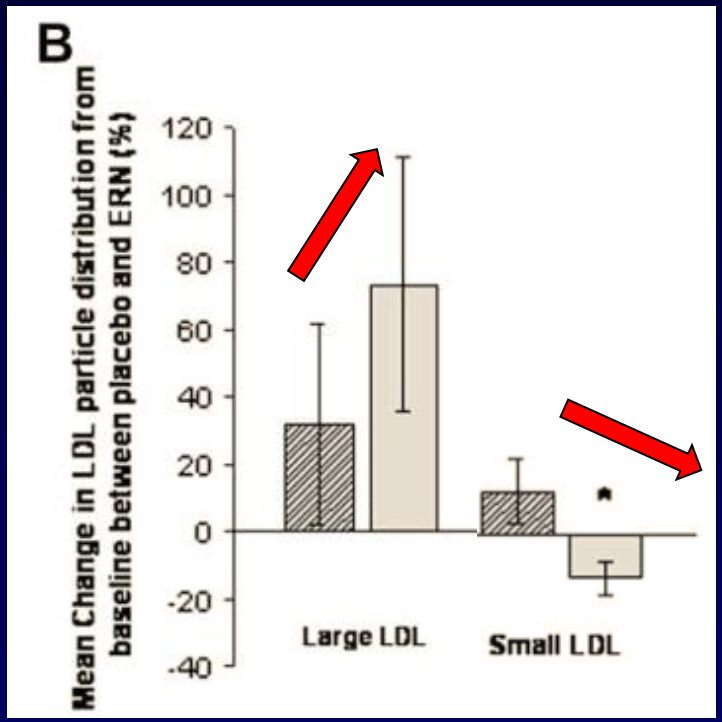


*PPD: peak particle diameter

Am J Cardiol 2003;91:667-672

NiacinER can increase LDL particle size





- 54 patients with stable coronary artery disease (CAD) and well-controlled LDL-C
- Lipoprotein particle number was analyzed by proton NMR spectroscopy at baseline and after 3 months.

J Clin Lipidol. 2009 Feb;3(1):45-50.

AIM-HIGH: subgroup analysis

- **For patients with CVD and marked atherogenic dyslipidemia (total 439 patients)**

TG levels ≧ 200 mg/dl &
HDL-C levels <32 mg/dl

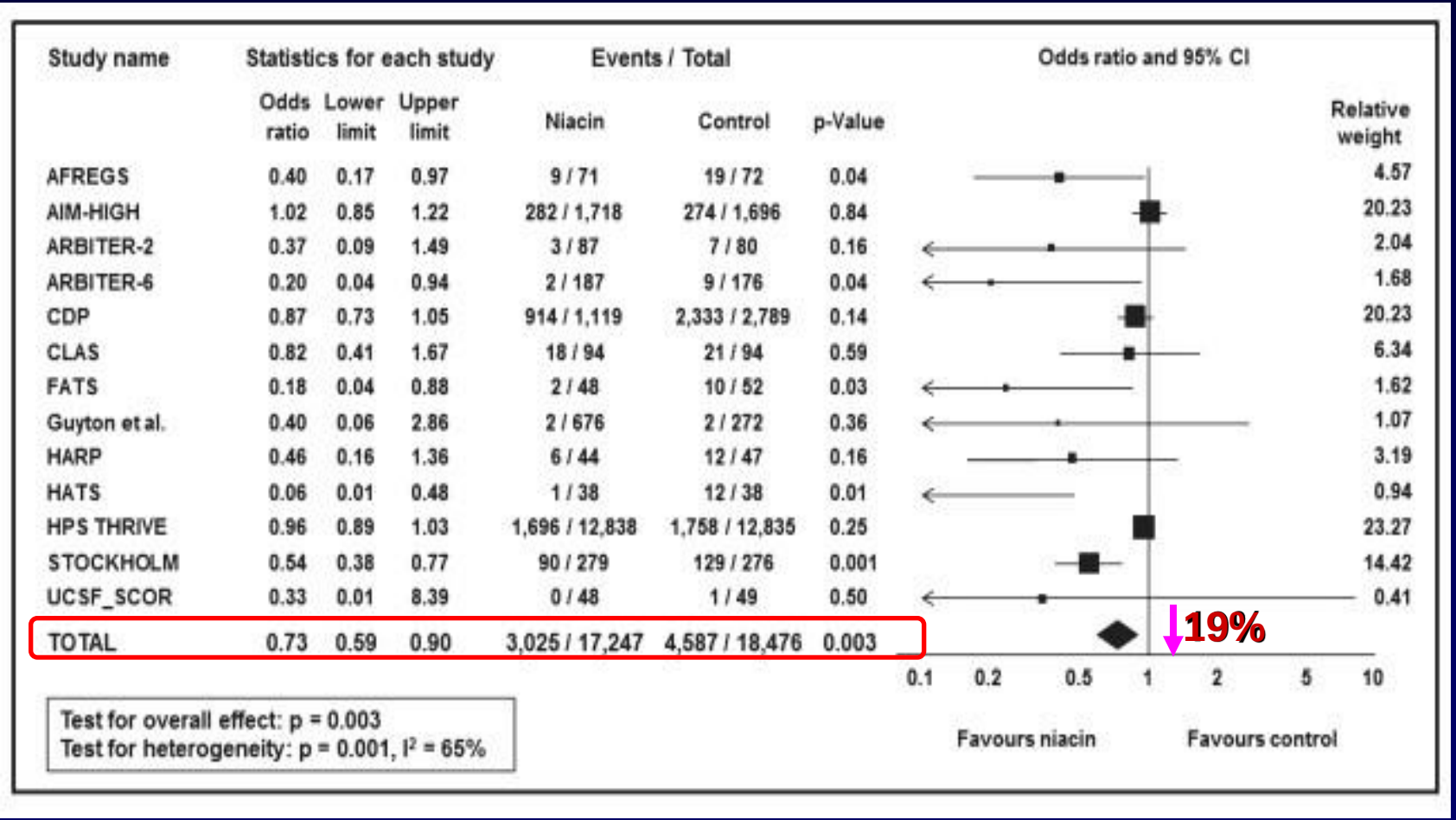
- A **significant 36% relative reduction** in the primary CV outcome (25.0% versus 16.7%, p = 0.032)

Niacin				
AIM-HIGH (n = 3,414) [61,62]	ER niacin titrating to 1500-2000	Patients with CVD with persistent atherogenic dyslipidaemia[3] Median LDL-C on statin 1.91 mmol/L [74 mg/dL]	Prematurely terminated; mean 3 years	• No significant outcomes benefit with ER niacin • Methodological issues; inadequately powered, placebo contained a low-dose of niacin (50 mg/capsule), imbalance in concomitant LDL-C lowering therapy between groups • For patients with marked atherogenic dyslipidaemia,[4] there was a 36% relative reduction in the primary CV outcome (25.0% versus 16.7%, p = 0.032)

Cardiovasc Diabetol. 2014 Jan 24;13:26.
J Am Coll Cardiol. 2013 Oct 22;62(17):1580-4.

2016 meta-analysis:
Niacin significantly reduces major CHD events

- Niacin treatment can reduce significantly more major coronary events than control *(OR 0.81, p=0.04).*

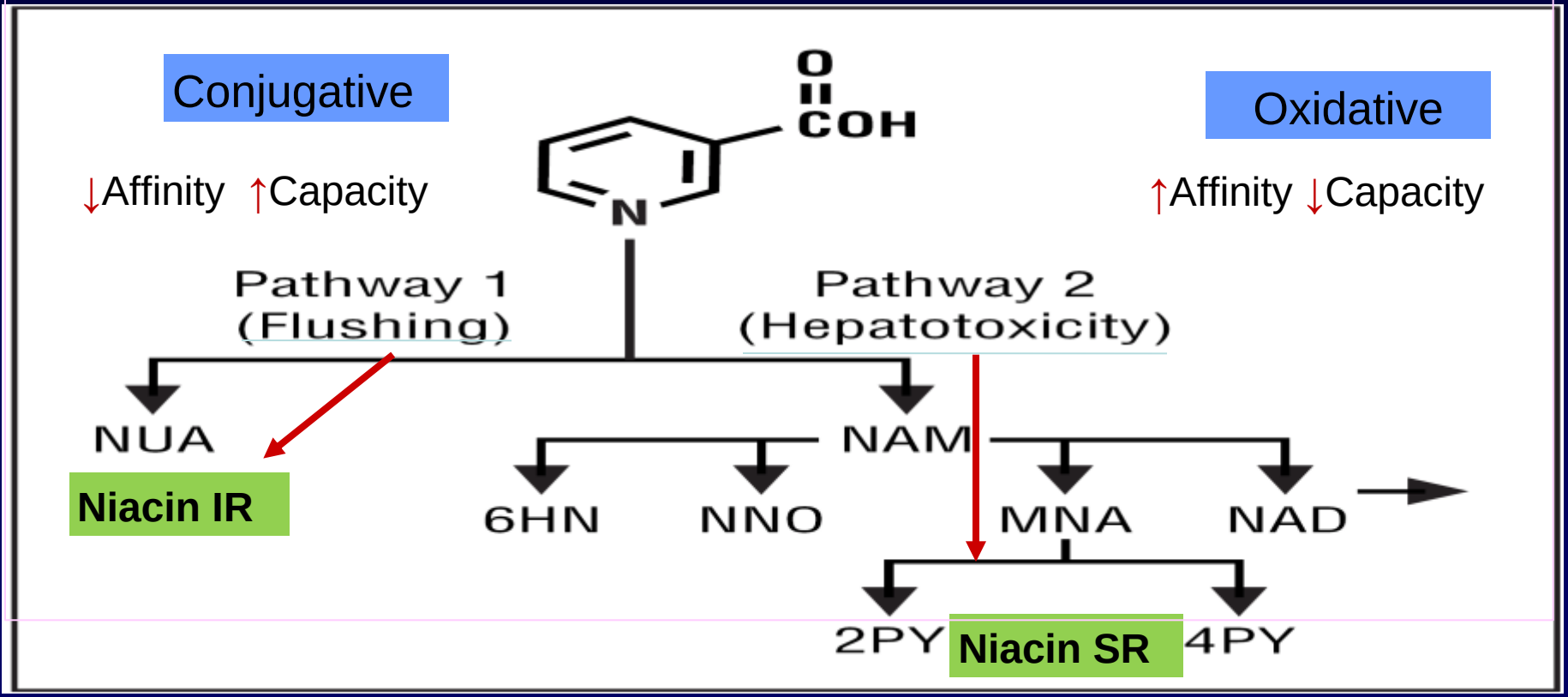


Study name	Odds ratio	Lower limit	Upper limit	Niacin	Control	p-Value	Relative weight
AFREGS	0.40	0.17	0.97	9 / 71	19 / 72	0.04	4.57
AIM-HIGH	1.02	0.85	1.22	282 / 1,718	274 / 1,696	0.84	20.23
ARBITER-2	0.37	0.09	1.49	3 / 87	7 / 80	0.16	2.04
ARBITER-6	0.20	0.04	0.94	2 / 187	9 / 176	0.04	1.68
CDP	0.87	0.73	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	

Acta Cardiol. 2016 Aug;71(4):463-72.

