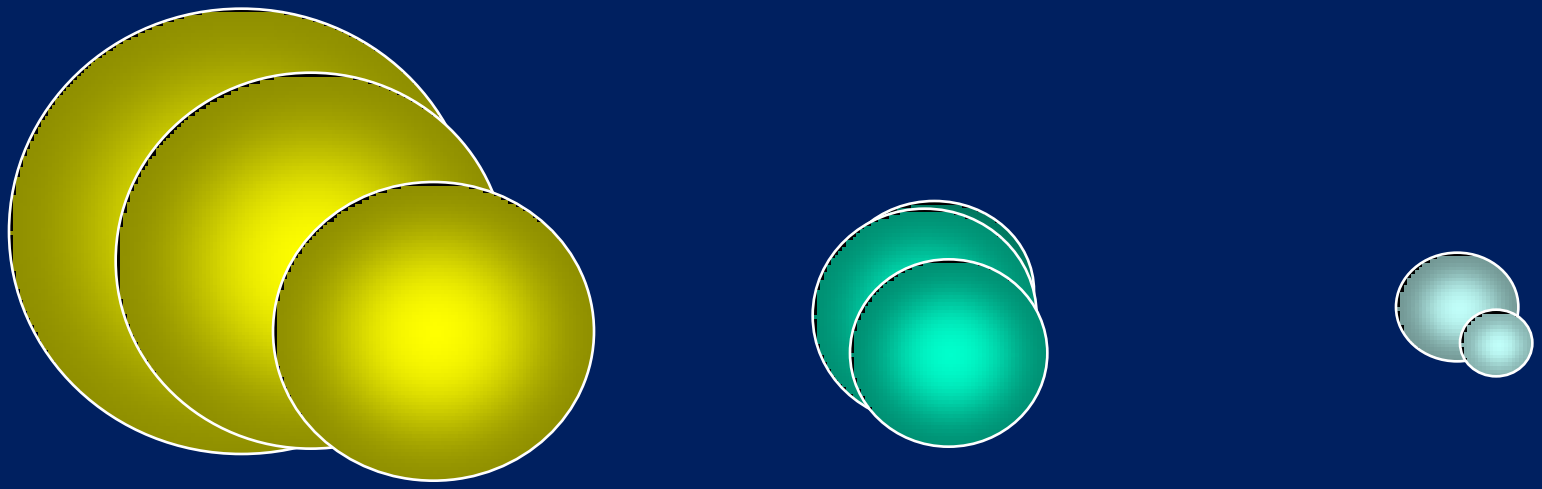
Beyond LDL-C, how can we achieve comprehensive lipid goal in T2DM with mixed type dyslipidemia?

高雄榮總 新陳代謝科
朱志勳

Lipoprotein classes and atherosclerosis



Chylomicrons, VLDL, and their catabolic remnants

LDL

HDL

Pro-atherogenic

Anti-atherogenic

Dyslipidemia

- Elevated LDL-C — Statin
- Elevated triglyceride — Fibrate
- Low HDL-C — Exercise, BW

All statin clinical outcome trials: Effects of baseline LDL-C

Relative risk reduction in major vascular events per 40 mg/dL reduction in LDL-cholesterol

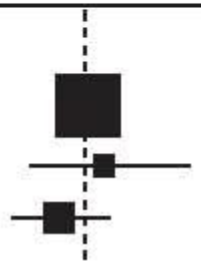
(26 Trials; 169,138 subjects; 24,323 events)

Baseline LDL-C	Number of Events: Treatment-arm (n=84573)	Number of Events: Control-arm (n=84565)	Relative risk (95% CI)
< 80 mg/dL	910	1012	0.78 (0.61-0.99)
80-100 mg/dL	1528	1729	0.77 (0.67-0.89)
100-120 mg/dL	1866	2225	0.77 (0.70-0.85)
120-150 mg/dL	2007	2454	0.76 (0.70-0.82)
> 150 mg/dL	4508	5736	0.80 (0.76-0.83)

CTT Collaborators. Lancet. 2010; 376:1670-1681.

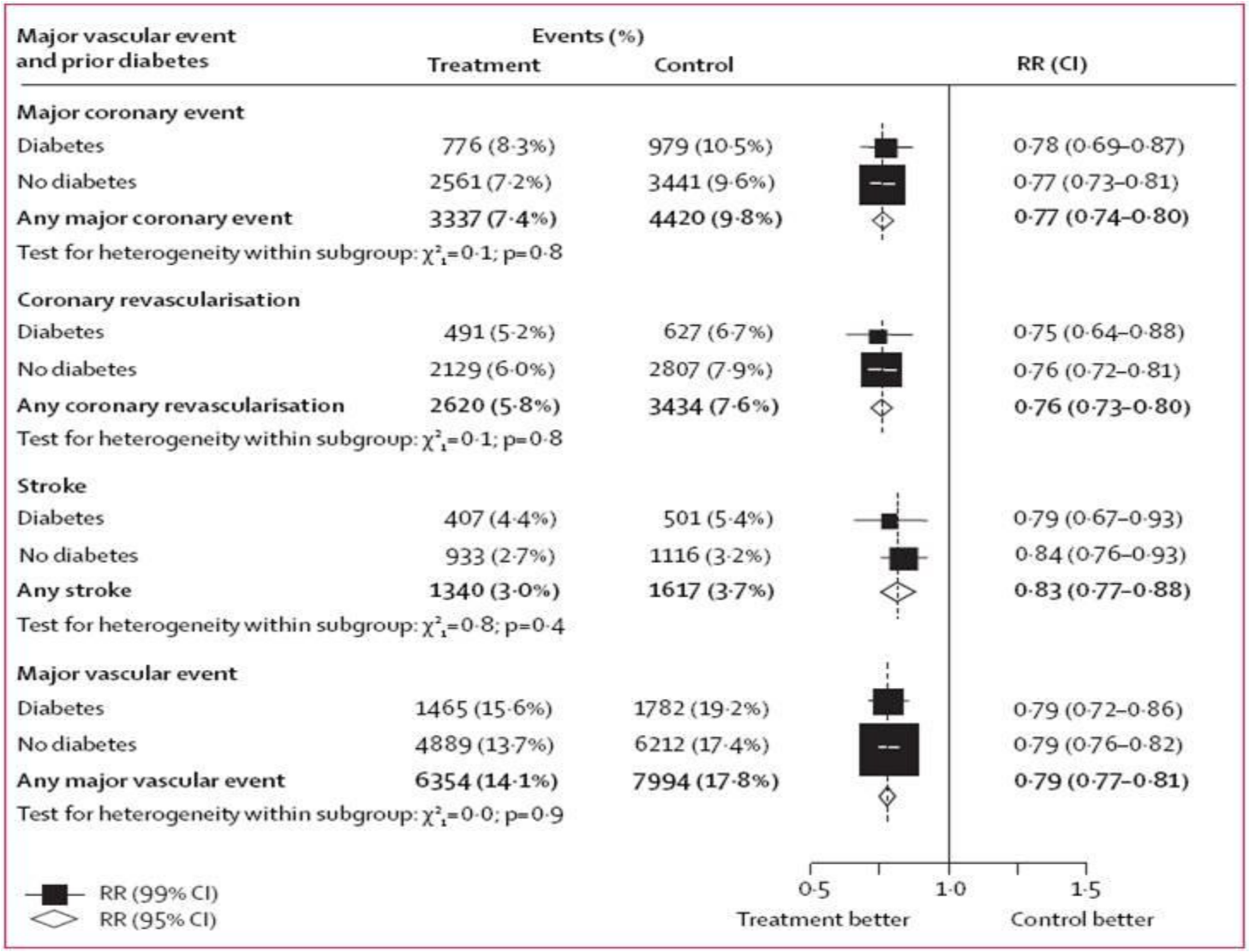
Benefits for patients with CHD

	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL-C	Heterogeneity/ trend test
	Statin/more	Control/less		
Previous vascular disease				
CHD	8395 (4·5%)	10123 (5·6%)	0·79 (0·76–0·82)	χ^2_2=2·28 (p=0·3)
Non-CHD vascular	674 (3·1%)	802 (3·7%)	0·81 (0·71–0·92)	
None	1904 (1·4%)	2425 (1·8%)	0·75 (0·69–0·82)	



CTT Collaborators. Lancet. 2010; 376:1670-1681.

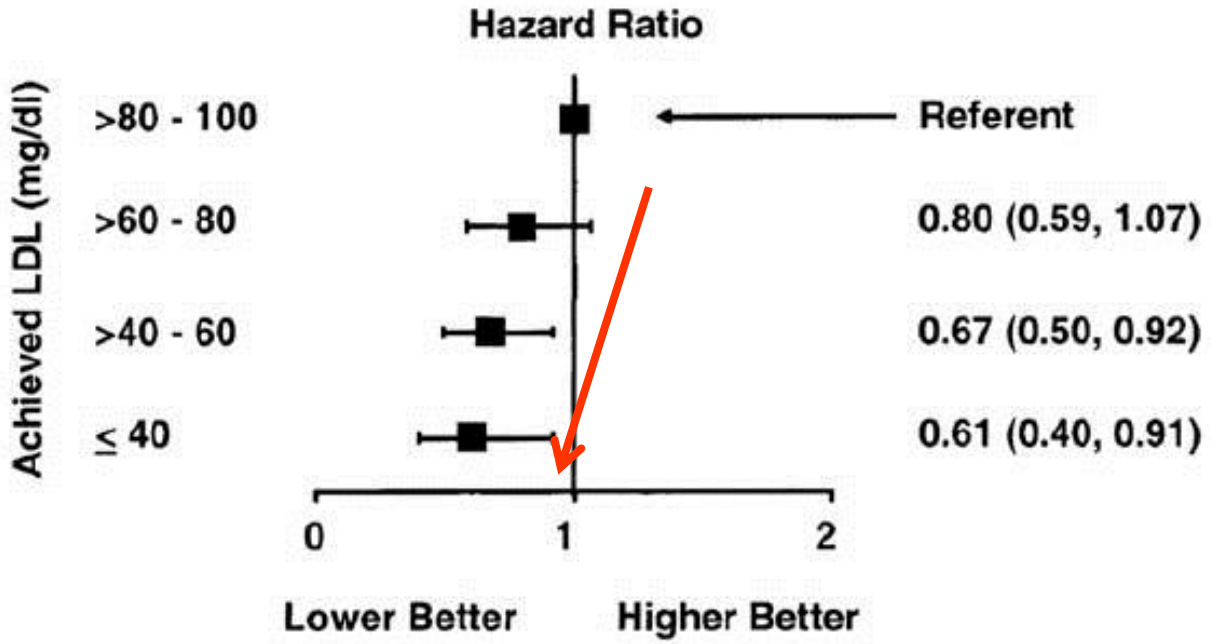
Benefits for patients with DM



CTT Collaborators. Lancet. 2010; 376:1670-1681.

CV Benefit from PROVE IT study

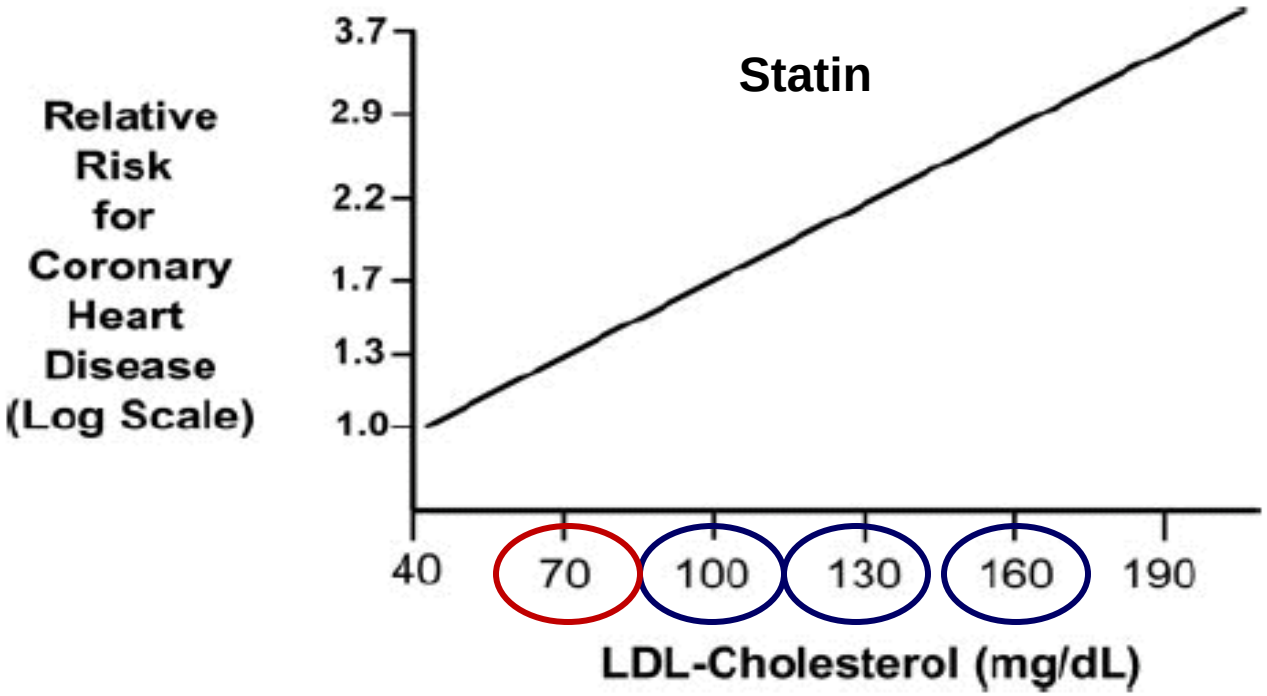
Hazard Ratio for Primary Endpoint (PROVE IT-TIMI 22)



Wiviott SD, et al. J Am Coll Cardiol. 2005;46:1411-1416.

NCEP Report

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines



Log-linear relationship between LDL-C levels and relative risk for CHD. This relationship is consistent with a large body of epidemiological data and with data available from clinical trials of LDL-lowering therapy. These data suggest that for every 30-mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by about 30%. The relative risk is set at 1.0 for LDL-C=40 mg/dL.

Circulation. 2004;110:227-239

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Four Major Statin Benefit Groups

- with clinical ASCVD,
- primary elevations of LDL–C >190 mg/dL,
- diabetes aged 40 to 75 years with LDL–C 70 to189 mg/dL and without clinical ASCVD,
- without clinical ASCVD or diabetes with LDL–C 70 to189 mg/dL and estimated 10-year ASCVD risk >7.5%.