Niacin ER:
improves tolerance and patient adherence

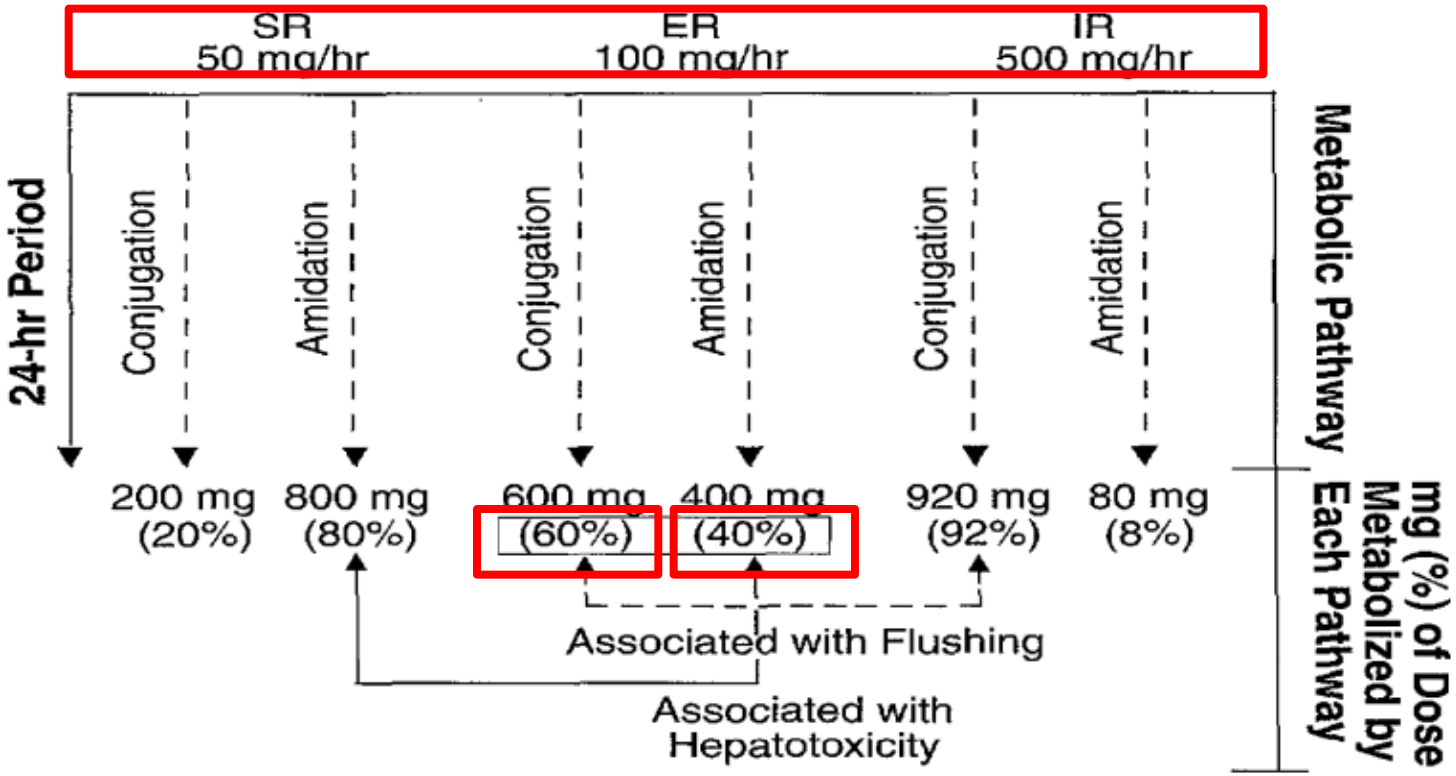
Immediate release **(IR)** is directly associated with flushing.
Sustained release **(SR)** is directly associated with hepatotoxicity.
Extended release **(ER)** has **intermediate dissolution rate** between IR and SR, thus it **reduces the risk of both flushing and hepatotoxicity.**



Expert Opin. Phatmacother.(2004) 5(6): 1385-1398
Arch Intern Med. 2004;164:697-705

Niacin ER:
improves tolerance and patient adherence

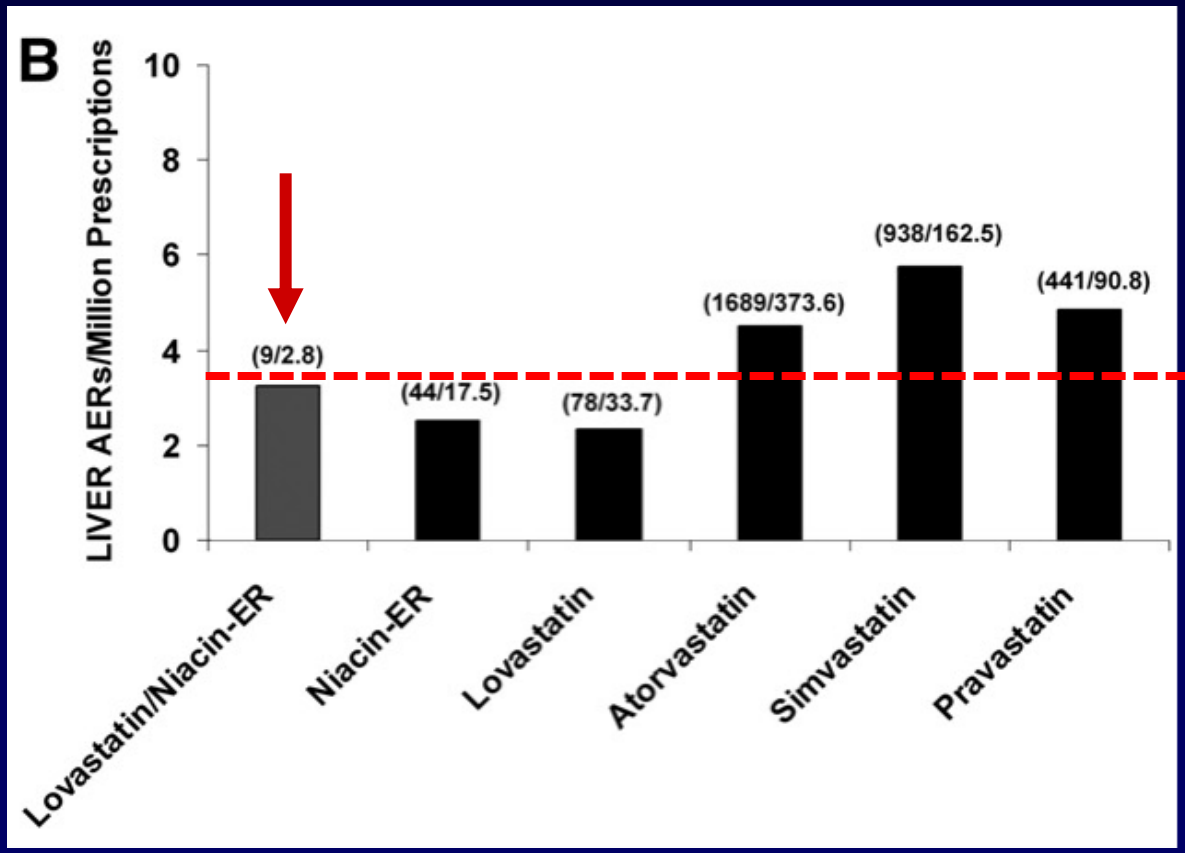
Figure 2. Simulation of niacin metabolism using a 1000-mg dose. SR = sustained release, ER = extended release, IR = immediate release.



Am J Health-syst Pharm-Vol 60 Jul, 2003 Suppl S2 S9-S14

Niacin ER: didn't increase the hepatotoxicity risk when combined with lovastatin

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

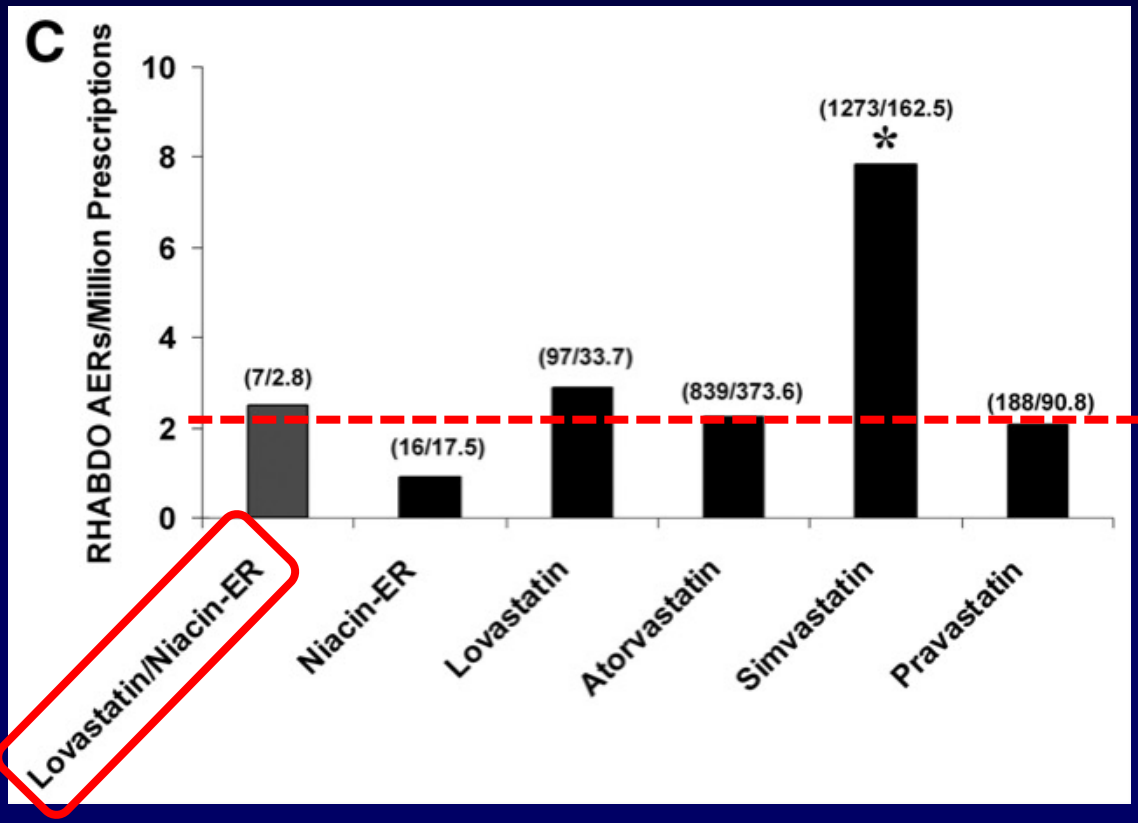


**Data above bars represent number of AERs/number of prescriptions in millions during study period.*

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

Niacin ER didn't increase the rhabdomyolysis risk when combined with lovastatin

- 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.