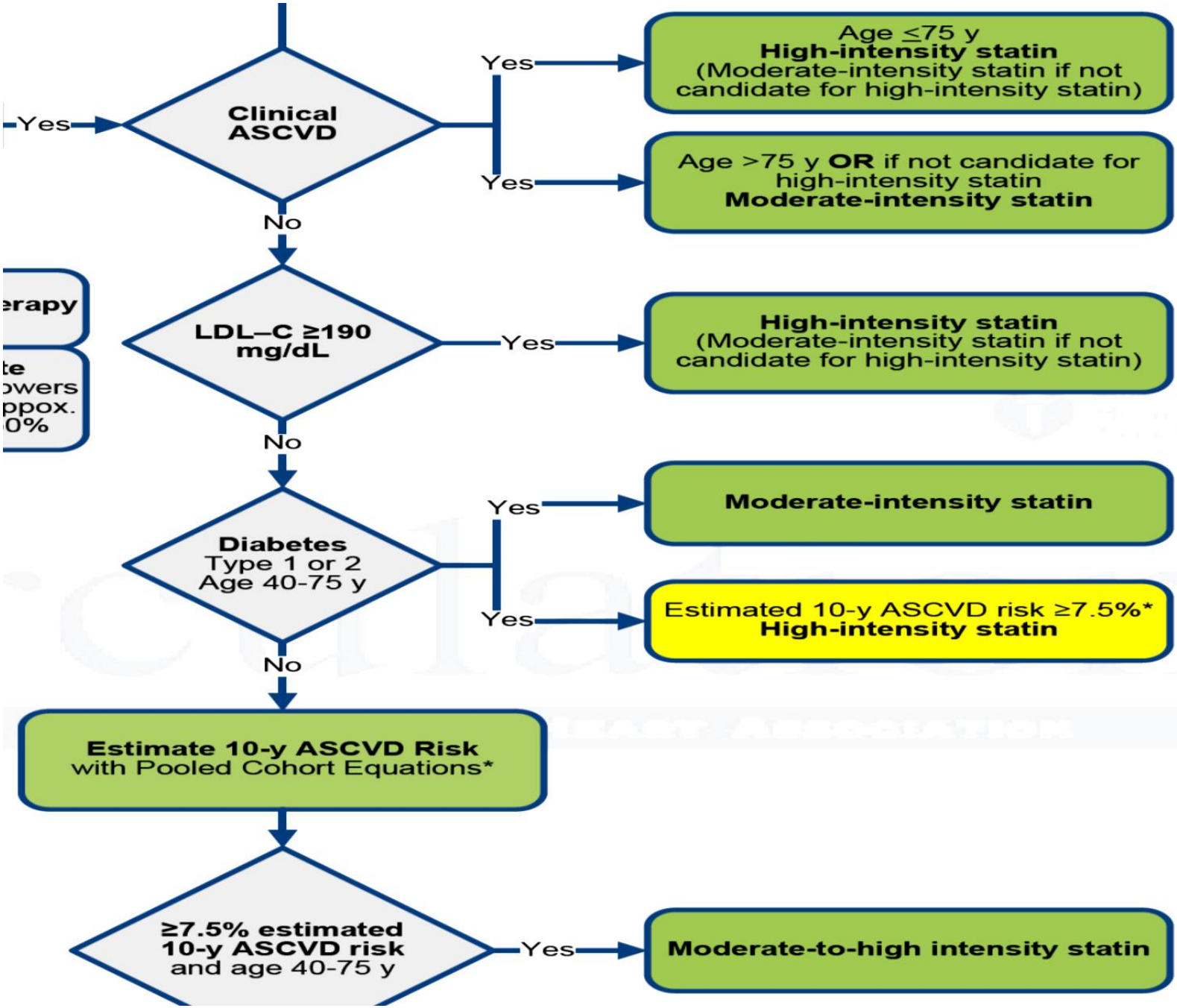

Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
erapy
te
owers
ppox.
0%
LDL–C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Diabetes
Type 1 or 2
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated 10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**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*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

No evidence was found that titration or combination drug therapy to achieve specific LDL–C or non-HDL–C levels or percent reduction improved ASCVD outcomes. Therefore, this guideline does not recommend their use as performance measures.

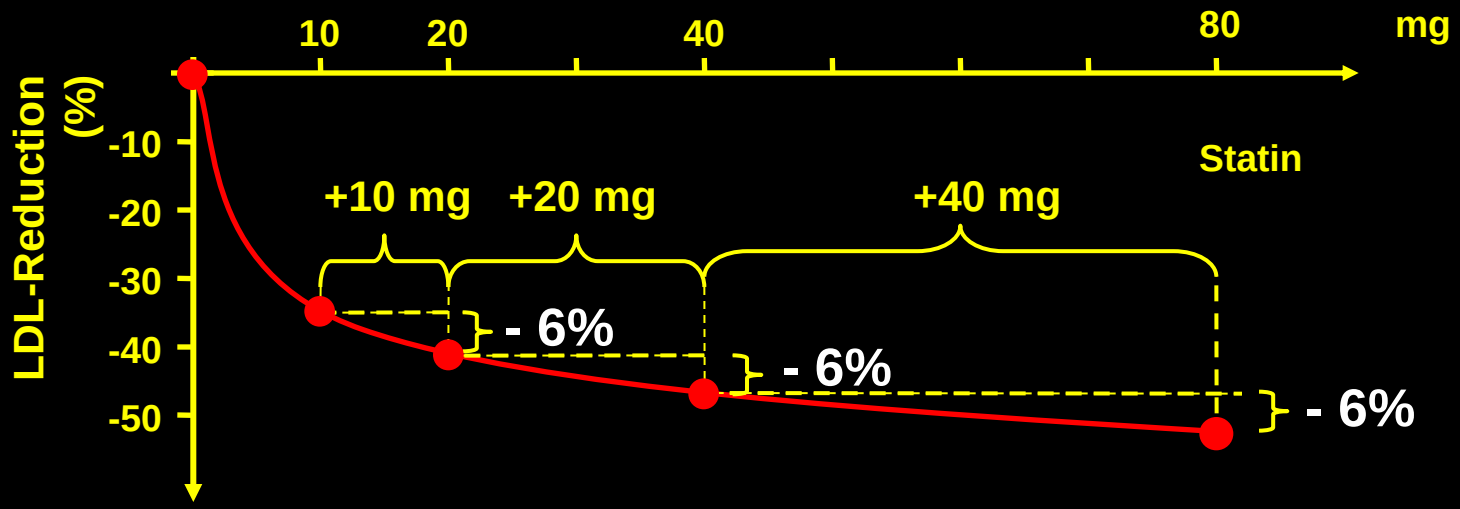
Medscape Medical News

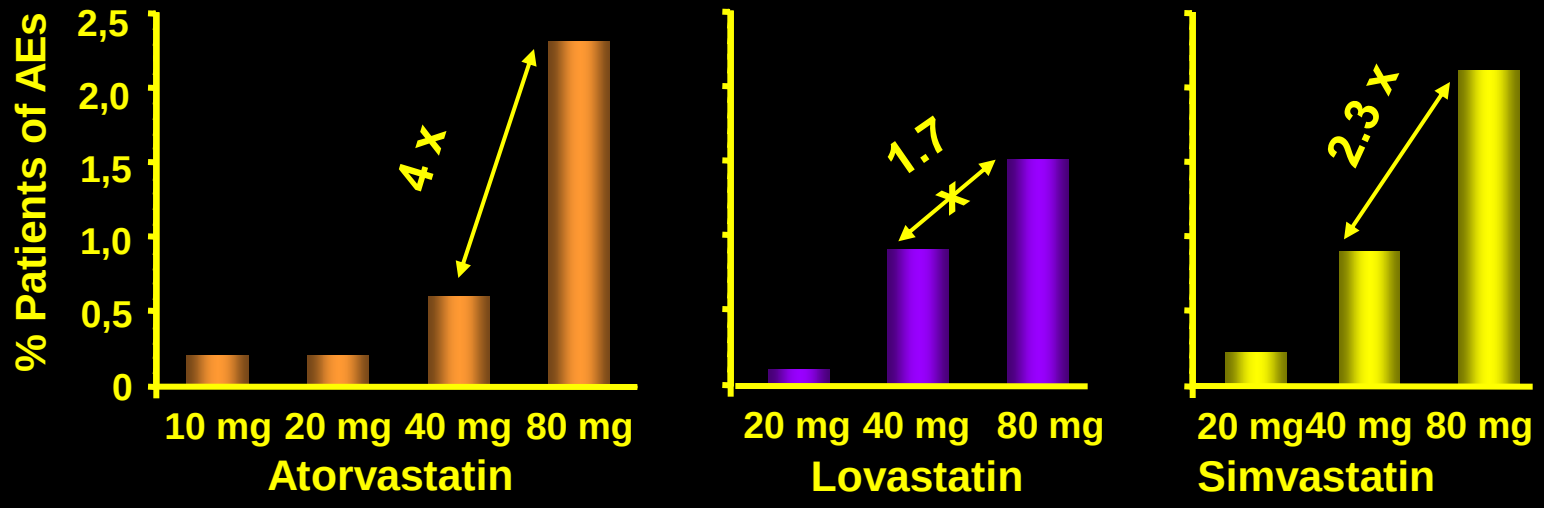
Endocrinology Group Rejects New AHA/ACC CVD Guidelines

December 13, 2013

- **The American Association of Clinical Endocrinologists (AACE) says it can't support the new cardiovascular risk guidelines issued by the American Heart Association (AHA) and the American College of Cardiology (ACC), saying the set of 4 guideline documents is out of step with its own recommendations.**
- **The 4 guidelines are:**
  - ✓ **The treatment of blood cholesterol in adults.**
  - ✓ **Lifestyle management to reduce cardiovascular risk.**
  - ✓ **Obesity management, in conjunction with The Obesity Society.**
  - ✓ **A "science advisory" on the management of hypertension, along with the Centers for Disease Control and Prevention.**

Statins limitation (rule of 6%)





"Physicians Desk Reference (PDR)"

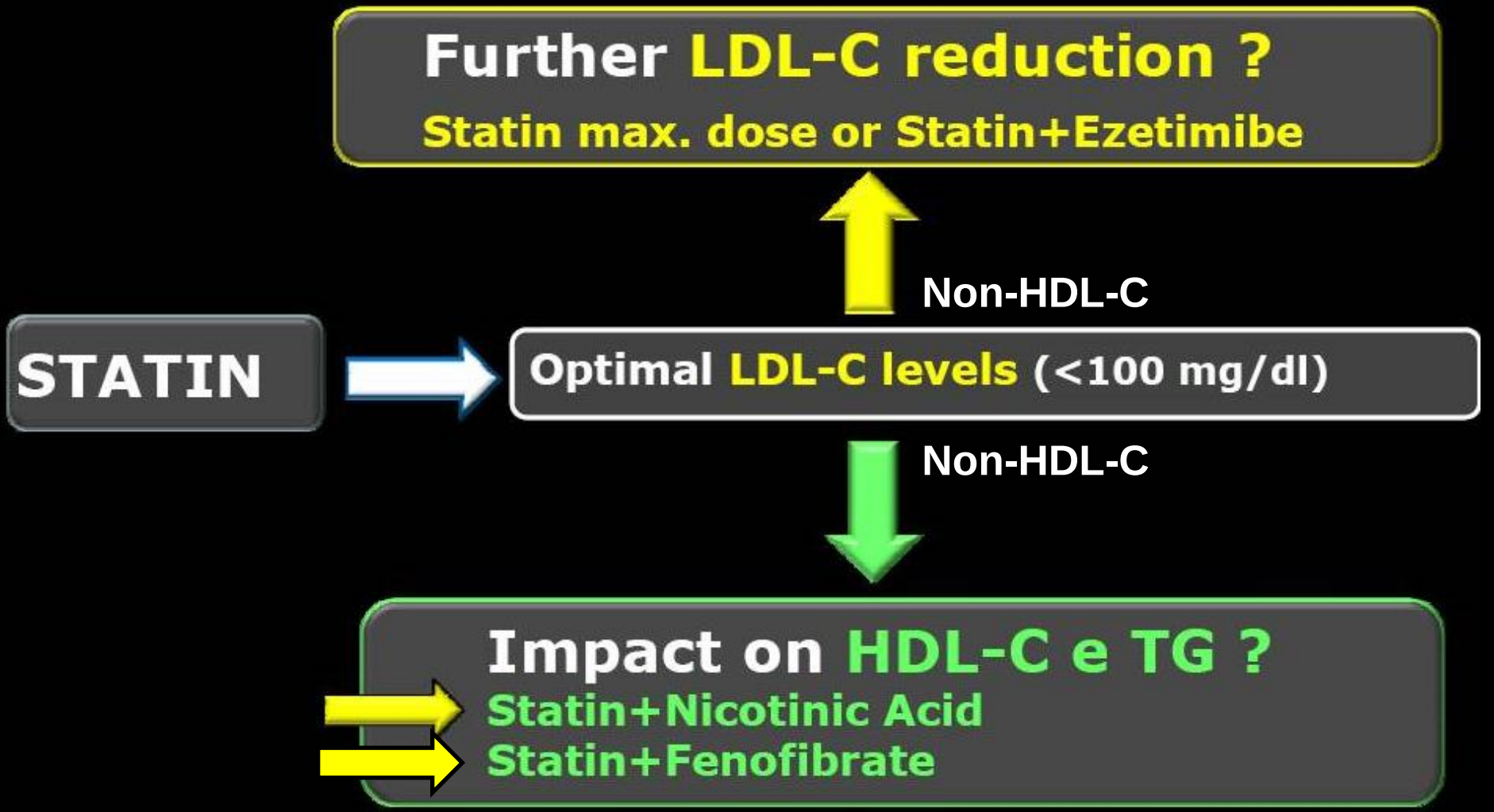
STELLAR: Effects of statins on lipids
Percentage changes in lipid parameters

		10 mg	20 mg	40 mg	80 mg
LDL-C	rosuvastatin	-46[A]	-52[BC]	-55[D]	-
	atorvastatin	-37	-43	-48	-51
	simvastatin	-28	-35	-39	-46
	pravastatin	-20	-24	-30	-
HDL-C	rosuvastatin	+7.7	+9.5	+9.6	-
	atorvastatin	+5.7	+4.8[b]	+4.4[bc]	+2.1[c]
	simvastatin	+5.3	+6.0	+5.2[bc]	+6.8
	pravastatin	+3.2[a]	+4.4[b]	+5.6[bc]	-
TG	rosuvastatin	-20	-24	-26	-
	atorvastatin	-20	-23	-27	-28
	simvastatin	-12	-18	-15	-18
	pravastatin	-8[a]	-8[bc]	-13[abc]	-

[A]$p<0.001$ rosuva 10 mg vs. A10, S10, S20, S40, P10, P20, P40; [B]$p<0.001$ rosuva 20 mg vs. A20, S20, S40, S80, P20, P40. [C]$p<0.002$ rosuva 20 mg vs. A40. [D]$p<0.001$ rosuva 40 mg vs. A40, S40, S80, P40 (for LDL-C). [a]$p<0.002$ vs. rosuva 10 mg, [b]$p<0.002$ vs. rosuva 20 mg, [c]$p<0.002$ vs. rosuva 40 mg (for all other parameters).

Jones PH *et al. Am J Cardiol* 2003;**92**:152–160.

Current Approach for Mixed Dyslipidemia



Treatment Objectives for Elevated *TG Levels*: NCEP Guidelines

TG 200- 499 mg/dL

High TG: At Risk for CHD

- Primary objective: LDL-C reduction
- Secondary objective: Non-HDL-C reduction

TG ≥500 mg/dL

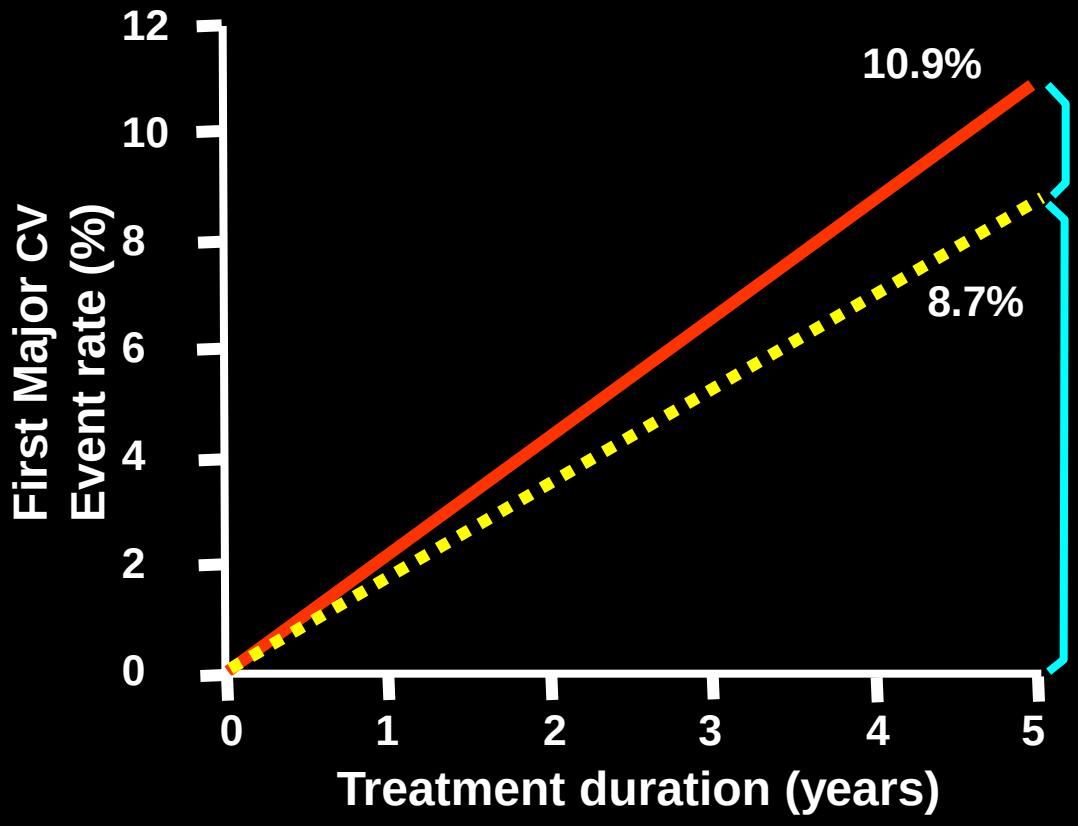
Very High TG: At Risk for Pancreatitis

- Primary objective: TG reduction
- Secondary objective: LDL-C and non–HDL-C reduction

Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). NIH Publication No. 02-5215; September 2002.

Treating to New Targets (TNT)

Intensive LDL-C lowering and residual risk of major cardiovascular disease events*



Relative Risk ↓ 22%

Modifiable Risk Factors

HDL-C, TG
Blood Pressure
Adiposity
Insulin resistance
Smoke
Inflammation

RESIDUAL CV RISK

Non-Modifiable Risk Factors

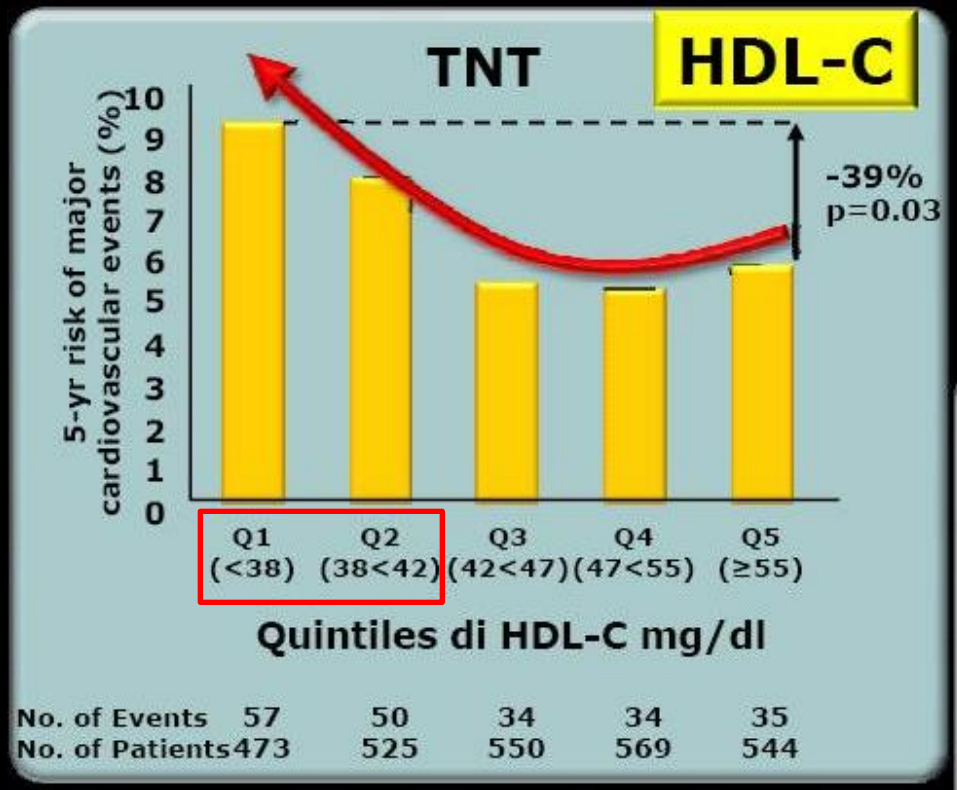
Age
Gender
Family history

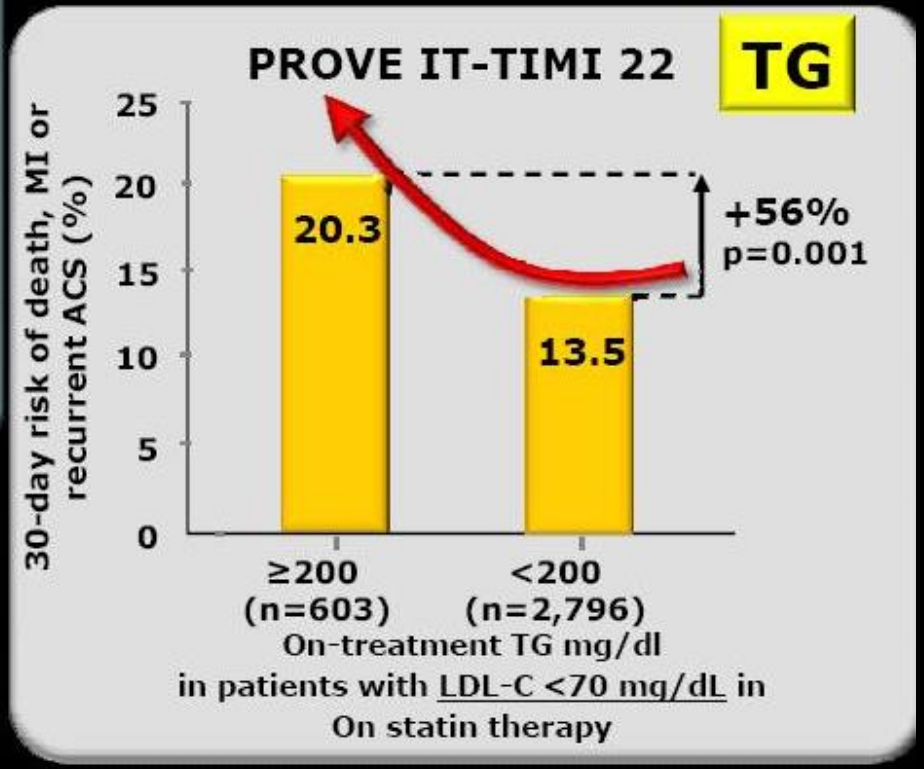
LDL-C: 100 mgl/dl (n=5006)
LDL-C: 70 mg/dl (n=4995)

* Composite of death from CHD, nonfatal MI, resuscitation after cardiac arrest, and fatal or nonfatal stroke.

(La Rosa 2005)

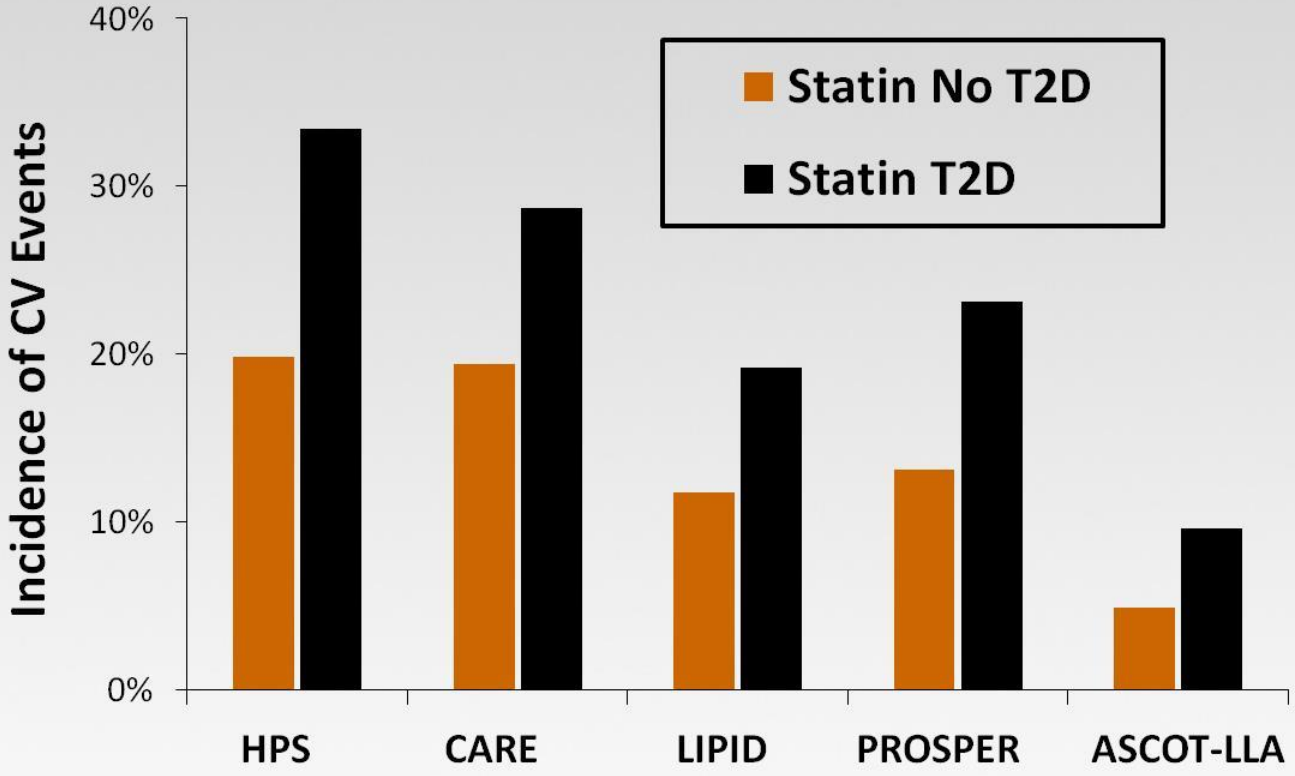
High Residual Risk associated with Low HDL-C and high TG even at optimal LDL-C levels (<70 mg/dl)





Barter P et al. *N Engl J Med.* 2007; 357:1301-10.
Miller M et al. *J Am Coll Cardiol.* 2008;51:724-30.

High Residual Risk of Diabetes: Observations from the Statin Trials



[1]HPS Collaborative Group. *Lancet*. 2003;361:2005-2016; [2]Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009, [3]LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; [5]Sever PS, et al. *Lancet*. 2003;361:1149-1158.

Lipid Levels and Risk of Major Cardiovascular Events in Statin-Treated Patients

Table 1. Lipid and Apolipoprotein Levels and Risk of Major Cardiovascular Events in Statin-Treated Patients[a]

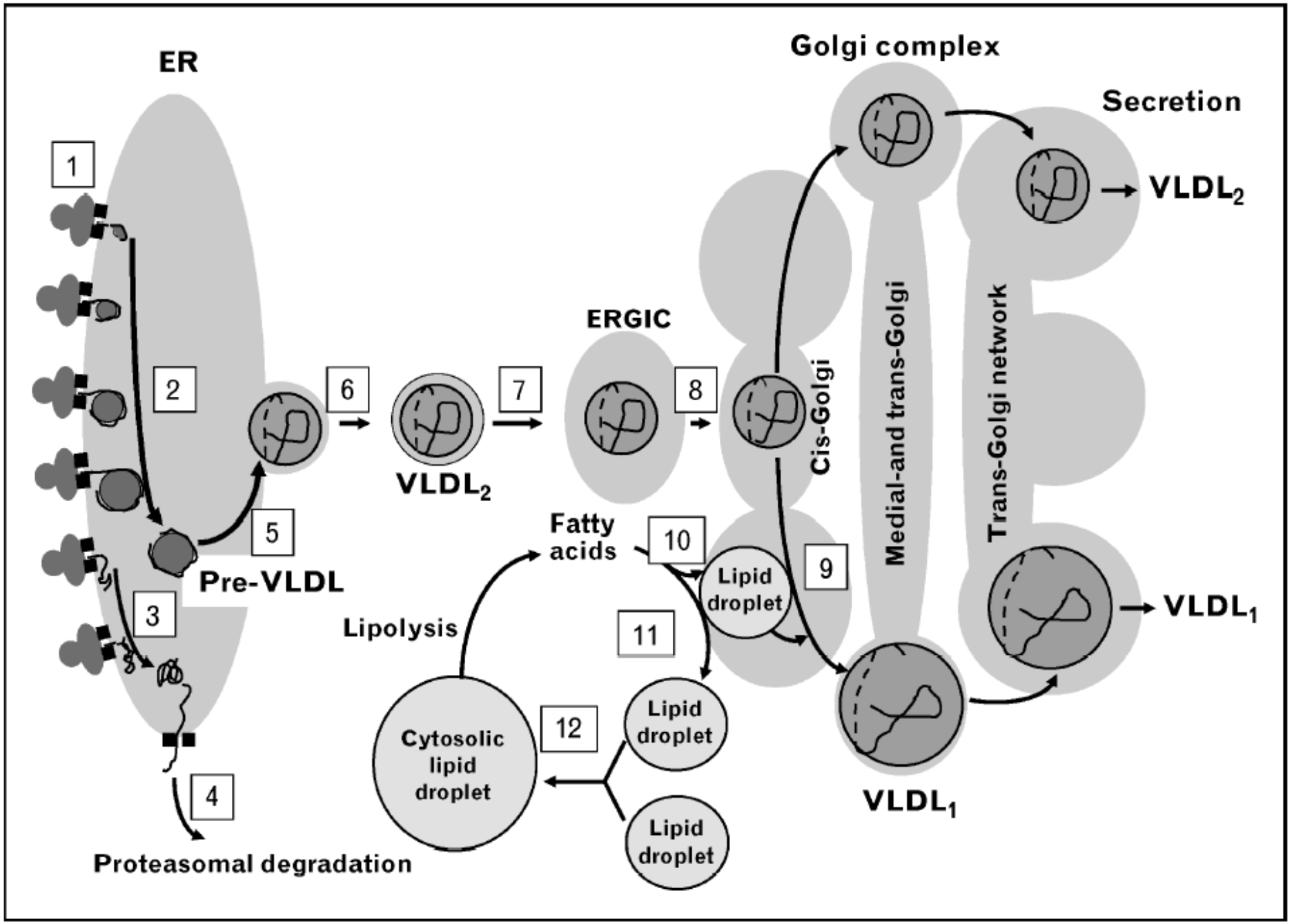
	Quartiles[b]				*P* Value[c]	per 1-SD Increase	*P* Value
	1	2	3	4			
LDL-C							
Mean, mg/dL	49	74	97	129			
Range, mg/dL	<62	62-85	86-108	≥109			
Event rate, %	7.3	14.2	17.1	17.9			
Events/total[d]	697/9538	1360/9573	1616/9478	1714/9564			
Hazard ratio (95% CI)[e]	1 [Reference]	1.06 (0.97-1.17)	1.15 (1.05-1.27)	1.26 (1.14-1.39)	<.001	1.13 (1.10-1.17)	<.001
Non–HDL-C							
Mean, mg/dL	69	98	124	161			
Range, mg/dL	<85	85-112	113-137	>137			
Event rate, %	7.3	14.2	16.4	18.7			
Events/total[d]	701/9659	1340/9404	1568/9564	1778/9526			
Hazard ratio (95% CI)[e]	1 [Reference]	1.12 (1.02-1.24)	1.17 (1.06-1.28)	1.42 (1.29-1.56)	<.001	1.16 (1.12-1.19)	<.001