Linicor: safer option for CKD patients

Renal dysfunction	Linicor (Niacin ER 500mg / Lovastatin 20mg)	Fenofibrate 160/200mg
Mild-to-moderate 30<CCR<60	**No adjustment needed (1000/40mg qd)**	**Dosage reduction** (100mgor 67mg qd)
Severe CCR<30	**> 500/20mg with caution**	**Contraindication**

Lipanthyl 160/200mg中文仿單
Linicor 500/20mg中文仿單

Linicor: safer option for CKD patients

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

National Kidney Foundation®
KDOQI

2012, KDOQI guideline for diabetes and CKD

RECOMMENDATION OF CLINICAL GUIDELINES ON NIACIN

2017-Taiwan lipid guideline

Journal of the Formosan Medical Association (2016) xx, 1–32

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

REVIEW ARTICLE

2017 Taiwan lipid guidelines for high risk patients☆

Yi-Heng Li [a], Kwo-Chang Ueng [b,c], Jiann-Shing Jeng [d], Min-Ji Charng [e,f], Tsung-Hsien Lin [g,h], Kuo-Liong Chien [i,j], Chih-Yuan Wang [j], Ting-Hsing Chao [a], Ping-Yen Liu [a], Cheng-Huang Su [k,l], Shih-Chieh Chien [k], Chia-Wei Liou [m], Sung-Chun Tang [d], Chun-Chuan Lee [k], Tse-Ya Yu [n], Jaw-Wen Chen [e,f,o], Chau-Chung Wu [j], Hung-I Yeh [k,l,*], for The Writing Group of 2017 Taiwan Lipid Guidelines for High Risk Patients

J Formos Med Assoc. 2017 Feb 24.

2017-Taiwan lipid guideline
LDL-C treatment goal for diabetic patients

Table 9 Lipid recommendations for diabetic patients.

Recommended Target	Individuals who should be targeted for lipid modification	Risk assessment algorithm
LDL-C: - Without CVD: < 100 mg/dL - With CVD: < 70 mg/dL or 30—40% reduction TG < 150 mg/dL HDL-C: Men: > 40 mg/dL Women > 50 mg/dL	1. All diabetic patients aged ≥40 y 2. Diabetic patients aged <40 y who have overt ASCVD or ASCVD risk factors	ASCVD risk factors include: - High blood pressure - Smoking - Overweight and obesity - Family history of premature ASCVD

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.

J Formos Med Assoc. 2017 Feb 24.

2017-Taiwan lipid guideline
Niacin related recommendation

Niacin may be considered an option in high-risk patients with low HDL-C and elevated LDL-C despite statin therapy.

Niacin is considered as adjunctive therapy for treatment of patients with severe hypertriglyceridemia (TG ≧ 500 mg/dL) who present a risk of pancreatitis.

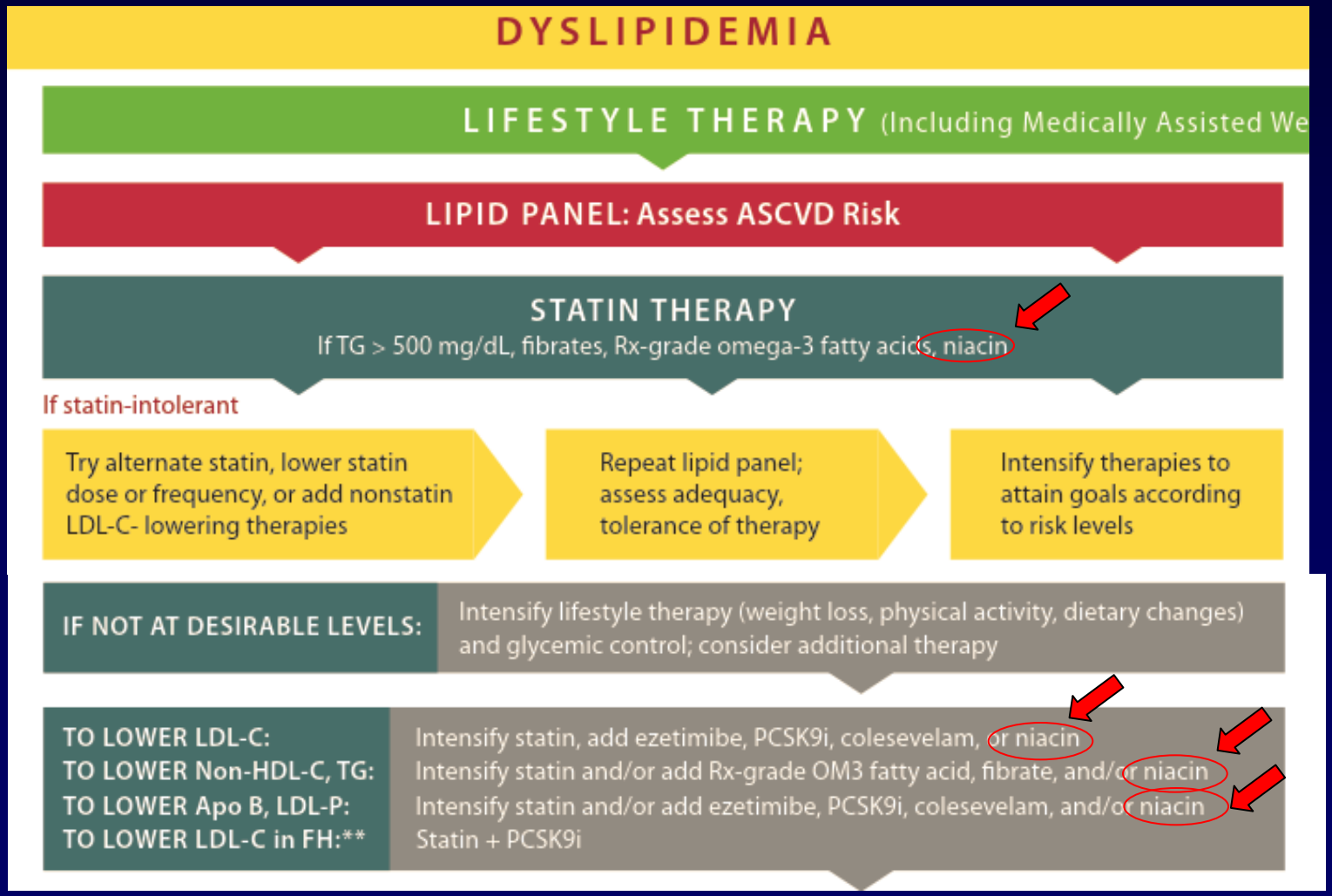
Niacin is indicated to reduce elevated TC, LDL-C, and TG levels, and to increase HDL-C in patients with mixed dyslipidemia.

Niacin in combination with statins may be appropriate options for patients with hypertriglyceridemia and associated low HDL-C.

J Formos Med Assoc. 2017 Feb 24.

2017- AACE consensus
Niacin improve multiple lipid levels

Niacin could decrease LDL-C, non-HDL-C, TG, ApoB and LDL-P



Endocr Pract. 2017 Feb;23(2):207-238

TWN EXPERIENCES OF LINICOR® (PMS DATA)

Linicor®: Basic information

商品名	Linicor F.C.T. 500/20 mg　理脂膜衣錠500/20毫克
藥品成分及劑量	Niacin ER 500mg and Lovastatin 20mg
健保價/健保碼	**10.3**元/錠 AC57216100
健保給付規範	降血脂給付規定 (適用通則及2.6.1.規定)
使用中醫學中心	多達**15**間醫學中心持續使用
衛署核准適應症	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種飲食療法。
使用劑量	起始劑量1# 睡前服用，間隔四週可提升至2#睡前服用

藥品許可證及藥品仿單

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

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**

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

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® Taiwan PMS data: 1084 patients (unpublished clinical experiences)

- 試驗用藥：Linicor(NiacinER/Lovastatin)
- 試驗目的：了解Linicor上市後國人使用的療效與安全性
- 收案人數：**1084人**
- 收案條件：20歲以上混合性血脂異常且符合健保給付規範 (不論原本有無服用血脂藥物)†
- 排除條件：藥物成份過敏、禁忌症‡或醫師評估不合適狀況
- 收案時間：**3個月**
- 劑量：**98.5%病患維持1顆Linicor共3個月 (自3年前開始收錄，臨床上仍以1顆處方後3個月，驗血評估再做劑量調整，本次資料並未包含3個月後2錠調整資料)**
- 觀察項目：
  - **Primary endpoint**：LDL-C改善數值及幅度
  - **Secondary endpoint** ：TG、HDL-C、TC改善數值及幅度、副作用比例及醫師整體評估

† 參考Linicor適應症為"高血脂症"、健保給付規定為"降血脂給付規定"，考量分析樣本規模，後續放寬收案條件，只要符合適應症與給付規定都在處方範圍

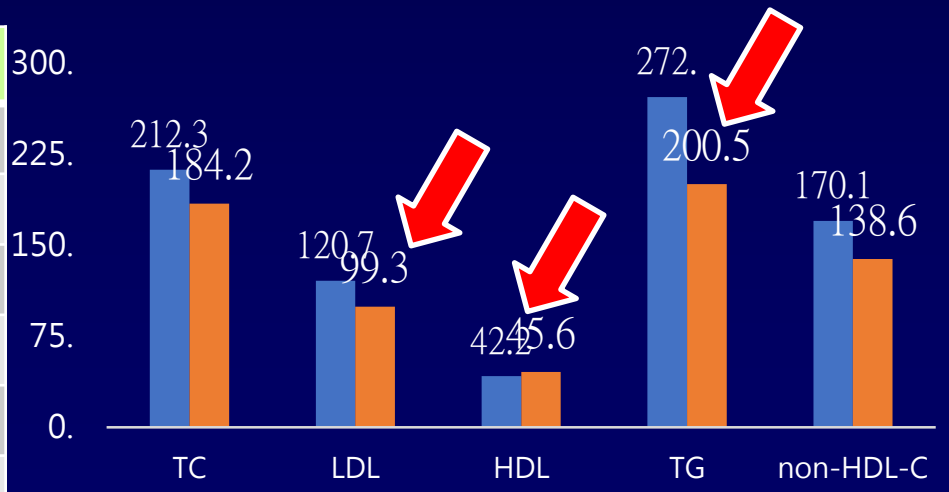
‡ 成分過敏、進展中肝病、持續升高的血漿轉胺酶、進展中消化性潰瘍或有動脈出血、懷孕和哺乳

2017 TSH Linicor PMS unpublished data

Linicor® Taiwan PMS data: 1084 patients
Lipid effects (overall)

Variables	V1 (Baseline)		V3 (84±14 days)		*P* value
	n / mean±SD				
Blood lipids					
TC, mg/dl	1084	212.3±49.3	1084	184.2±35.1	<0.0001
TG, mg/dl	1084	272.0±177.8	1084	200.5±111.8	<0.0001
LDL, mg/dl	1084	120.7±38.4	1084	99.3±30.0	<0.0001
HDL, mg/dl	1084	42.2±12.4	1084	45.6±12.4	<0.0001
Non-HDL-C	1084	170.1±48.6	1084	138.6±34.7	<0.0001

Overall improvement after 3M of Linicor		
	Change	**Significance**
TC	**-13%**	***P<0.0001***
LDL-C	**-18%**	***P<0.0001***
HDL-C	**+8%**	***P<0.0001***
TG	**-26%**	***P<0.0001***
nonHDL-C	**-19%**	***P<0.0001***