JAMA. 2012;307(12):1302-1309

General Features of the Metabolic Syndrome and T2 DM

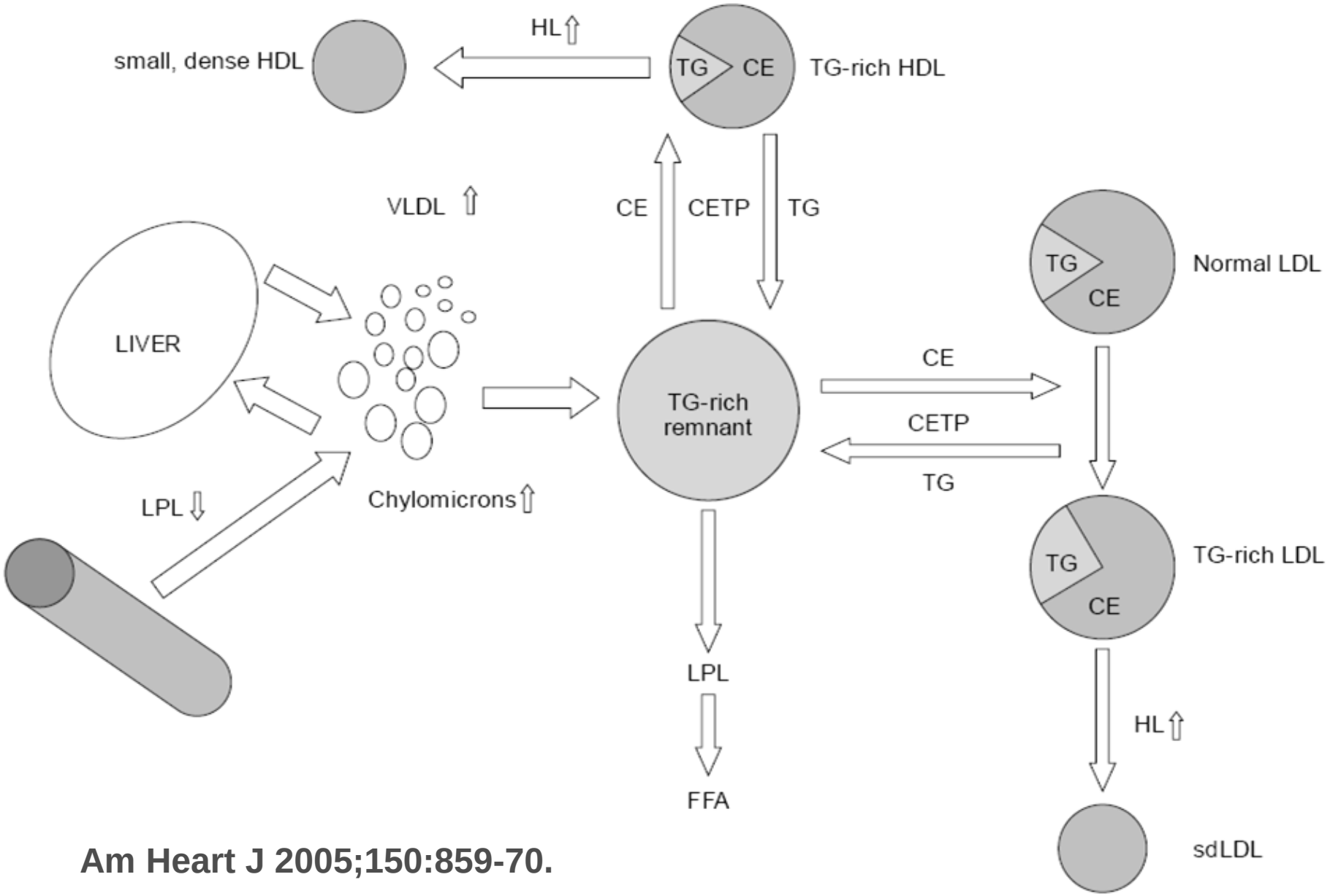
- Abdominal obesity
- Atherogenic dyslipidemia (lipid triad)
  - Elevated triglycerides
  - Small LDL particles
  - Low HDL cholesterol
- Raised blood pressure
- Insulin resistance (± glucose intolerance)
- Prothrombotic state
- Proinflammatory state

NCEP ATP III 2001



Curr Opin Lipidol 17:238–246. 2006

Proposed mechanism for generation of sdLDL and lowering of HDL



Am Heart J 2005;150:859-70.

Definitions for small, dense LDL

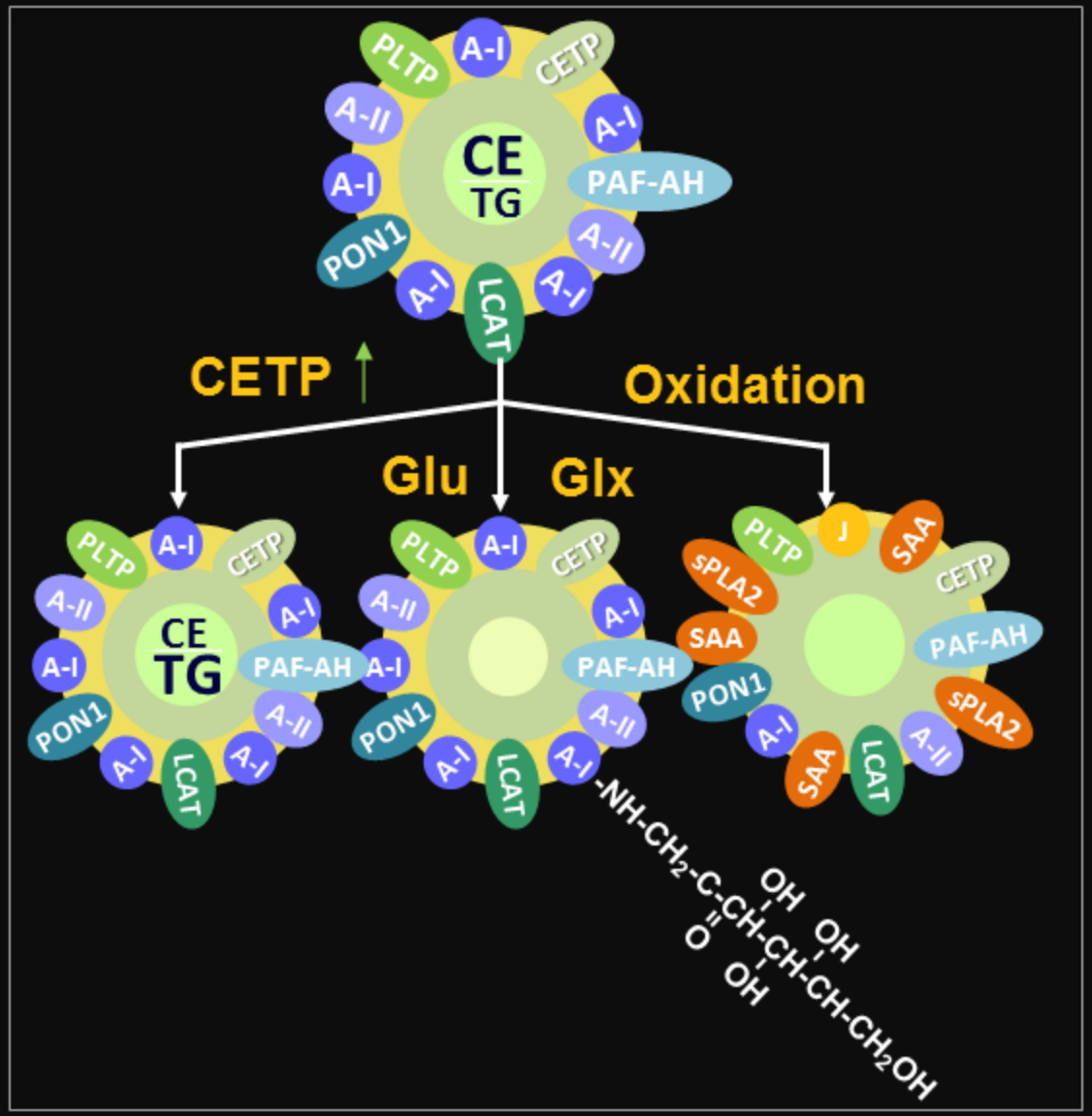
P·B·I

Lipoproteins	VLDL	L LDL	sd LDL *	HDL
Diameter (nm)	30 – 80	25.5 - 28.0	22.0 - 25.5	7 – 10
Density (g/mL)	<1.006	1.019 - 1.044	1.044 - 1.063	1.063 - 1.210

* Definition employed at Denka Seiken. The density range of 1.044 – 1.063 g/mL corresponds to a diameter range of 22.0 – 25.5 nm, that is, Pattern B.

Why is small dense LDL highly atherogenic?

- Small particle size favors the penetration of LDL particles into the arterial intima.
- The prolonged residence time of small dense LDL due to its poor binding to LDL receptor gives more time for particles to infiltrate into the arterial intima.
- Small dense LDL increase susceptibility to oxidation and glycation.
- Oxidized LDL in the intima trigger a cascade of processes leading to the formation of foam cells and the plaque formation.



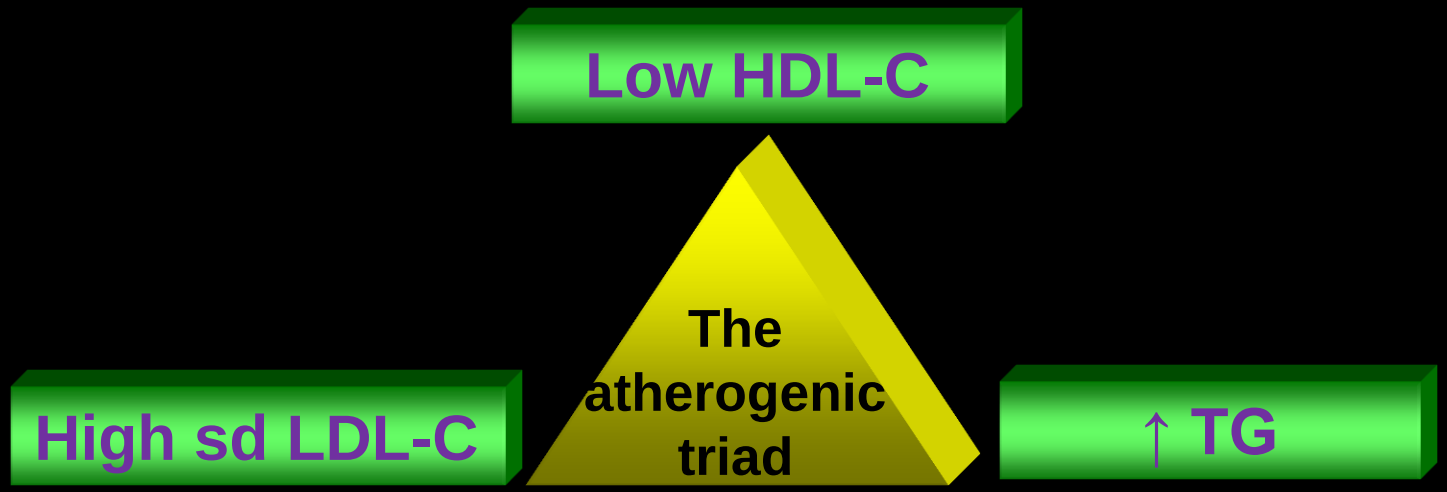
- ABCA1-mediated cholesterol efflux ↓
- LCAT activation ↓
- PON1 ↓
- Anti-oxidative activity ↓
- Protection against apoptosis ↓
- Stimulation of eNOS/NO ↓
- Inhibition of VCAM-1 and ICAM-1 expression ↓
- Inhibition of neutrophil infiltration ↓
- Stimulation of re-endothelialization ↓

Dysfunctional HDL in diabetes

Management of Diabetic Dyslipidemia

After LDL-C goal is met

- Atherogenic triad = ↑ TG + ↓HDL + ↑ Small dense LDL particles



Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA 2001;285:2486-2497.

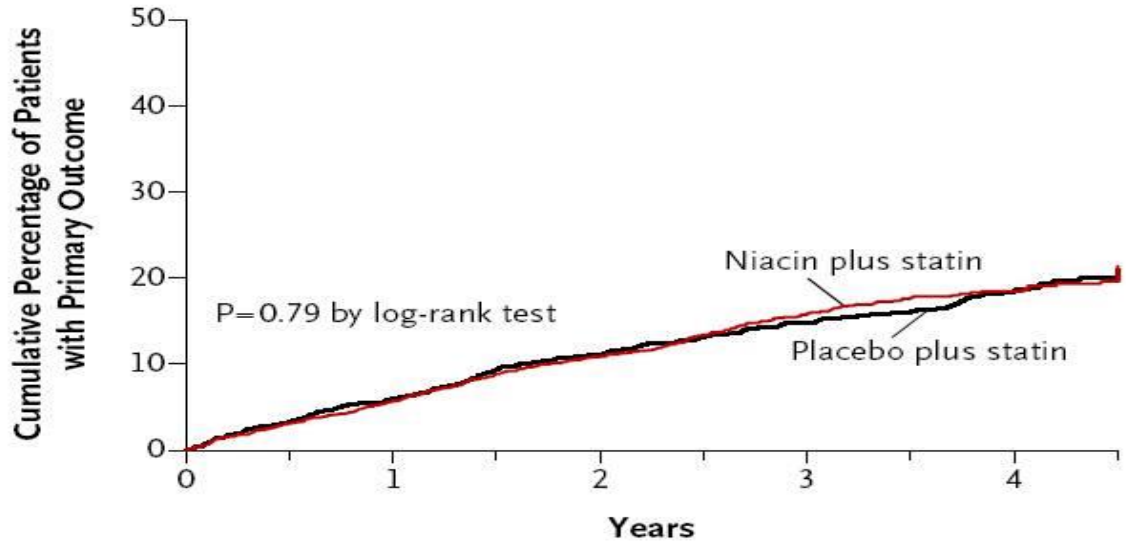
ESC/EAC guidelines

Table 18 Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias

• In combined dyslipidaemia an increase of HDL-C and a decrease of TG, on top of the LDL-C reduction that can be achieved with a statin, may be considered. Therefore a combination of statin with nicotinic acid can be considered, but the adverse effect of flushing may affect compliance.
• A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.
• If TG are not controlled by statins or fibrates, prescription of *n*-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.