2017 TSH Linicor PMS unpublished data

Linicor® Taiwan PMS data: 1084 patients
Biochemistry level

- Linicor不會對血糖、尿酸與肌肉和肝臟功能造成異常影響

Variables	V1 (Baseline)		V3 (84±14 days)	
	n / mean±SD			
Biochemistry				
Fasting blood glucose, mg/dl	219	146.9±59.2	219	145.6±59.1
HbA1c, %	531	7.4±1.6	531	7.2±1.5
Uric acid, mg/dl	427	6.4±1.7	427	6.2±1.5
Creatine kinase, U/L	95	126.3±65.2	95	126.9±56.3
Creatinine, mg/dl	226	1.1±0.6	226	1.0±0.7
ALT, U/L	569	32.0±22.8	569	29.2±16.3
AST, U/L	500	29.8±13.4	500	29.2±14.3

2017 TSH Linicor PMS unpublished data

Linicor® Taiwan PMS data: 1084 patients Adverse event

	V1 (Baseline)		V2 (42±14 days)		V3 (84±14 days)	
	n / %					
Adverse event						
Flush						
yes	1	0.1	6	0.6	15	1.4
no	1083	99.9	1078	99.4	1069	98.6
Myopathy						
yes	0	0	2	0.2	10	0.9
no	1084	100	1082	99.8	1074	99.1
GI symptom						
yes	2	0.2	1	0.1	3	0.3
no	1082	99.8	1083	99.9	1081	99.7
Others						
yes	2	0.2	1	0.1	2	0.2
no	1082	99.8	1083	99.9	1082	99.8

2017 TSH Linicor PMS unpublished data

Linicor: cost-effective option

商品名	成份	健保價	LDL /TG	LDL/HDL
Linicor	**Niacin ER 500mg / Lovastatin 20mg**	**10.3**	**10.3~20.6**	**10.3~20.6**
Crestor	Rosuvastatin 10mg	20.9	20.9+5.6	NA
Crestor	Rosuvastatin 5mg	17.9	17.9+5.6	NA
Lipitor	Atorvastatin 20mg	25.2	25.2+5.6	NA
Lipitor	Atorvastatin 10mg	15.7	15.7+5.6	NA
Lescol	Fluvastatin 80mg	14.6	14.6+5.6	NA
Mevalotin	Pravastatin 40mg	20	20+5.6	NA
Livalo	Pitavastatin 2mg	17.9	17.9+5.6	NA
Vytorin	Ezetimibe 10mg/ Simvastatin 20mg	28.3	28.3+5.6	NA
Lipanthyl	Fenofibrate 160/200mg	5.6	5.6+(14.6~28.3)	NA

2017年4月1日生效的調整後健保藥價

Conclusions

- Diabetic dyslipidemia consists of low HDL-C, High TG, and small dense LDL issue. This pattern is frequently seen in T2DM and may be a treatable risk factor for subsequent cardiovascular disease.

- The combination of Niacin ER and Lovatatin improve multiple lipid abnormalities and thus Linicor serves a new therapeutic choice for mixed-dyslipidemia patients. Linicor improves multiple lipid level including LDL-C, TG and HDL-C. Besides, LDL particle size is also improved.

- Due to the novel formulation, Niacin ER improves the safety issue. Local clinical experiences indicates Taiwanese patients have good tolerance (rare flush and hepatotoxicity).


Thank You

Linicor: 仿單資訊 (1)

適應症	・ 高血脂症，且適合同時使用Niacin及lovastatin治療者。
療效 (詳見仿單)	・ 在1000/40mg治療劑量可下降36% LDL-C、增加20% HDL-C、下降39%TG
劑量用法	・ 以500/20mg 為初始劑量，搭配低脂食物睡前服用，間隔四週劑量調升至1000/40 mg。停藥超過一週，請由初始劑量開始調整。 ・ 65歲以上老人：每日使用劑量為500/20~1000/40mg口服，每日最高使用劑量為1000/40毫克。 ・ 肝功能：活動性肝病及不明原因升高之肝指數為用藥使用禁忌。 ・ 腎功能：CCR排除速率小於30ml/dL，每日使用劑量超過500/20毫克時須小心謹慎使用。 ・ 小兒劑量：尚無18歲以下研究

Linicor: 仿單資訊 (2)

代謝/排泄	・ 吸收：(Lovasatin)5%; (Niacin)60~76% (身體可吸收性) ・ 達血中最高濃度：(Lovastatin)2小時; (Niacin)4~5小時 ・ 蛋白質結合率：(Lovastatin)95%; (Niacin)20% ・ 分佈：(Lovastatin)肝、穿過BBB、胎盤; (Niacin)肝、腎、乳汁、脂肪。 ・ 代謝：Lovastatin and Niacin在肝臟代謝 ・ 腎臟排除：(Lovastatin)10%; (Niacin)60~76% ・ 其他排除糞便排除：(Lovastatin)80%
Half-Life	・ Lovastatin：4.5 hrs ・ Niacin：20-48 mins
禁忌	・ 成分過敏、進展中肝病、持續升高的血漿轉胺酶、進展中消化性潰瘍或有動脈出血、懷孕和哺乳。
警語	・ 凝血異常、糖尿病、痛風、過量飲酒、肝病、低血壓、肌病、腎功能不全。
副作用	・ 常見副作用為潮紅、疼痛、噁心、搔癢

Patient education- how to avoid flushing

認識潮紅	・ 潮紅機轉：Niacin刺激皮膚細胞釋出prostaglandin D2，可能造成臉部、脖子、軀幹潮紅及發熱、搔癢等，一般在剛開始服藥或增加劑量時會較明顯，隨著服藥時間越長，潮紅頻率會減少。 ・ 潮紅是暫時性的，研究結果顯示，服藥前2個月約4至8個晚上潮紅約2小時，持續服藥24週後，高達80%病患的潮紅現象會消退。
積極配合事項，可避免或減少潮紅	・ 睡前使用Linicor錠劑，並與低脂點心併用。 ・ 謹慎遵守處方的藥物劑量指示。 ・ 避免同時攝取酒精、熱飲、辛辣食物和洗熱水澡。 ・ 避免同時服用其它含大量Niacin或者相關複合物如Nicotinamide營養補充物或維他命。 ・ 如經上述服藥措施無法改善潮紅，經由門診醫師處方阿斯匹靈325毫克，約在Linicor錠劑前30分鐘服用，可減少臉潮紅反應。

DEBATE ON NIACIN RELATED CLINICAL TRIAL (AIM-HIGH AND HPS-2 THRIVE)

AIM-HIGH study / HPS2-Thrive study

Study	Patients	Treatment (follow-up)	Principal findings with niacin
AIM-HIGH	• With established CV disease (N=3,414) • Mean baseline: **TG 163 mg/dL HDL-C 35mg/dL LDL-C 74 mg/dL**	Niacin ER vs. Placebo (on **pre-existing statin with or without ezetimibe therapy**), 3y	• No significant difference in primary endpoint of cardiovascular disease events • For patients with marked atherogenic dyslipidaemia, there was a **36% relative reduction in the primary CV outcome** (25.0% versus 16.7%, p = 0.032)
HPS2-THRIVE	• With pre-existing occlusive arterial disease (N=25,673) • Mean baseline **TG 125mg/dL HDL-C 44mg/dL LDL-C 63 mg/dL**	NiacinER/Laropiprant vs. Placebo (on **pre-existing statin with or without ezetimibe therapy**), 3.9y	• No reduction in CVD events compared to statins alone. • Additional adverse events occurred which were not found in Niacin-related study previously.

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

N Engl J Med. 2011 Dec 15;365(24):2255-67

N Engl J Med. 2014 Jul 17;371(3):203-12

AIM-HIGH study / HPS2-ThRIVE study: debate

	AIM-HIGH	HPS2-THRIVE
Intervention drug	Niacin-ER 1500~2000mg per day **(with background statin therapy)**	**NiacinER 2000mg and Laropiprant** 40mg per day ≠ NiacinER and Lovastatin **(with background statin therapy)**
Lipid baseline	**LDL-C=74, TG=163, HDL-C=35**	**LDL-C=63, HDL-C=44, TG=125**

Placebo group	• Small dose of Niacin IR (50-100mg) in placebo-treated patients
	• Liberal use of hypolipidemic agents
	  • **Higher frequency of simvastatin 80mg in placebo group** (24.7% vs. 17.5%, P =0.02)
	  • **Higher frequency of ezetimibe in placebo group** (21.5% vs. 9.5%, P<0.001)
		Simvastatin 40mg (±ezetimibe 10mg) as background therapy in both placebo and treatment group

Heterogeneity	men (85%) and white (92%)	better heterogeneity of ethic groups
Adverse events	A small numeric increase in stroke rates in Niacin-ER arm, affecting 1.7% vs. 1.1% in the placebo arm (P = 0.09). Inconsistent with prior trials and NOT Niacin-associated.	Higher rate of bleeding events and infection NOT found in Niacin-related studies previously: use of laropiprant
Subgroup analysis	**TG levels≧200 mg/dl and HDL-C levels <32 mg/dl** → 36% relative reduction of CV outcome	A trend of **higher LDL-C (≧77mg/dl)** having a more significant outcome benefits

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

J Lipid Res. 2013 Oct;54(10):2586-94.

J Cardiovasc Pharmacol Ther. 2014 Mar;19(2):141-58.

AIM-HIGH study: debate (I)

- Contemporary optimal medical therapy and aggressive secondary prevention
  - Well controlled lipid profile at baseline: **LDL-C=74, TG=163, HDL-C=35**. Thus, it's increasingly difficult to demonstrate incremental treatment superiority.
  - ACS and acute MI patients were excluded.
  - The result of AIM-HIGH was limited in their generalization, given the high enrolment of men (85%) and white individuals (92%).
- Minimized differences between placebo and niacin
  - It's possibly due to small dose of Niacin IR (100-200mg) in placebo-treated patients, which could have minimized between-group event rate differences.
  - Although Niacin-treated patients were found with a 25% of HDL-C increase, placebo-treated patients were with 11.8%.

J Lipid Res. 2013 Oct;54(10):2586-94
Nat Rev Endocrinol. 2012 Sep;8(9):517-28
N Engl J Med. 2011 Dec 15;365(24):2255-67

AIM-HIGH study: debate (II)

- Higher Simvastatin/Ezetimide adjustment in placebo-treated patients
  - During the follow-up period, more patients in the placebo group than in the niacin group were taking 80mg SImvastatin per day *(24.7% vs. 17.5%, P = 0.02).* More patients in the placebo group than in the niacin group were taking ezetimibe *(21.5% vs. 9.5%, P<0.001)*.
- Was the observation time sufficient for significant differences in CV events?
  - The original treatment duration of AIM-HIGH was set as 4-6 years. Due to the lack of efficacy, the trial was terminated earlier and the total observation time is around **3 years**.

J Lipid Res. 2013 Oct;54(10):2586-94
Nat Rev Endocrinol. 2012 Sep;8(9):517-28
N Engl J Med. 2011 Dec 15;365(24):2255-67

AIM-HIGH study: debate (III)

- Niacin causes a higher ischemic stroke?
  - A small but unexplained increase in stroke rates was reported in the ER-niacin arm, affecting 1.7% versus 1.1% in the placebo arm (*P* = 0.09).
  - This trend in stroke risk is likely **due to chance** rather than a pathophysiological process.
  - **This result is out of keeping with prior trials that have demonstrated benefits of niacin therapy.** In particular, the CDP demonstrated a 24% reduction in strokes in the niacin arm. Similarly, the ARBITER-6–HALTS trial demonstrated a significant improvement in the surrogate endpoint of cIMT in patients randomly allocated to receive ER-niacin as add-on therapy to statin treatment.