European Heart Journal (2011) 32,1769-1818

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy



No. at Risk

Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428

Figure 1. Kaplan–Meier Curve for the Primary End Point.

• All patients received simvastatin, 40 to 80 mg per day, plus ezetimibe, 10 mg per day, if needed, to maintain an **LDL cholesterol level of 40 to 80 mg per deciliter**.

• The primary end point was the first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

AIM-HIGH trial. *N Engl J Med 2011;*365(24):2255-67.

Pharma & Healthcare |
12/20/2012 @ 9:58上午 |7,192 views
HPS2-THRIVE: No Benefit、Signal Of Harm For Niacin Therapy

- After a median follow up of 3.9 years, the combination of niacin and laropiprant ”did not significantly further reduce the risk of the combination of coronary deaths, non-fatal heart attacks, strokes or revascularizations compared to statin therapy,” according to Merck.
- Even more troubling, the company reported that there was “a statistically significant increase in the incidence of some types of non-fatal serious adverse events in the group that received extended-release niacin/laropiprant.”

Fibric Acid Derivatives

Bezafibrate

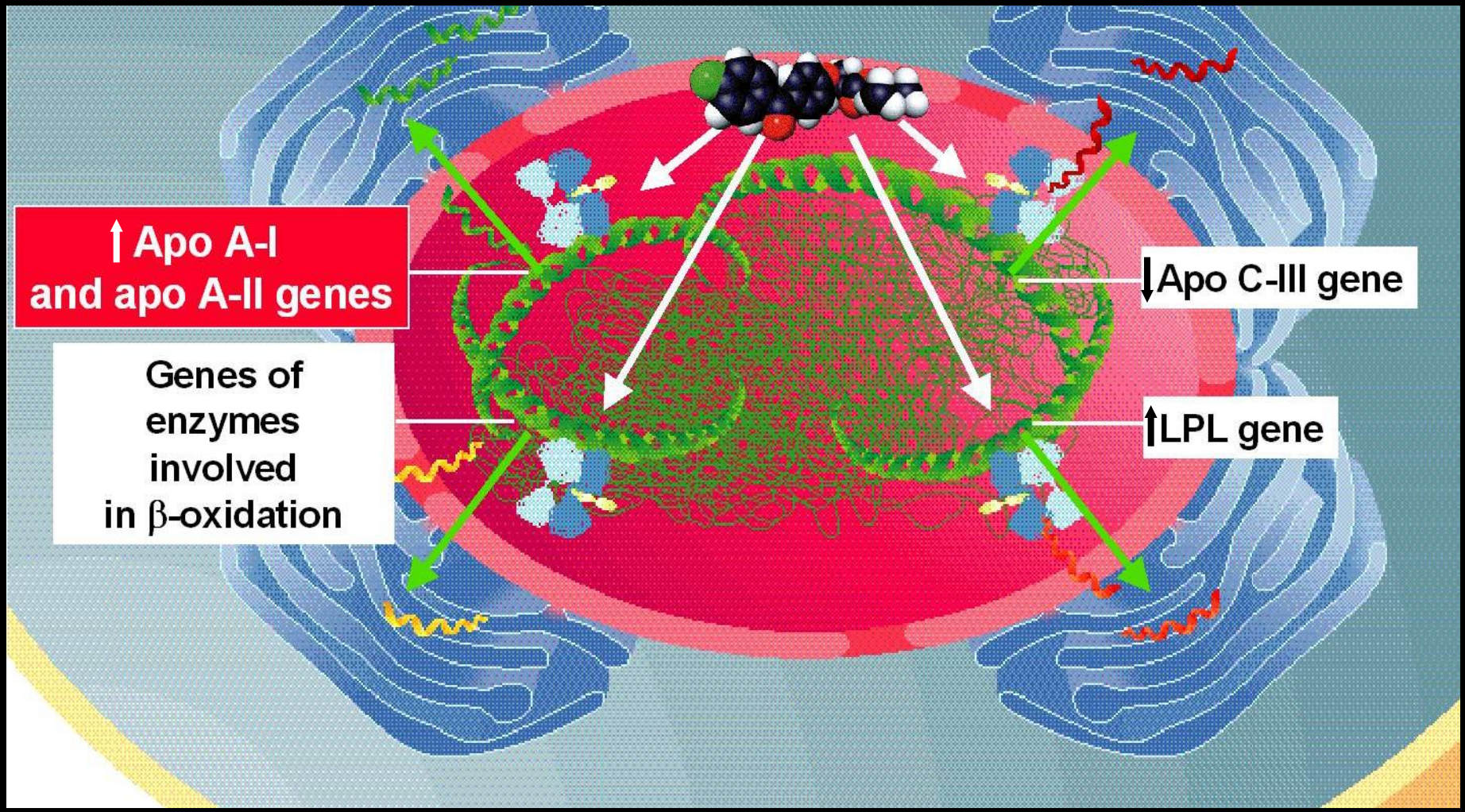
Ciprofibrate

Etofibrate

Fenofibrate

Gemfibrozil (Lopid)

Fenofibrate 的作用
~ 活化PPARα改善血脂之效果

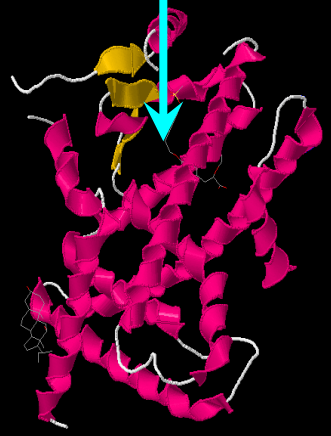


Fibrate mechanisms of action

Fibrate

↑ LDL particle size

↓ Triglycerides



diminished apo C-III production

increases LPL gene expression

PPARα

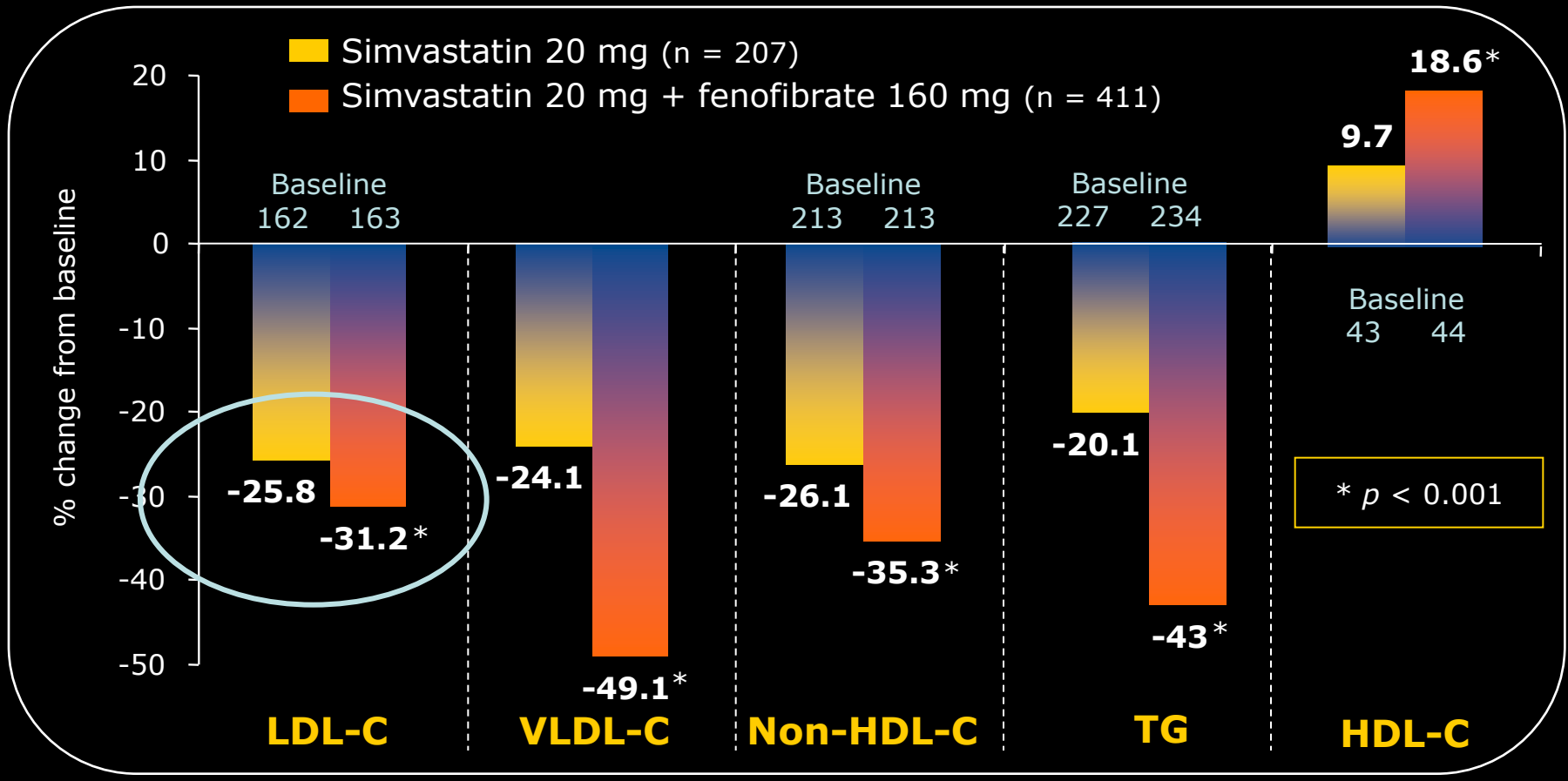
increases apo A-I and apo A-II gene expression

↑ HDL synthesis

Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia: the SAFARI trial

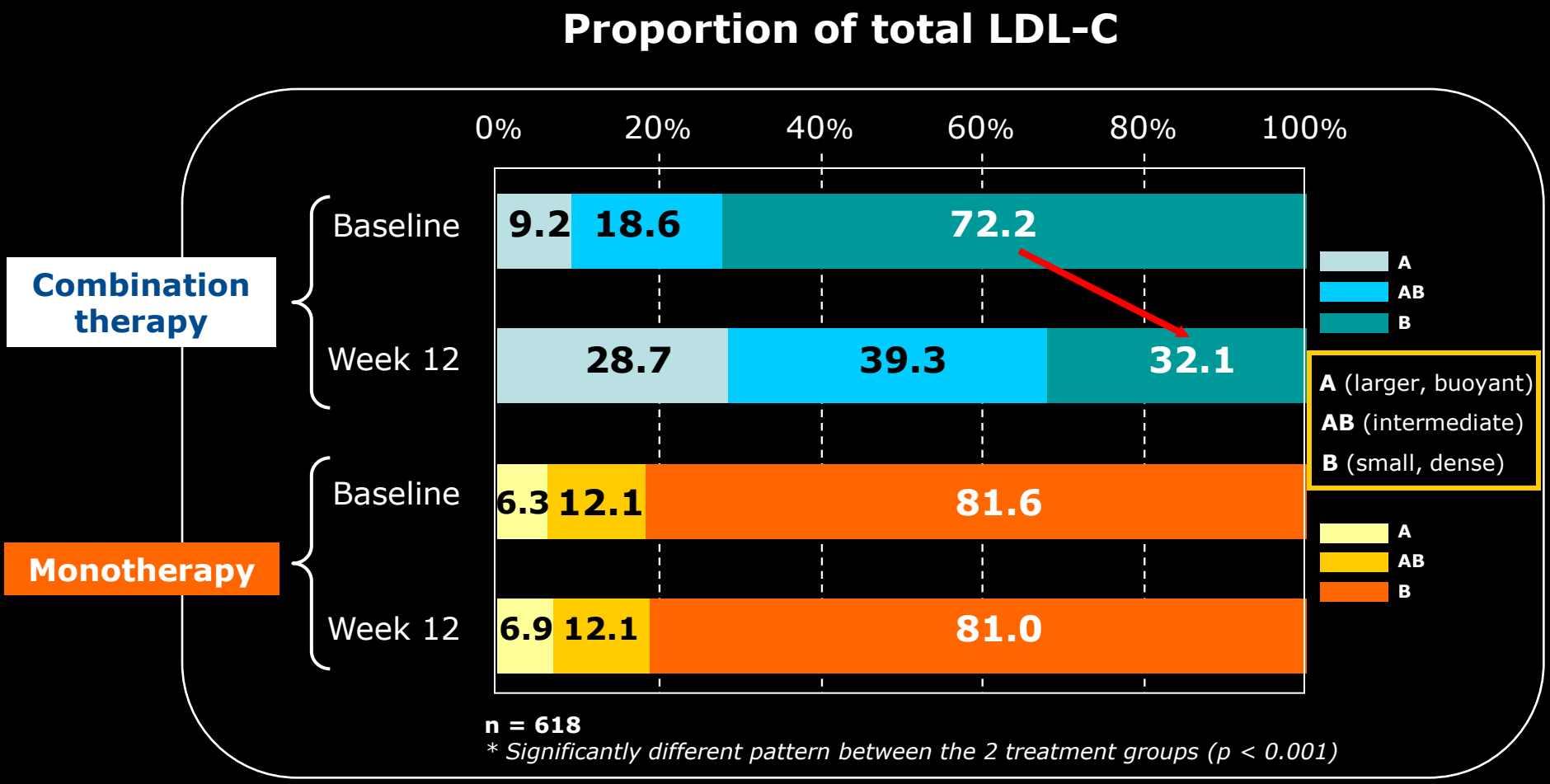
12-week, double-blind, randomized study in 618 patients with combined hyperlipidemia

(TG 150-500 mg/dl, LDL-cholesterol > 130 mg/dl)