J Lipid Res. 2013 Oct;54(10):2586-94
Nat Rev Endocrinol. 2012 Sep;8(9):517-28
N Engl J Med. 2011 Dec 15;365(24):2255-6

AIM-HIGH: subgroup analysis

- For patients with CVD and marked atherogenic dyslipidemia (total 439 patients)

TG levels ≧ 200 mg/dl &
HDL-C levels <32 mg/dl

- A **significant 36% relative reduction** in the primary CV outcome (25.0% versus 16.7%, p = 0.032)

Niacin				
AIM-HIGH (n = 3,414) [61,62]	ER niacin titrating to 1500-2000	Patients with CVD with persistent atherogenic dyslipidaemia[3] Median LDL-C on statin 1.91 mmol/L [74 mg/dL]	Prematurely terminated; mean 3 years	• No significant outcomes benefit with ER niacin • Methodological issues; inadequately powered, placebo contained a low-dose of niacin (50 mg/capsule), imbalance in concomitant LDL-C lowering therapy between groups • For patients with marked atherogenic dyslipidaemia,[4] there was a 36% relative reduction in the primary CV outcome (25.0% versus 16.7%, p = 0.032)

Cardiovasc Diabetol. 2014 Jan 24;13:26.
J Am Coll Cardiol. 2013 Oct 22;62(17):1580-4.

HPS2-THRIVE debate

- A remarkably stable and exceedingly well treated population
  - The lipid baseline was TC=128, **LDL-C=63, TG=125, HDL-C=44**. The study participants already had a well-controlled lipid profile.
- The use of laropiprant in the niacin arm of the study increased adverse events and/or reduced benefits.
  - There's a paucity of scientific information relating to the known pathologic effects of PGD2. it's has been observed that laropiprant at low concentrations may prevent the inhibitory effects of PGD2 on platelet function, including effects on platelet aggregation and thrombus formation, while laropiprant at higher concentrations may attenuate platelet activation induced by thromboxane and inhibit thrombus formation.
  - Prostaglandins play a key role in the generation of the inflammatory response. Their biosynthesis is significantly increased in inflamed tissue and they contribute to the development of the cardinal signs of acute inflammation. However, their role in the resolution of inflammation is more controversial.

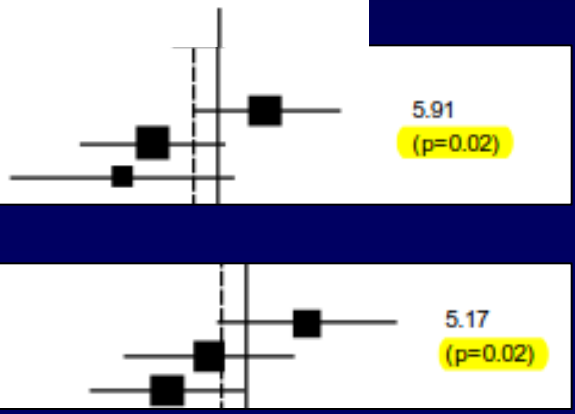
Eur Heart J. 2013 May;34(17):1279-91 Nat Rev Endocrinol. 2012 Sep;8(9):517-28
J Lipid Res. 2013 Oct;54(10):2586-94 Arterioscler Thromb Vasc Biol. 2011;31:986-1000

HPS-2 THRIVE: subgroup analysis

- Niacin might still be relevant for particular patient groups (patient at high risk for vascular events who **have high levels of LDL cholesterol**).

The nominally significant trend ***(p=0.02)*** *toward* ***a greater reduction in risk in the subgroup with a higher baseline LDL-C*** *may be related, at least in part, to the greater reduction in the LDL-C in that subgroup.*

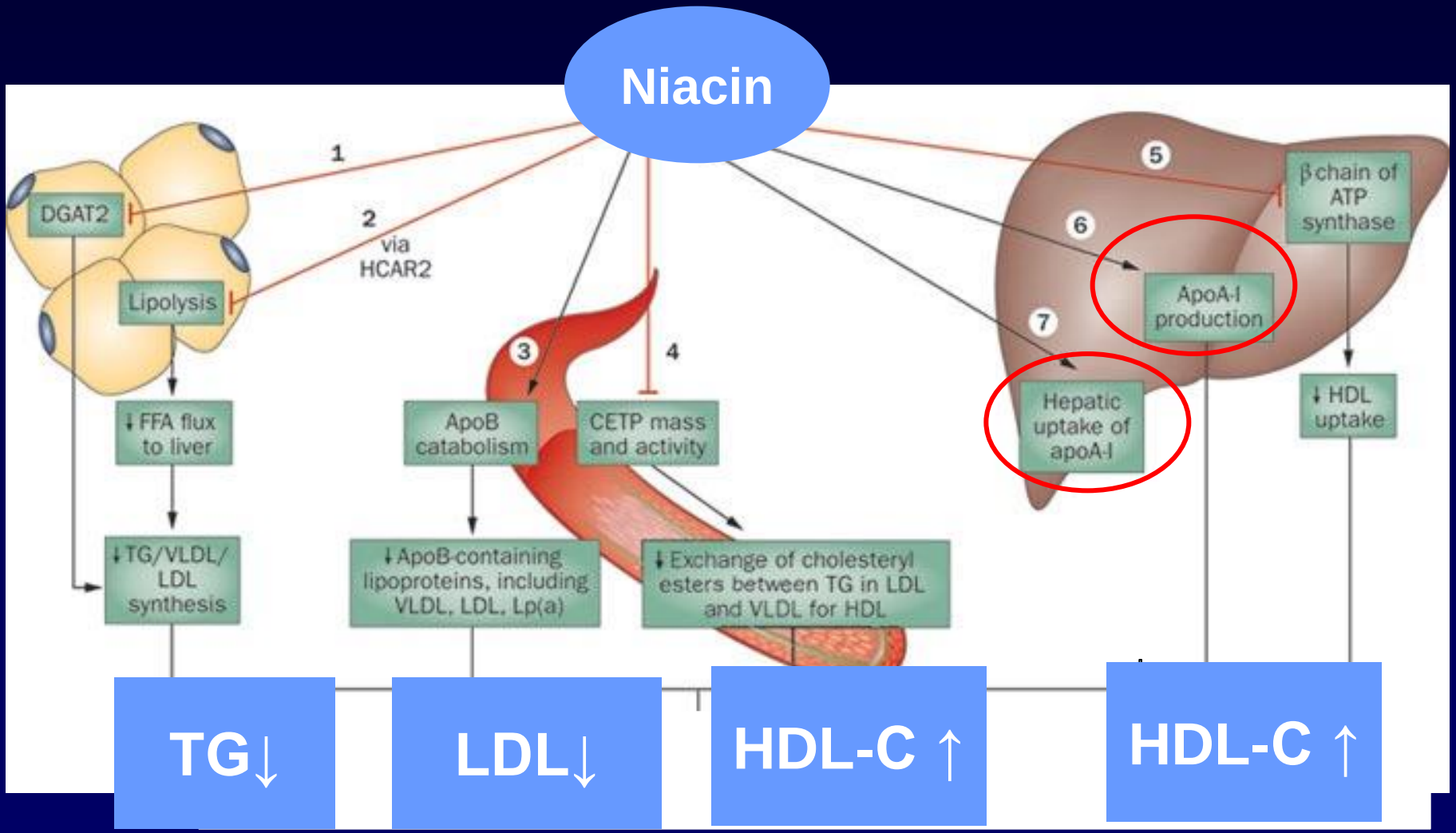
Baseline characteristic	Study average difference (mg/dL) LDL-C	HDL-C	Niacin/laropiprant-allocated (n=12838)	Placebo-allocated (n=12835)
LDL cholesterol (mg/dL)				
<58	-7	6	724 /4933 (14.7%)	679 /4927 (13.8%)
≥58 <77	-10	6	685 /5505 (12.4%)	761 /5549 (13.7%)
≥77	-15	7	287 /2400 (12.0%)	318 /2359 (13.5%)
Apolipoprotein B (mg/dL)				
<60	-7	6	507 /3595 (14.1%)	483 /3695 (13.1%)
≥60 <70	-9	6	540 /4159 (13.0%)	569 /4132 (13.8%)
≥70	-13	6	649 /5084 (12.8%)	706 /5008 (14.1%)



N Engl J Med. 2014 Jul 17;371(3):203-12

NIACIN MECHANISM AND FUNCTIONAL HDL-C

Niacin Mechanism



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

Niacin increases functional HDL-C

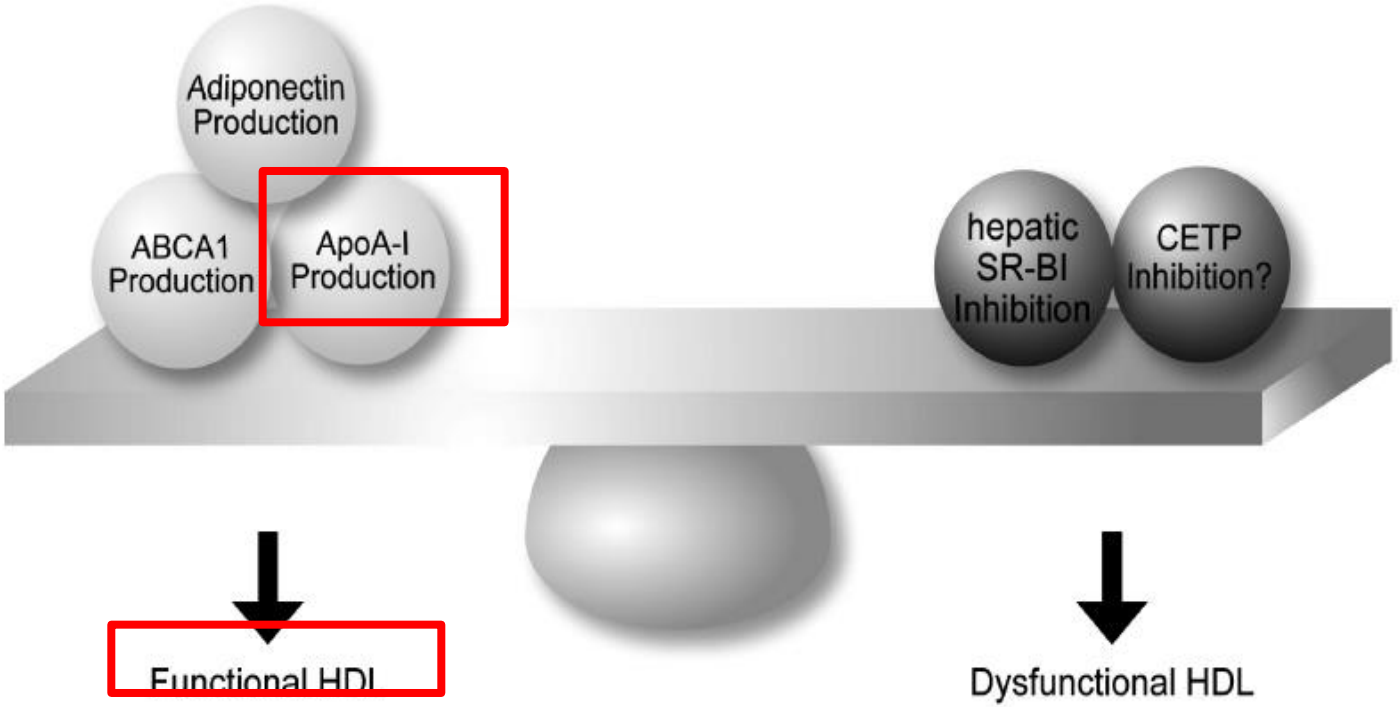


Fig. 8. Mechanisms underlying increases in functional and dysfunctional HDL by statins.

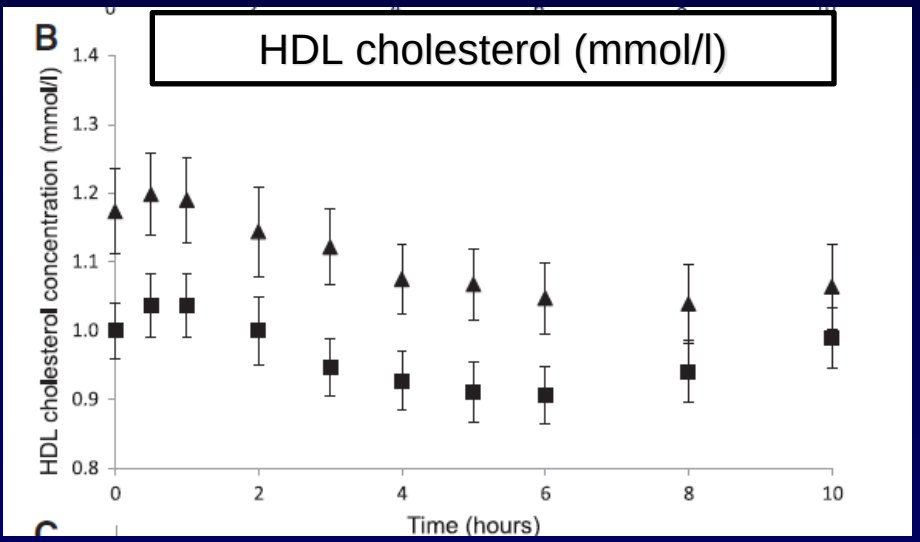
Statins elevate preβ-HDL-producing ability via the production of ApoA-I, ABCA1 and adiponectin to increase functional HDL. On the other hand, statins may produce dysfunctional HDL by CETP inhibition. Whether HDL produced by a statin is functional is determined by a balance between CETP inhibitory ability and pre-β-HDL-producing ability.

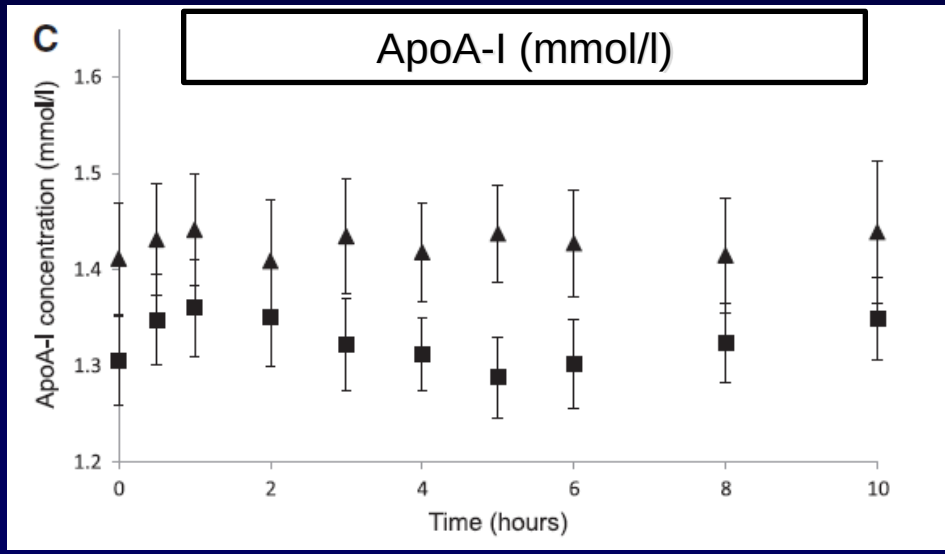
Abbreviations: ApoA-I, apolipoprotein A-I; ABCA1, ATP-binding cassette transporter A1; CETP, cholesteryl ester transfer protein.

Niacin increases ApoA-I in diabetic patients

- For T2DM patietns under optimal rosuvastatin therapy, a randomization was performed for rosuvastatin alone or rosuvastatin plus niacin ER for 12 weeks.
- **Compared with rosuvastatin alone, add-on niacin could additionally increase HDL-C and ApoA-I.**

▲: Niacin+Rosuvastatin
■: Placebo+Rosuvastatin





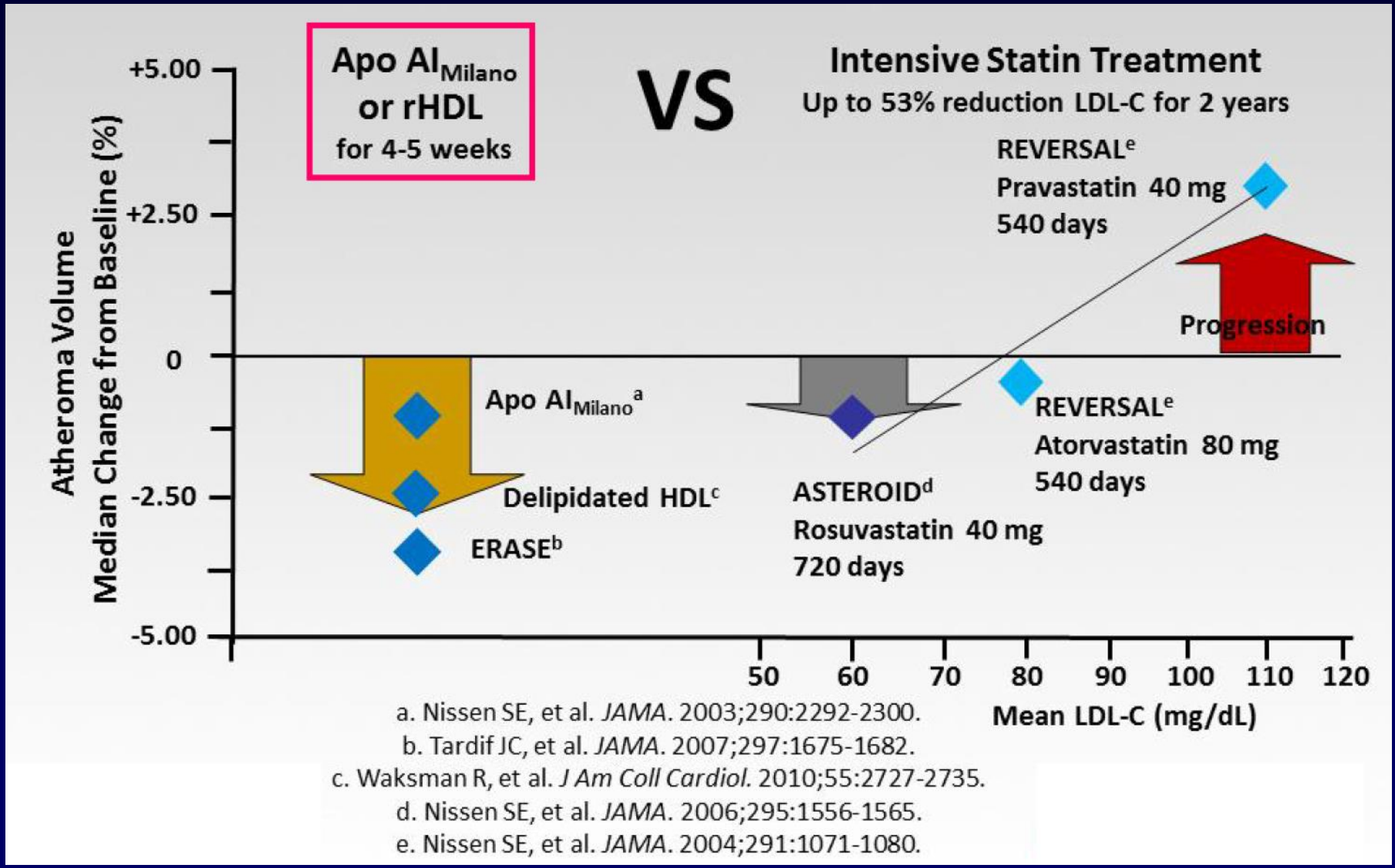
***Rosuva. Plus Niacin* vs. *Rosuva.*:**

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

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

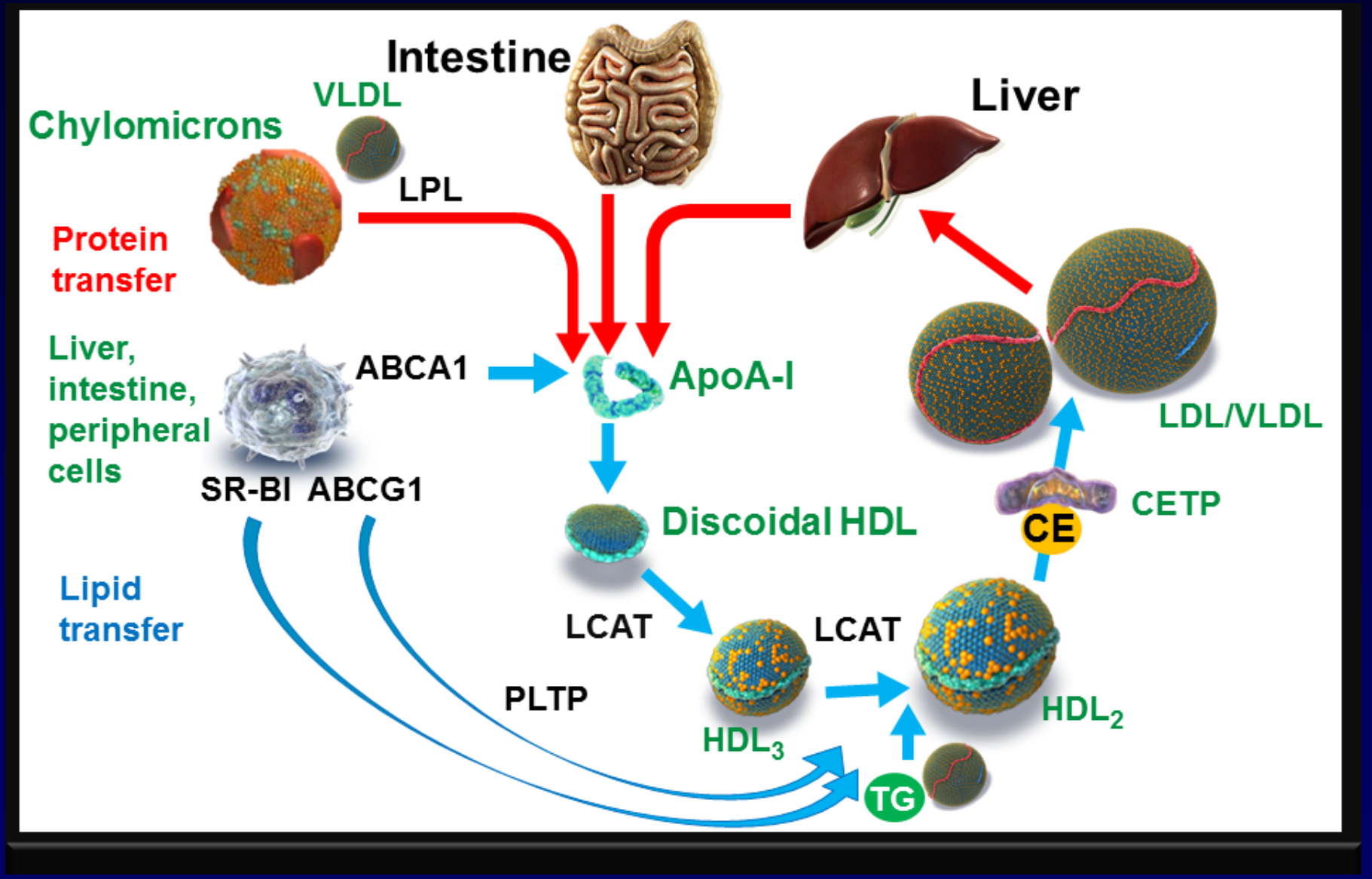
Arterioscler Thromb Vasc Biol. 2014 Feb;34(2):427-32