Grundy et al. Am J Cardiol 2005;95:462-8

SAFARI trial: effects on LDL-cholesterol particle subclasses



Grundy et al. Am J Cardiol 2005;95:462-8

Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial

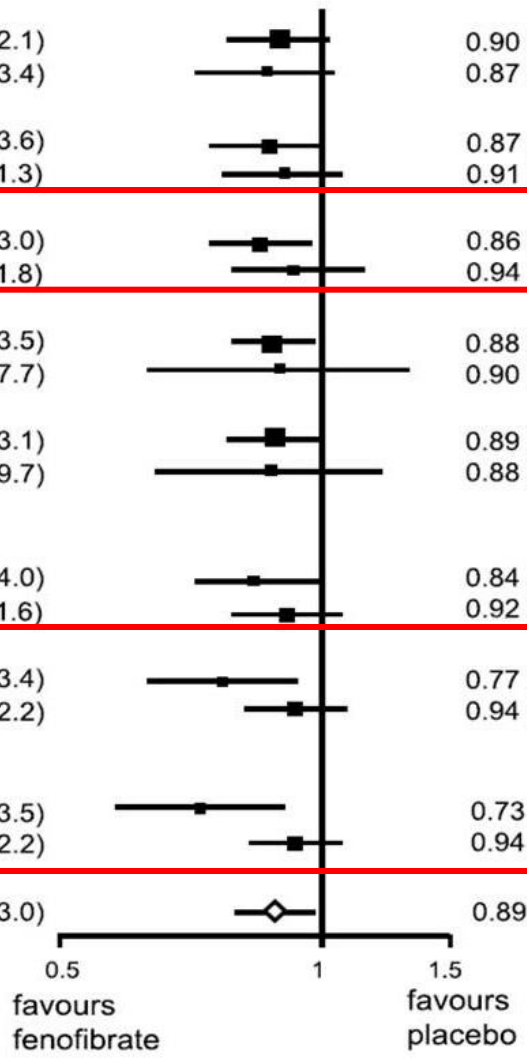
	Placebo (n=4900)		Fenofibrate (n=4895)		HR (95% CI)	Log-rank p
	Number (%)*	Rate/1000 person-years at risk	Number (%)*	Rate/1000 person-years at risk		
Primary outcome						
Coronary events	288 (6%)	11·7	256 (5%)	10·4	0·89 (0·75–1·05)	0·16
Coronary heart disease mortality	93 (2%)	3·7	110 (2%)	4·4	1·19 (0·90–1·57)	0·22
Non-fatal myocardial infarction	207 (4%)	8·4	158 (3%)	6·4	0·76 (0·62–0·94)	0·010

	Placebo group (n=4900)		Fenofibrate group (n=4895)	
	Change from baseline (%)	Number (%) at final visit*	Change from baseline (%)	Number (%) at final visit*
Cardiovascular medication				
Any antithrombotic	24·0	2744 (56%)	22·7	2688 (55%)
Aspirin	18·2	2348 (48%)	17·2	2291 (47%)
Other	9·2	622 (13%)	9·1	613 (13%)
Angiotensin-converting enzyme inhibitor	12·7	2348 (48%)	9·8	2197 (45%)
Angiotensin II receptor antagonist	14·8	991 (20%)	13·8	956 (20%)
β blocker	11·0	1290 (26%)	8·6	1179 (24%)
Calcium antagonist	7·1	1335 (27%)	5·4	1277 (26%)
Digoxin	5·6	201 (4%)	5·8	242 (5%)
Diuretic	7·7	1157 (24%)	5·0	1043 (21%)
Nitrate	5·6	577 (12%)	5·8	543 (11%)
Lipid-lowering agent†	36·0	1776 (36%)	19·0	944 (19%)
Blood-glucose-lowering medication				
Oral	9·9	3818 (78%)	9·7	3829 (78%)
Insulin	15·9	1464 (30%)	15·9	1467 (30%)

*Within 3 months of study close. †For this category only, defined as the cumulative number of patients who had used non-study lipid-lowering treatment for more than 3 months at any time. Signficant differences at study close: angiotensin-converting enzyme inhibitors p=0·003, β blockers p=0·011, diuretics p=0·006, digoxin p=0·045, lipid-lowering agents p=<0·0001.

Table 4: **Patients on concominant medication between baseline and study close**

	Placebo (n=4900) n (%)	Placebo (n=4900) total CVD(%)	Fenofibrate (n=4895) n (%)	Fenofibrate (n=4895) total CVD(%)	HR (95% CI)	p value	p for interaction
Increased Waist							
yes	3320(67.8)	443(13.3)	3327 (68.0)	402 (12.1)	0.90 (0.78, 1.03)	0.119	
no	1580(32.2)	240(15.2)	1568 (32.0)	210 (13.4)	0.87 (0.72, 1.04)	0.135	0.777
TG ≥1.7 mmol/L							
yes	2525(51.5)	388(15.4)	2568 (52.5)	349 (13.6)	0.87 (0.75, 1.00)	0.057	
no	2375(48.5)	295(12.4)	2327 (47.5)	263 (11.3)	0.91 (0.77, 1.07)	0.263	0.704
Reduced HDLc							
yes	2896(59.1)	437(15.1)	2924 (59.7)	379 (13.0)	0.86 (0.75, 0.99)	0.030	
no	2004(40.9)	246(12.3)	1971 (40.3)	233 (11.8)	0.94 (0.79, 1.12)	0.493	0.446
Hypertension							
yes	4095(83.6)	612(14.9)	4086 (83.5)	550 (13.5)	0.88 (0.79, 0.99)	0.034	
no	805(16.4)	71 (8.8)	809 (16.5)	62 (7.7)	0.90 (0.64, 1.27)	0.544	0.914
MS criteria							
yes	4103(83.7)	593(14.5)	4080 (83.4)	533 (13.1)	0.89 (0.79, 1.00)	0.052	
no	797(16.3)	90 (11.3)	815 (16.6)	79 (9.7)	0.88 (0.65, 1.19)	0.375	0.910
TG ≥1.7 mmol/L reduced HDLc							
yes	1824 (37.2)	296 (16.2)	1886 (38.5)	264 (14.0)	0.84 (0.71, 1.00)	0.044	
no	3076 (62.8)	387 (12.6)	3009 (61.5)	348 (11.6)	0.92 (0.79, 1.06)	0.24	0.468
TG ≥2.3 mmol/L							
yes	1222 (24.9)	210(17.2)	1295 (26.5)	173 (13.4)	0.77 (0.63, 0.94)	0.010	
no	3678 (75.1)	473(12.9)	3600 (73.5)	439 (12.2)	0.94 (0.83, 1.07)	0.344	0.093
TG ≥2.3 mmol/L reduced HDLc							
yes	970 (19.8)	173 (17.8)	1044(21.3)	141 (13.5)	0.73 (0.58, 0.91)	0.005	
no	3930 (80.2)	510 (13.0)	3851(78.7)	471 (12.2)	0.94 (0.83, 1.06)	0.321	0.053
Any criteria	4900 (100)	683 (14.0)	4895 (100)	612 (13.0)	0.89 (0.80, 0.99)	0.032	



FIELD study

Diabetes Care 32:493–498, 2009

ACCORD Lipid

3 treatment strategies were tested

	Intensive	Standard
A1C	**<6%**	**<7.5%**
SBP	**<120 mm Hg**	**<140 mm Hg**
Lipids	**Statin to ↓ LDL + Fenofibrate to↑HDL-C and ↓ TG**	**Statin to ↓ LDL alone**

A1C = glycosylated hemoglobin. Available at: www.accordtrial.org/public/purpose.cfm.

ACCORD Lipid

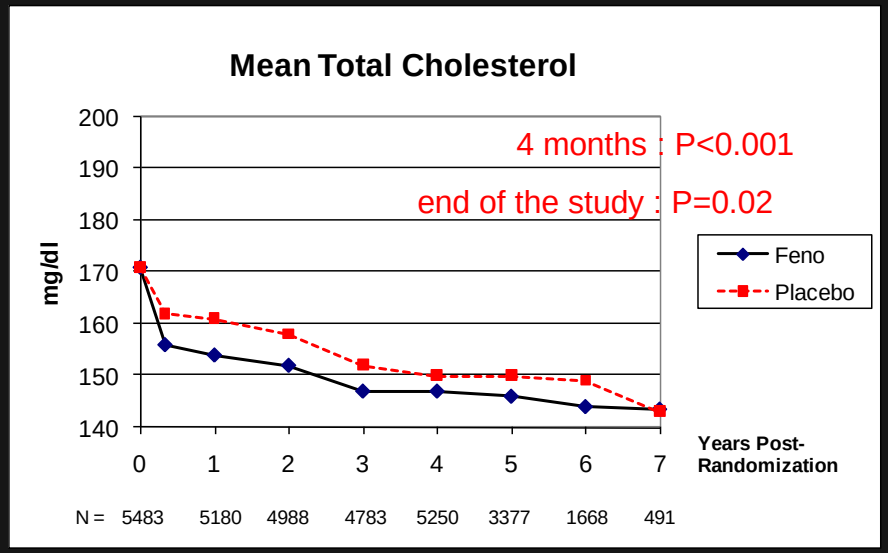
Baseline Characteristics – Lipids

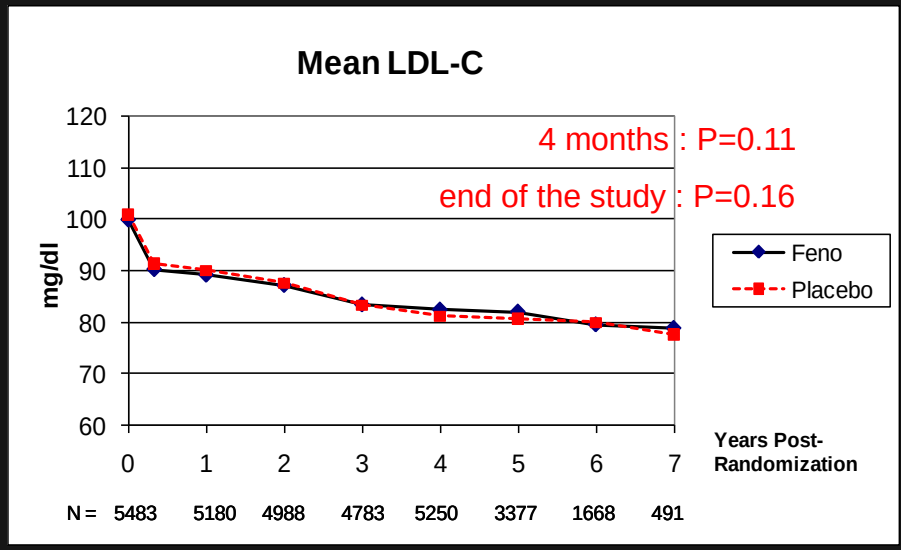
Baseline lipids	Simvastatin + Fenofibrate (n=2,765)	Simvastatin (n=2,753)	Overall (n=5,518)
Mean total cholesterol	174.7	175.7	175.2
Mean LDL-C	100.0	101.1	100.6
Mean HDL-C	38.0	38.2	38.1
Median TG	164	160	162

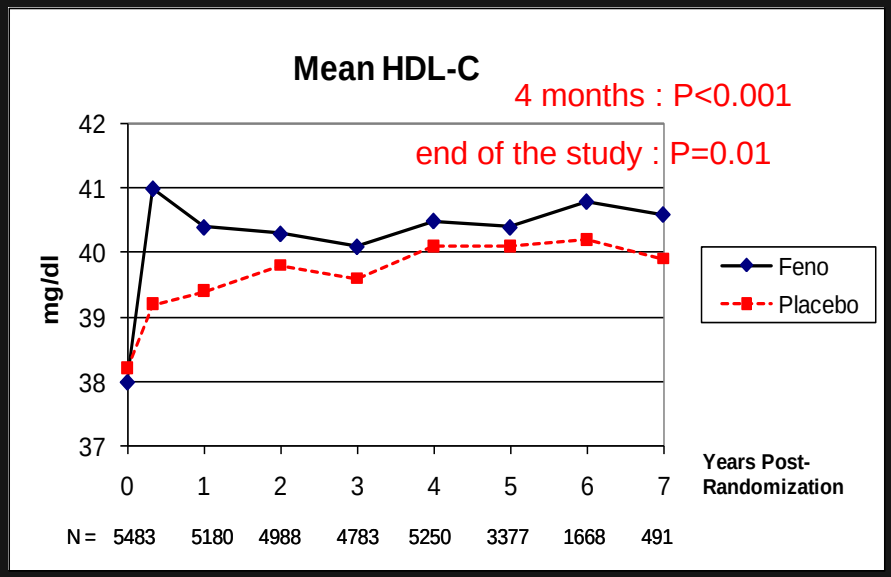
Data presented as mg/dL. To convert values for cholesterol to mmol/L, multiply by 0.02586. To convert triglycerides to mmol/L, multiply by 0.01129.

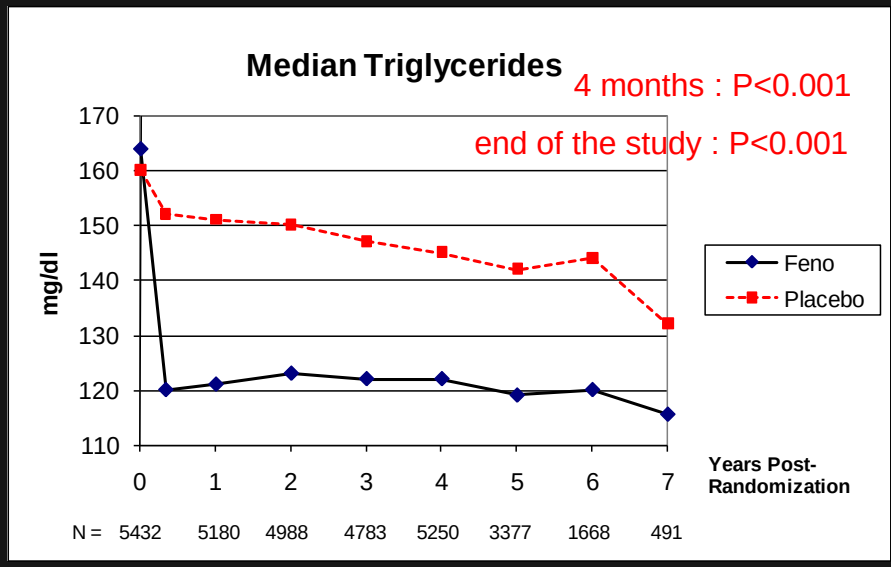
ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

Effects of fenofibrate on lipid levels

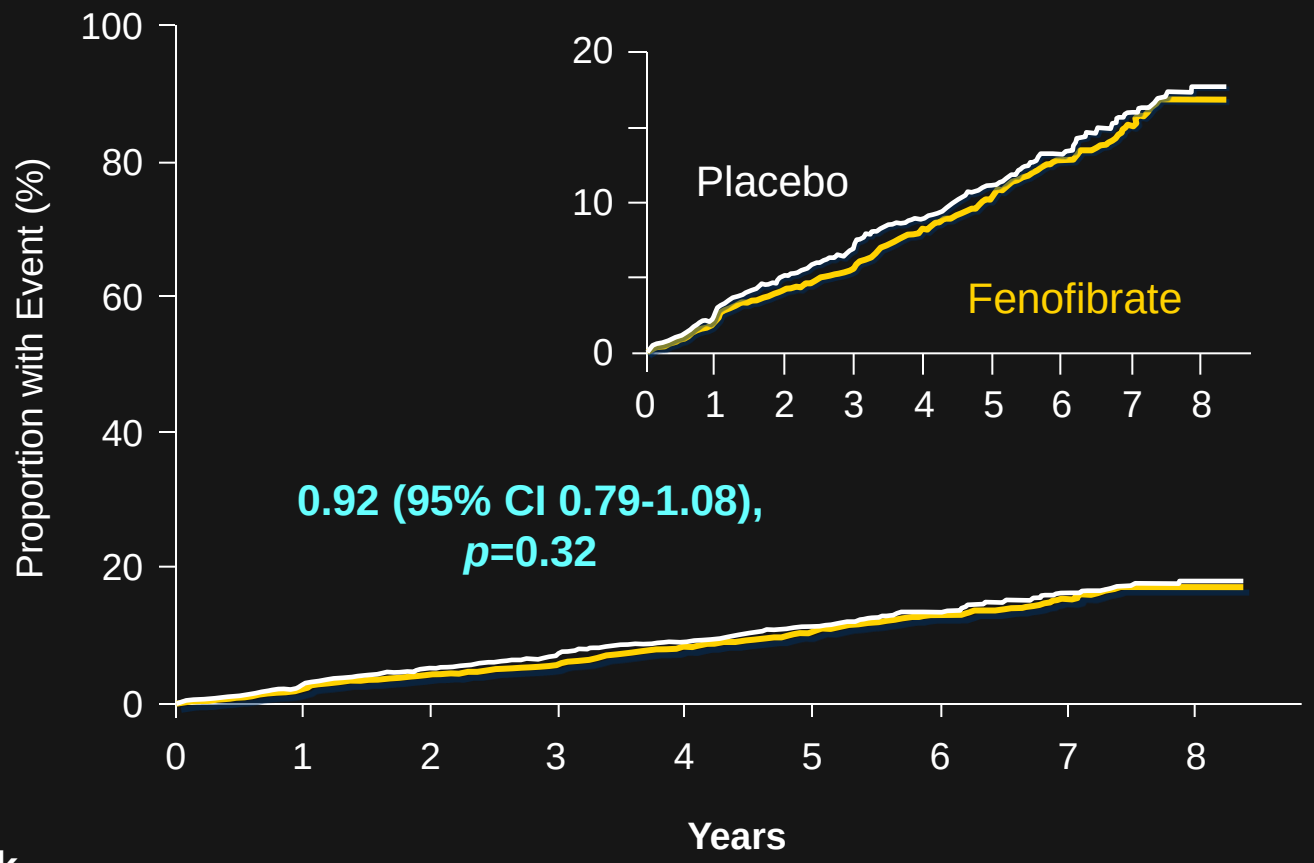








Primary endpoint
Major CV events (overall population)



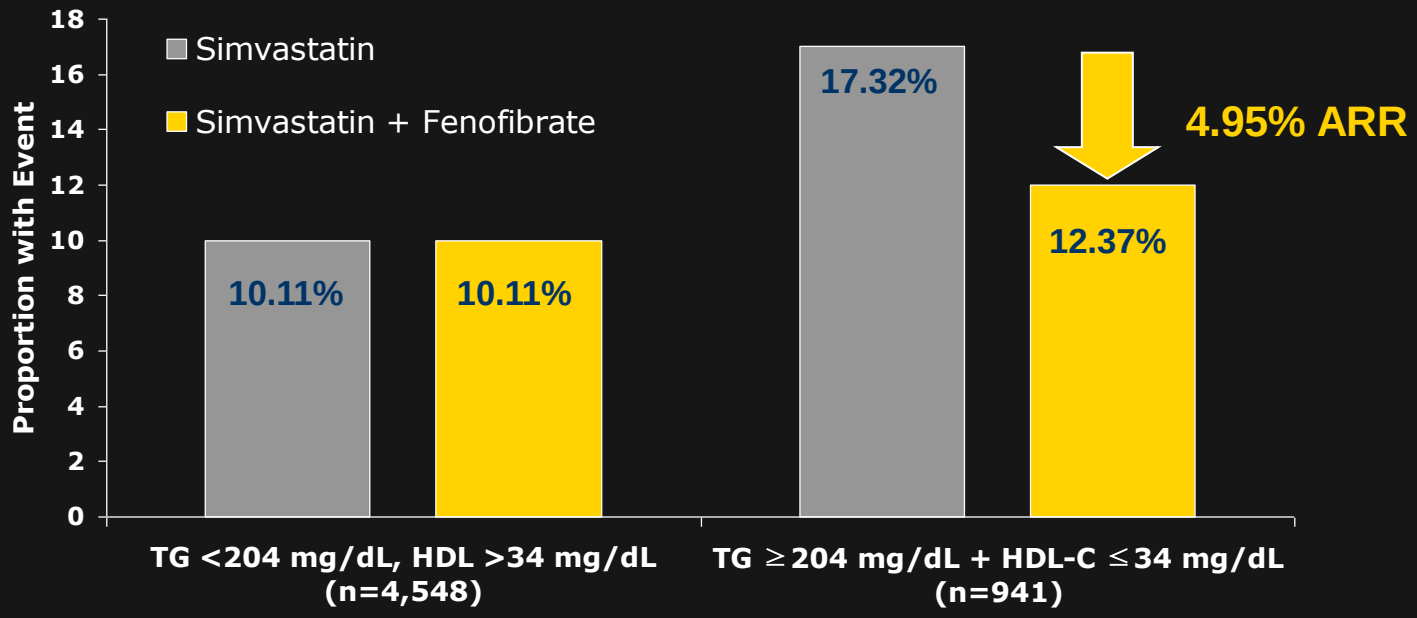
No. At Risk									
Fenofibrate	2765	2644	2565	2485	1981	1160	412	249	137
Placebo	2753	2634	2528	2442	1979	1161	395	245	131

Major CV events defined as CV death, nonfatal MI and nonfatal stroke

ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

Fenofibrate reduces the residual risk associated with elevated TG and low HDL-C

- Patients in the dyslipidaemia subgroup had a 70% higher relative risk of major CV events* compared to those with TG <204 mg/dL and HDL >34 mg/dL, despite achieving a mean LDL-C of 80 mg/dL

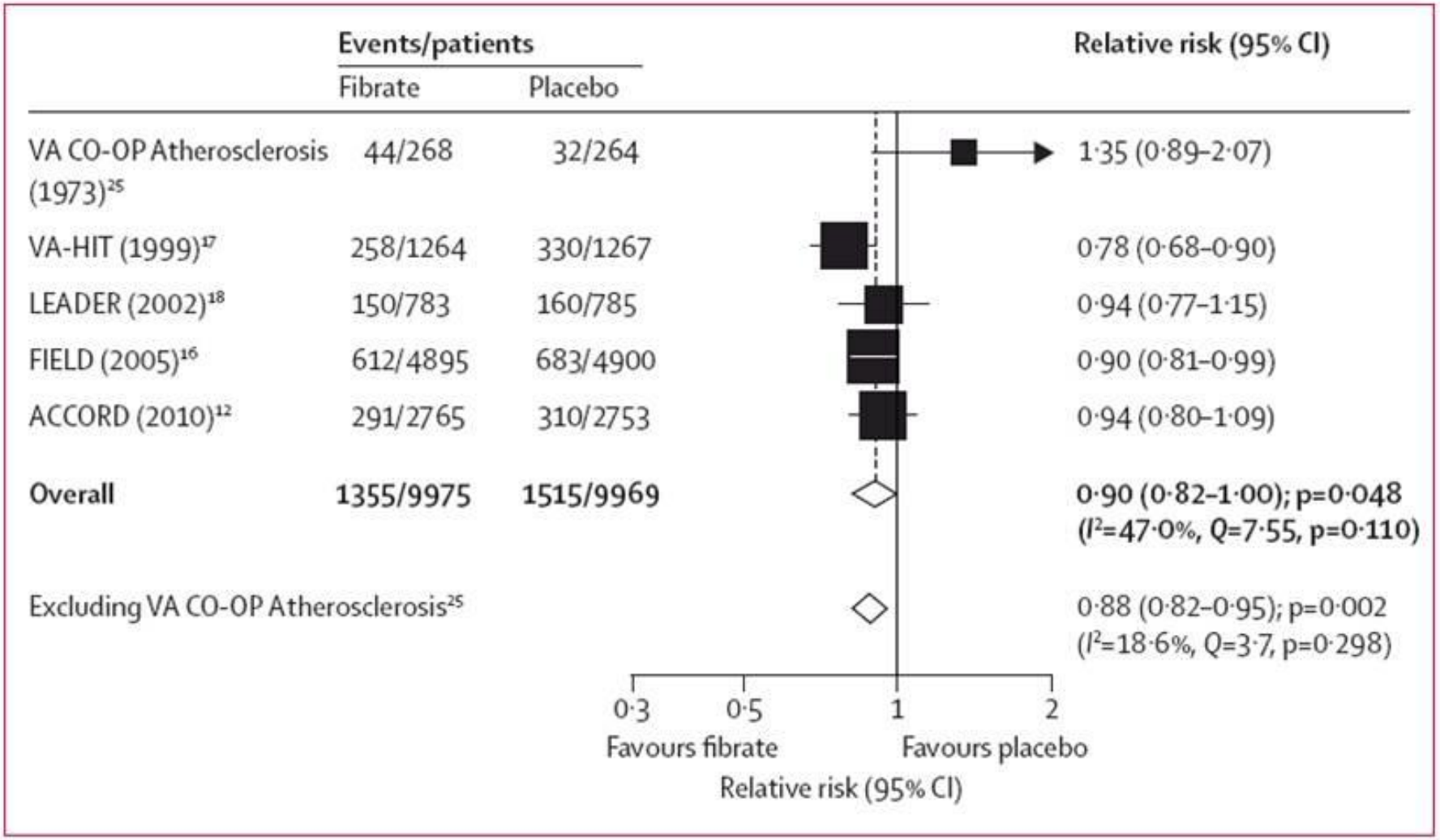


ARR: absolute risk reduction

*Major CV events defined as CV death, nonfatal MI and nonfatal stroke

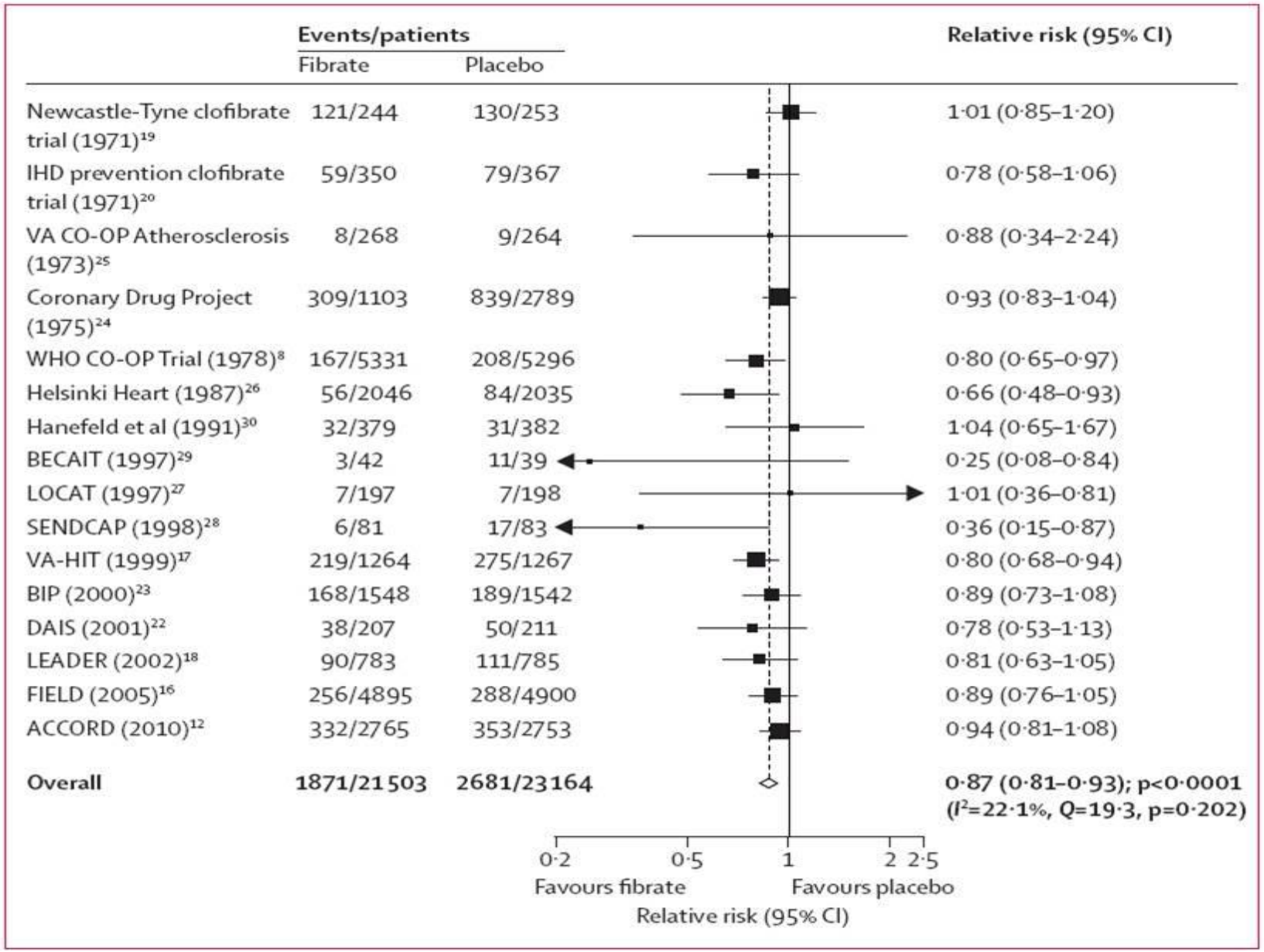
ACCORD Study Group. N Engl J Med March 14, 2010. Epub.