Effects of *Apo-A1 vs LDL* interventions on coronary atherosclerosis by IVUS

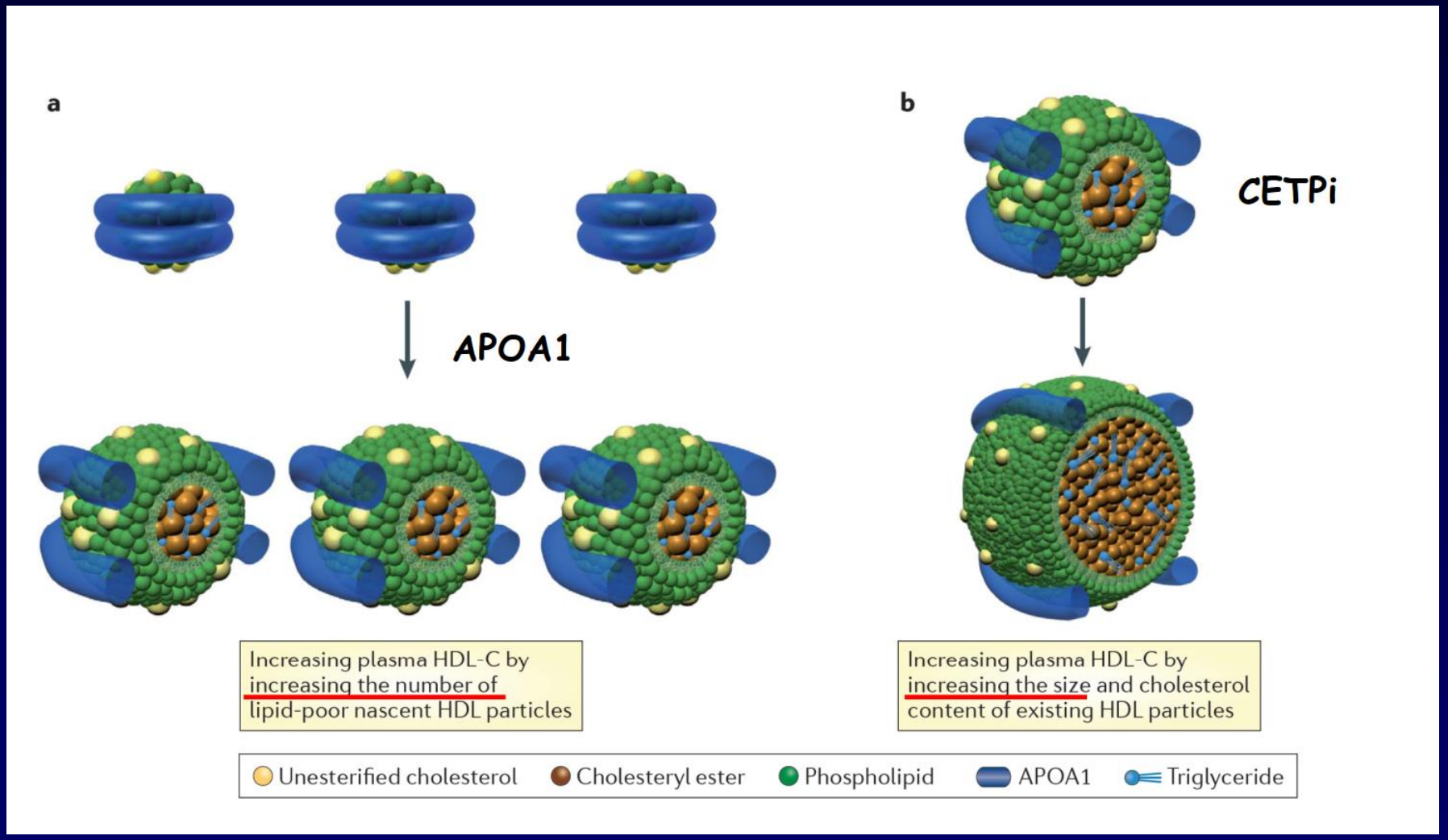


a. Nissen SE, et al. *JAMA*. 2003;290:2292-2300.
b. Tardif JC, et al. *JAMA*. 2007;297:1675-1682.
c. Waksman R, et al. *J Am Coll Cardiol*. 2010;55:2727-2735.
d. Nissen SE, et al. *JAMA*. 2006;295:1556-1565.
e. Nissen SE, et al. *JAMA*. 2004;291:1071-1080.

Niacin increases functional HDL-C

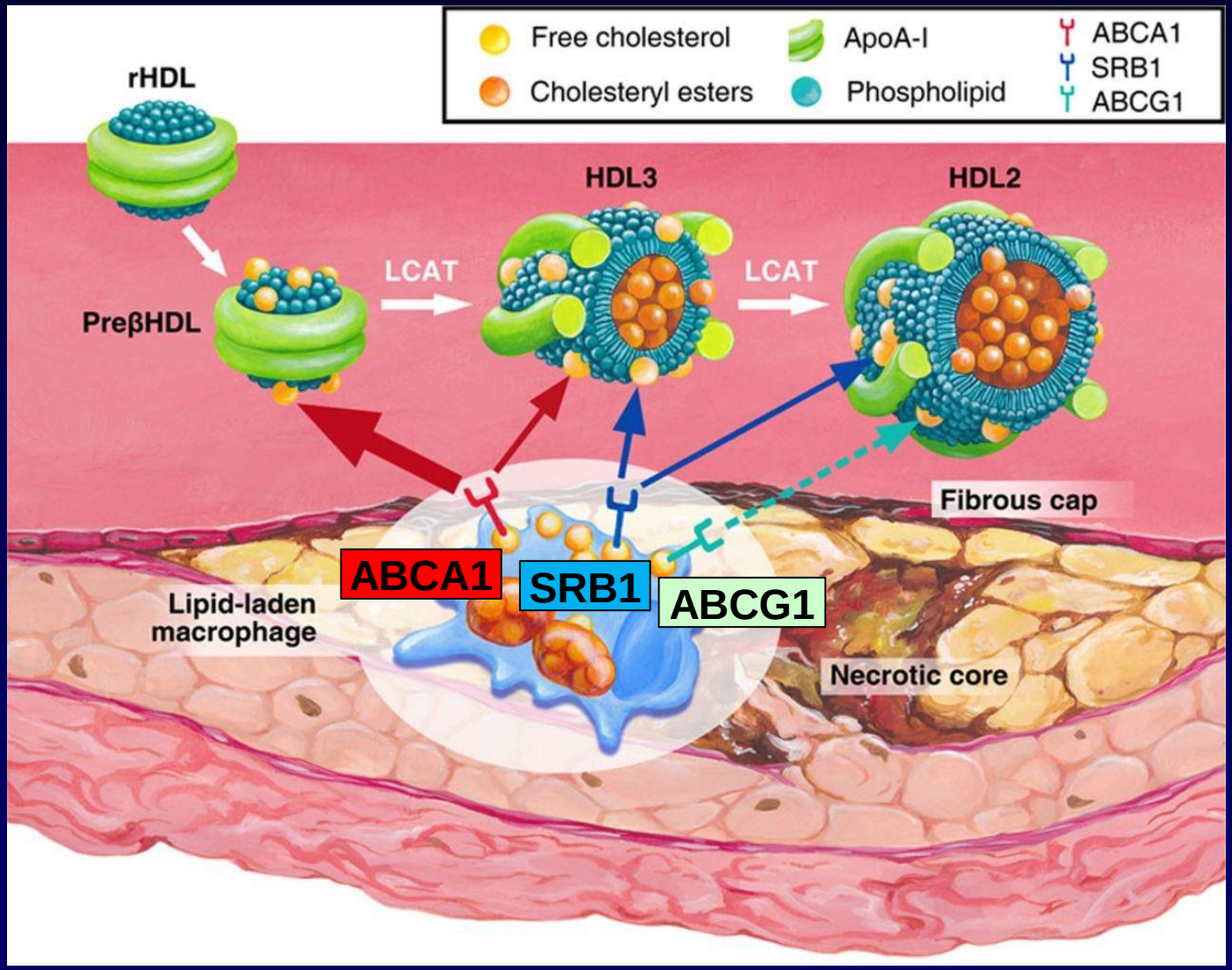


Niacin increases functional HDL-C



Nat Rev Drug Discov. 2014 Jun;13(6):445-64.

Cholesterol Removal From Vulnerable Plaques



ABCA1

SRB1

ABCG1

Circulation. 2013 Sep 3;128(10):1112-21

Niacin significantly increases ApoA-I and SR-BI-mediated efflux

- ER niacin therapy in patients with a history of primary dyslipoproteinemia had a beneficial effect on **SR-BI-mediated efflux** and that it was related to the change in level of HDL-C.

Table 2 High-density lipoprotein cholesterol component's change from baseline

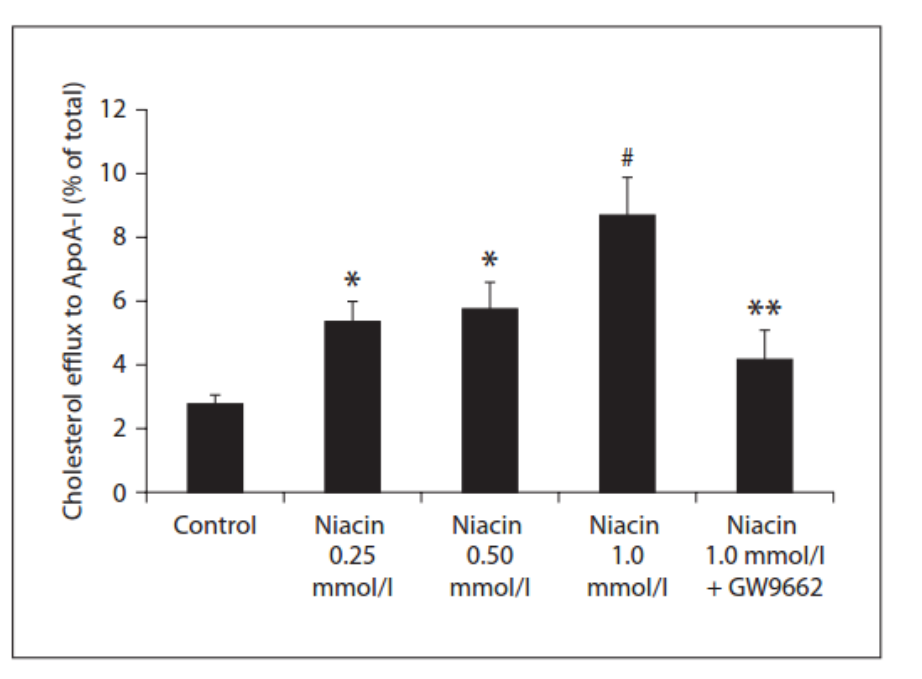
	Extended-release niacin	Crystalline niacin	Placebo
HDL-C			
mmol [95% CI]	0.50 [0.30 to 0.69]*	0.67 [0.33 to 1.00]*	0.02 [0.00 to 0.05]
mg/dL [95% CI]	19.4 [11.9 to 27.0]	26.2 [13.2 to 39.2]	7 [0 to 1.6]
HDL_2-C			
mmol [95% CI]	0.17 [0.07 to 0.28]*	0.22 [0.10 to 0.33]*	−0.1 [−0.04 to 0.02]
mg/dL [95% CI]	6.8 [2.9 to 10.8]	8.4 [3.8 to 13.0]	−0.4 [−1.8 to 0.9]
HDL_3-C			
mmol [95% CI]	0.31 [0.21 to 0.41]*	0.52 [0.26 to 0.78]*	0.05 [0 to 0.11]
mg/dL [95% CI]	12.0 [8.1 to 16.0]	20.2 [10.2 to 30.3]	2 [−0.2 to 4.2]
ApoA-I (mg/dL) [95% CI]	27.8 [19.3 to 36.2]*	32.6 (17.5 to 47.6)*	4.6 [−1.1 to 10.2]
Cholesterol efflux (%) [95% CI]	2.7 [1.1 to 4.4]*	3.4 [0.6 to 6.2]*	0.2 ± 3.5 [−1.2 to 2.3]

ApoA-I = apolipoprotein A-I; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol.
*Statistically significantly ($P < 0.001$).

J Clin Lipidol. 2007 Dec;1(6):614-9.

Niacin Promotes Cholesterol Efflux via ABCA1 pathway

- Niacin may promote cholesterol efflux from adipocytes to ApoA-I via **activation of the PPAR-LXR⟨ -ABCA1 pathway**
- Cholesterol efflux rate was increased in a dose-dependent manner with increasing concentrations of niacin.



Pharmacology. 2009;84(5):282-7.

DEBATE ON ADA GUIDELINE

2017年ADA(美國糖尿病學會)建議

- 與2016年版本相同
- 內文引用文獻資料為AIM-HIGH試驗

LIPID MANAGEMENT

- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone and may increase the risk of stroke and is not generally recommended. A

J Diabetes. 2017 Jan 10

AIM-HIGH試驗結果爭議說明
常見學會與文獻討論

療效性

- AIM-HIGH試驗收案族群經statin達**良好血脂治療狀態，【LDL-C=74, TG=163, HDL-C=35】**較難看出Add-on Niacin額外差異
- **次族群分析【TG≧200且HDL<32】有顯著臨床助益**

安全性

- **統計結果p值為0.09，並未達統計學差異**；且發生比率數值很低。Statin單獨治療後中風發生率為1.1%，而合併Niacin治療後中風發生率為1.7%
- 相關討論認為**與先前Niacin的研究結果不一致**，無法判斷是否有因果關係，可能是隨機發生狀況，有待更多大型研究
- **後續回歸分析顯示與Niacin並無顯著關係**

AIM-HIGH study次分析
針對混合性族群具顯著心血管風險改善效果

- 針對已有心血管疾病患者且LDL-C已使用Statin(±Ezetimibe)治療達標，但具混合性血脂異常患者(共439個病患)：

TG levels ≧ 200 mg/dl &
HDL-C levels <32 mg/dl

- 相較於對照組(placebo)，Add-on Niacin**可顯著改善36% primary CV outcome的相對風險** (25.0% versus 16.7%, p = 0.032)

Niacin				
AIM-HIGH (n = 3,414) [61,62]	ER niacin titrating to 1500-2000	Patients with CVD with persistent atherogenic dyslipidaemia[3] Median LDL-C on statin 1.91 mmol/L [74 mg/dL]	Prematurely terminated; mean 3 years	• No significant outcomes benefit with ER niacin • Methodological issues; inadequately powered, placebo contained a low-dose of niacin (50 mg/capsule), imbalance in concomitant LDL-C lowering therapy between groups • For patients with marked atherogenic dyslipidaemia,[4] there was a 36% relative reduction in the primary CV outcome (25.0% versus 16.7%, p = 0.032)

Cardiovasc Diabetol. 2014 Jan 24;13:26.
J Am Coll Cardiol. 2013 Oct 22;62(17):1580-4.

中風趨勢增加
統計分析並無顯著差異

- Statin單獨治療後中風發生率為1.1%，而合併Niacin治療中風發生率為1.7%
- 發生比率數值很低，且p值為0.09，並未達統計學差異

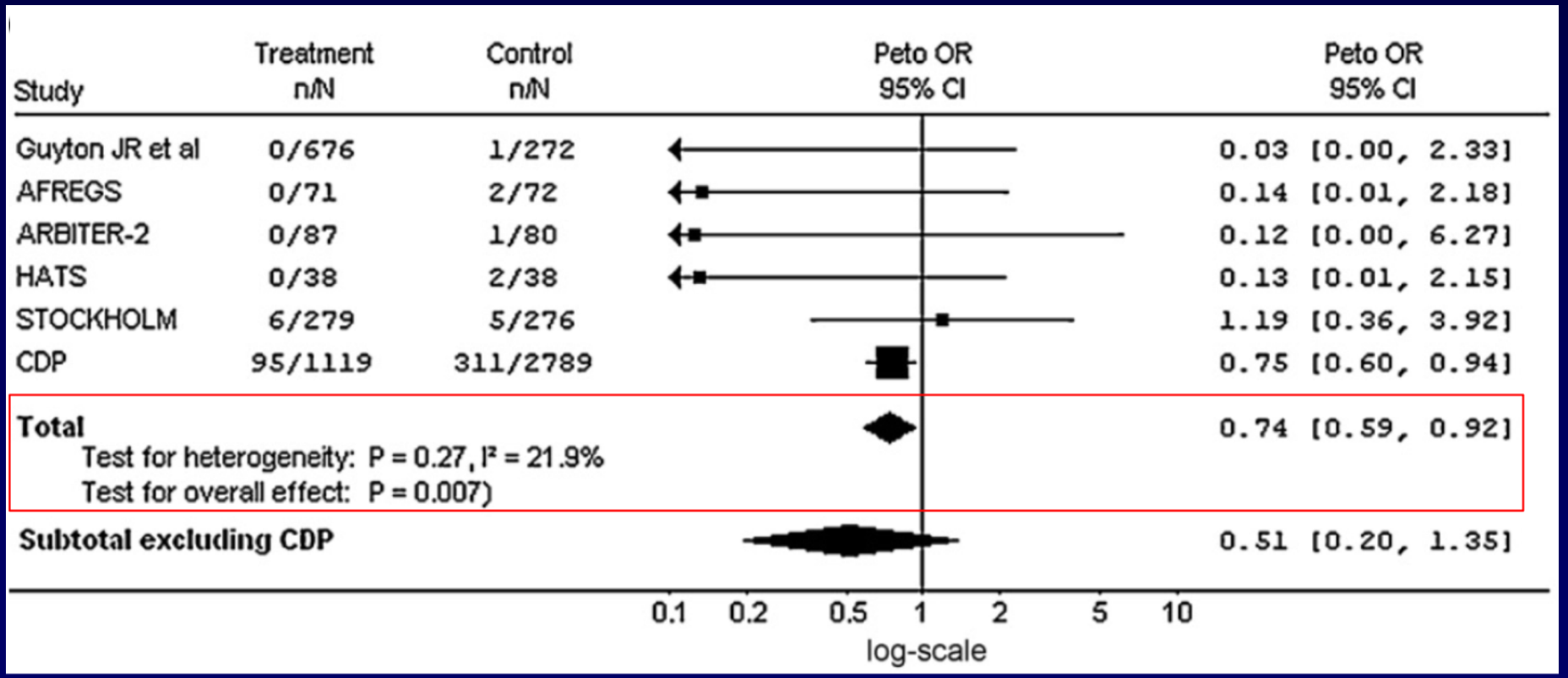
Table 4. Primary, Secondary, and Tertiary End Points.

End Point	Placebo plus Statin (N=1696)	Extended-Release Niacin plus Statin (N=1718)	Hazard Ratio with Niacin (95% CI)	P Value*
	number of patients (percent)			
Ischemic stroke‡	18 (1.1)	29 (1.7)	1.61 (0.89–2.90)	0.11
Ischemic stroke or stroke of uncertain origin	18 (1.1)	30 (1.7)	1.67 (0.93–2.99)	0.09

N Engl J Med. 2011 Dec 15;365(24):2255-67

中風趨勢增加
與先前Niacin研究結果不一致

- 2010 Atherosclerosis meta-analysis中的odds ratio顯示，Niacin相關治療之試驗組較對照組顯著降低中風風險 (OR=0.74, p=0.007)



Atherosclerosis. 2010 Jun;210(2):353-61.

中風趨勢增加
後續回歸分析與Niacin並無顯著關係

- Although there were numerically more ischemic strokes with addition of ERN to simvastatin that reached nominal significance, *the number was small, and multivariable analysis accounting for known risk factors did not support a significant association between niacin and ischemic stroke risk.*

Table 5. Association of Risk Factors With Ischemic Stroke and Composite of Ischemic Stroke and TIA by Multivariate Analysis

Parameter	Hazard Ratio (95% CI)	*P* Value
Ischemic stroke		
Age ≥65 vs <65 y	3.58 (1.82–7.05)	0.0002
History of stroke/TIA/presence of carotid disease	2.18 (1.23–3.88)	0.008
Lp(a) by tertiles		
Highest vs lowest tertile	2.31 (1.00–5.30)	
Middle vs lowest tertile	2.80 (1.25–6.26)	0.042
Randomization assignment		
Combination vs statin alone	1.74 (0.97–3.11)	0.063
Ischemic stroke or TIA		
Age ≥65 vs <65 y	2.56 (1.54–4.27)	0.0003
History of stroke/TIA/presence of carotid disease	2.76 (1.74–4.38)	<0.0001
Lp(a) by tertiles		
Highest vs lowest tertile	2.30 (1.19–4.42)	
Middle vs lowest tertile	2.49 (1.31–4.73)	0.0156

CI indicates confidence interval; and TIA, transient ischemic attack.

Stroke. 2013 Oct;44(10):2688-93