Effect of fibrates on risk of major cardiovascular outcomes



Lancet 2010; 375: 1875–84

Effect of fibrates on risk of coronary events



Lancet 2010; 375: 1875–84

Combination Lipid Therapy in Type 2 Diabetes

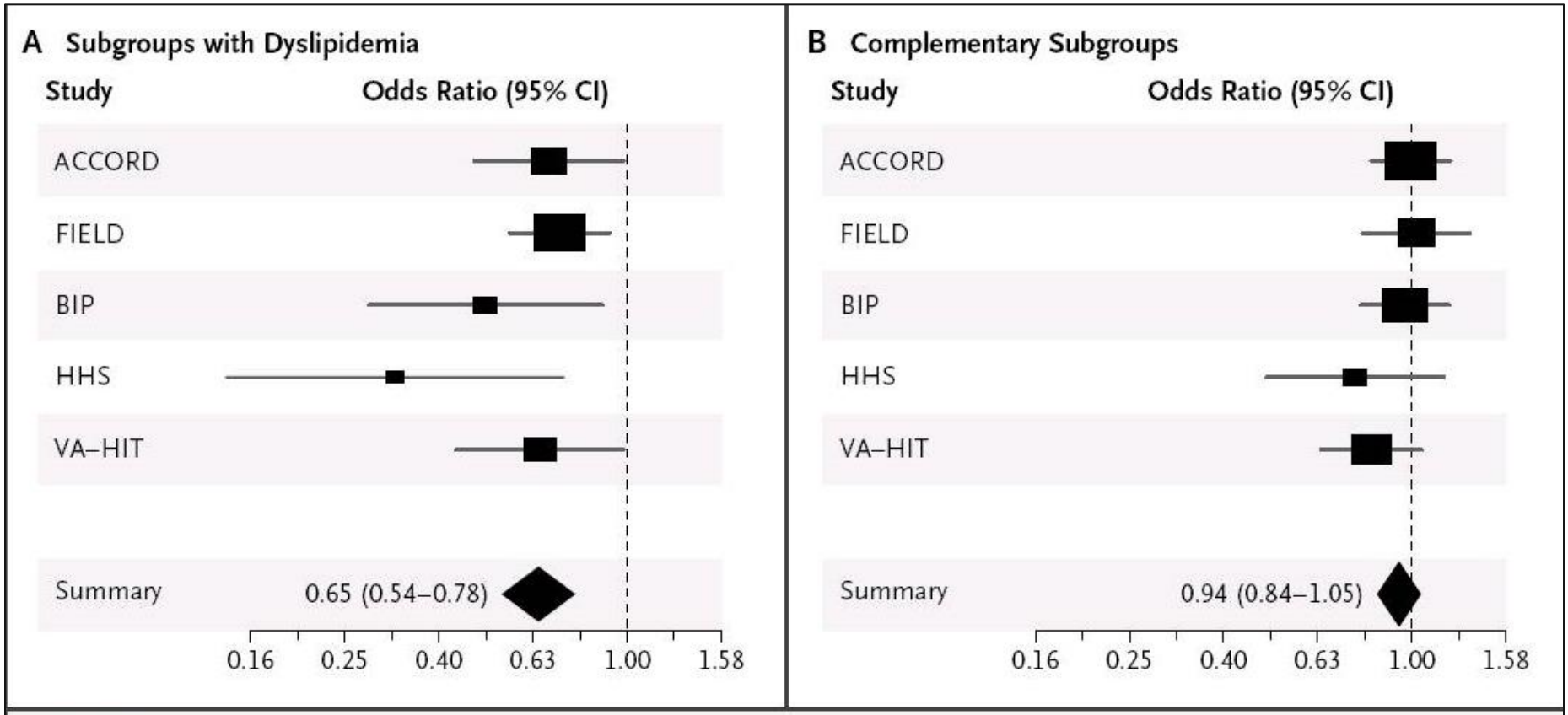
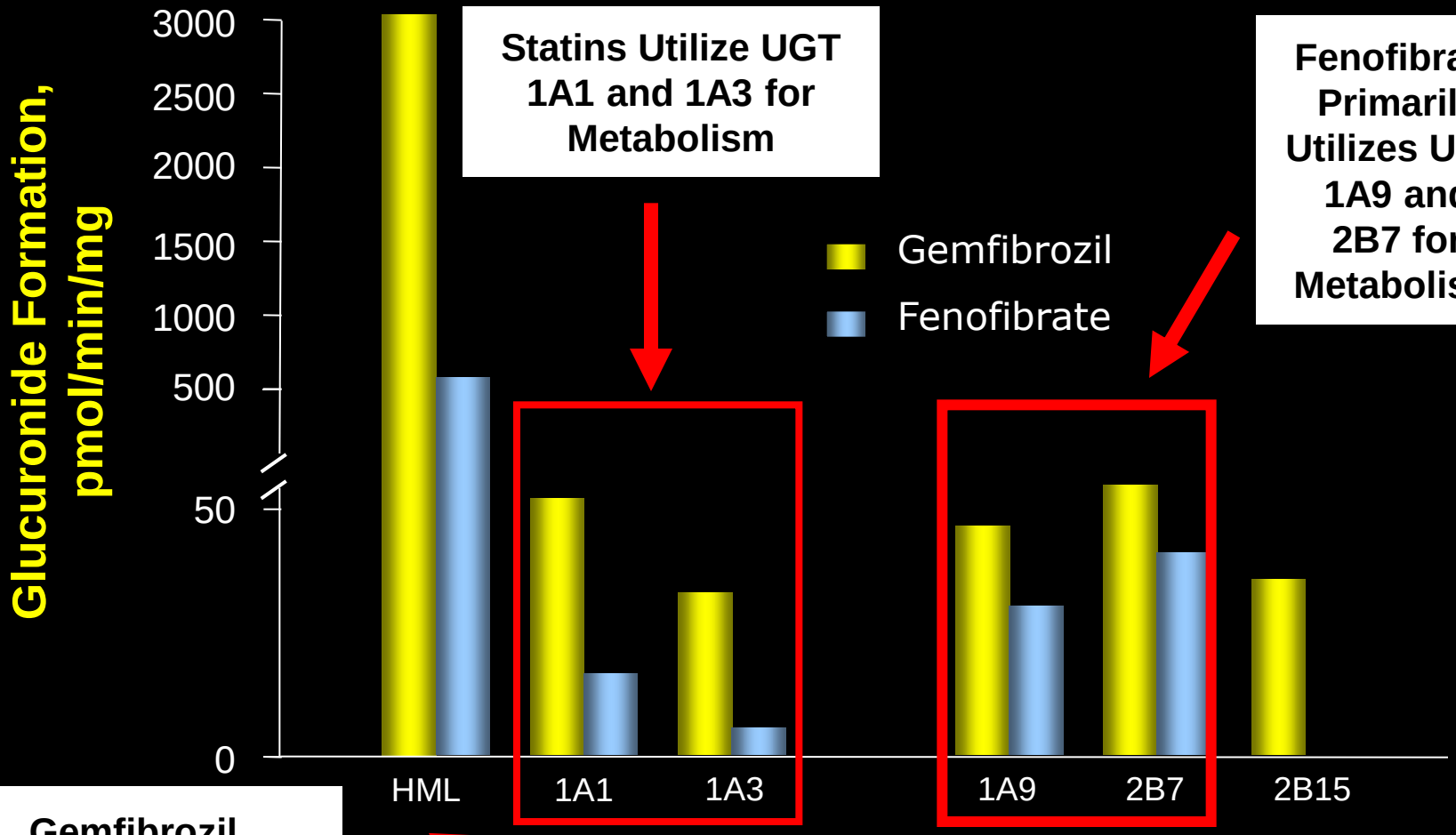


Figure 1. Forest Plot of the Treatment Effect in Subgroups.

Data from a meta-analysis of randomized trials of fibrate drugs are shown; an odds ratio of less than unity indicates a beneficial therapeutic effect. Panel A shows data from subgroups of patients with dyslipidemia (i.e., high levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol), and Panel B shows data from the complementary subgroups without this type of dyslipidemia. The subgroup with dyslipidemia defined according to criteria prespecified in the ACCORD Lipid trial (a triglyceride level of ≥204 mg per deciliter and an HDL cholesterol level of ≤34 mg per deciliter) and the subgroup with levels closest to these lipid criteria in each of the other trials were used.

N Engl J Med. 2010;363:692-5

Glucuronidation of Fibrates



UGT = UDP glucuronosyltransferases

Drug Metab Dispos 2002;30:1280-1287.

J Pharmacol Exper Ther 2002;301:1042-1051

Statin-fibrate combination therapy: pharmacokinetic interactions

	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max} (expected)	No clinically relevant interaction
Simvastatin	↑ in C_{max} by 2-fold	
Pravastatin	↑ in C_{max} by 2-fold	
Rosuvastatin	↑ in C_{max} by 2-fold	
Fluvastatin	No effect	
Cerivastatin	↑ in C_{max} by 2- to 3-fold	
Lovastatin	↑ in C_{max} by 2.8-fold	Not available

Pan et al. J Clin Pharmacol 2000;40:316-23
Backman et al. Clin Pharmacol Ther 2000;68:122-9
Kyrklund et al. Clin Pharmacol Ther 2001;69:340-5
Backman et al. Clin Pharmacol Ther 2002;72:685-91
Davidson et al. Am J Cardiol 2002;90 (suppl):50K-60K
Prueksaritanont et al. Drug Metab Dispos 2002;30:1280-7
Martin et al. Clin Ther 2003; 25: 459-71

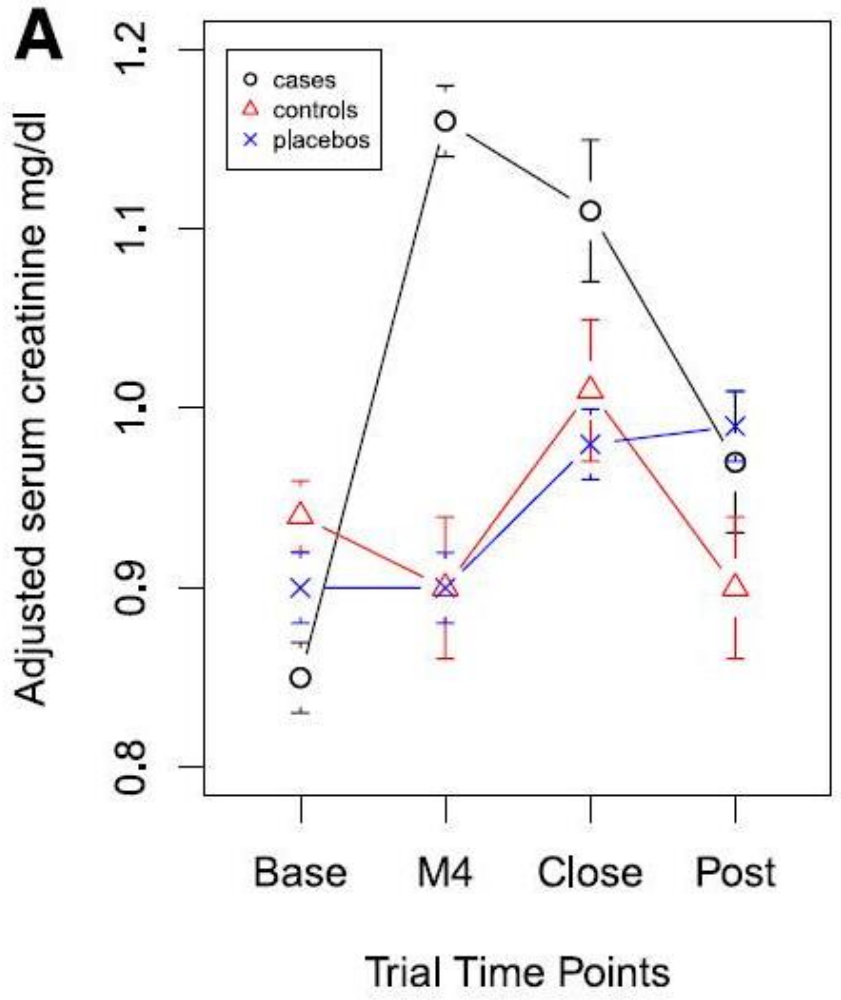
Follow-up Adverse Events in ACCORD Lipid Trial

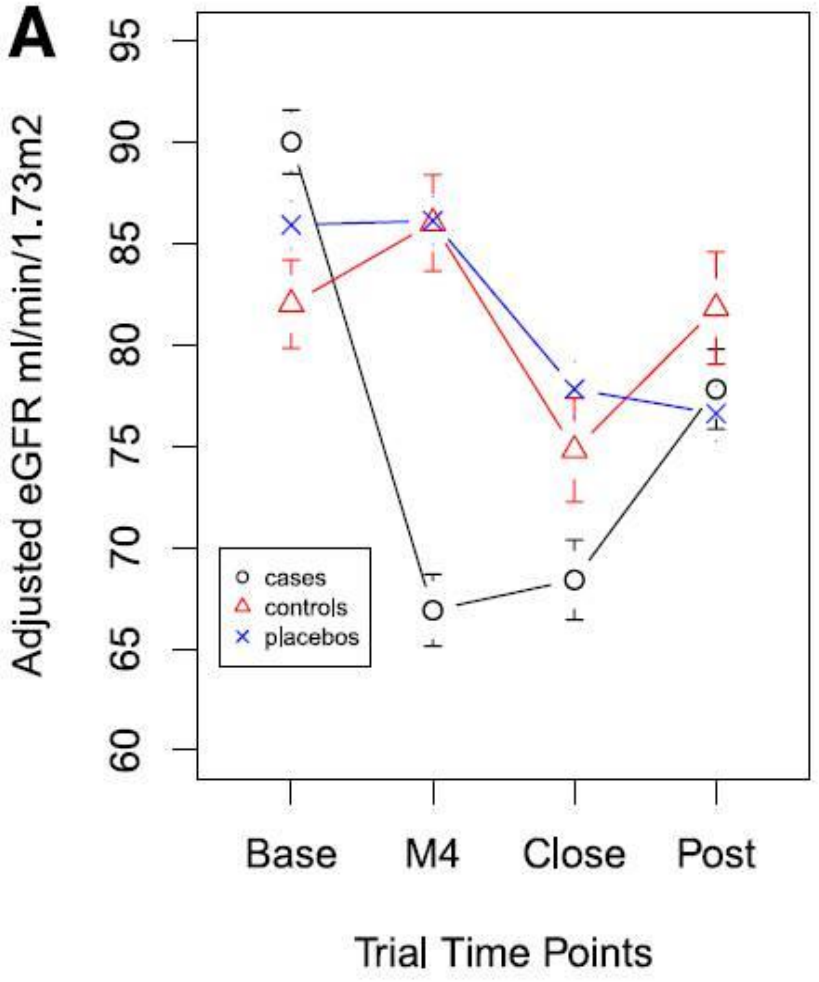
	Fenofibrate (N=2765)	Placebo (N=2753)	P value
Serious adverse events [SAEs] (no. (%))			
Any occurrence of out of the ordinary severe muscle aches/pains not associated with known activities:			
These aches/pains, regardless of CPK	1110 (40.1%)	1115 (40.5%)	0.79
These aches/pains, Plus CPK > 5 X ULN	7 (0.3%)	8 (0.3%)	0.79
These aches/pains, Plus CPK > 10 X ULN*	1 (0.04%)	2 (0.07%)	0.62
Any nonhypoglycemic SAE	54 (2.0%)	43 (1.6%)	0.27
Any Myopathy/Myositis/ Rhabdomyolysis SAE*	4 (0.1%)	3 (0.1%)	1.00
Any Hepatitis SAE*	3 (0.1%)	0 (0.0%)	0.25
Any SAE attributed to lipid Medications	27 (1.0%)	18 (0.7%)	0.18
Other Safety Results (no. (%))			
Any gall bladder-related event	7 (0.3%)	5 (0.2%)	0.57
Pulmonary emboli	0	0	---
Deep vein thrombosis	0	0	---

Follow-up Laboratory Measures in ACCORD Lipid Trial

	Fenofibrate (N=2765)	Placebo (N=2753)	P value
Laboratory Measures (no. (%))			
ALT ever > 3X ULN	52 (1.9%)	40 (1.5%)	0.21
ALT ever > 5X ULN	16 (0.6%)	6 (0.2%)	0.03
CPK ever > 5X ULN	51 (1.9%)	59 (2.2%)	0.43
CPK ever > 10X ULN	10 (0.4%)	9 (0.3%)	0.83
Serum creatinine elevation			
Women ever > 1.3 mg/dl	235 (27.9%)	157 (18.7%)	<0.001
Men ever > 1.5 mg/dl	698 (36.7%)	350 (18.5%)	<0.001
Post-randomization incidence of microalbuminuria (≥ 30 to < 300 mg/g**)	1050 (38.2%)	1137 (41.6%)	0.01
Post-randomization incidence of macroalbuminuria (≥ 300 mg/g**)	289 (10.5%)	337 (12.3%)	0.04

Reversibility of Fenofibrate Therapy–Induced Renal Function Impairment in ACCORD Type 2 DM Participants





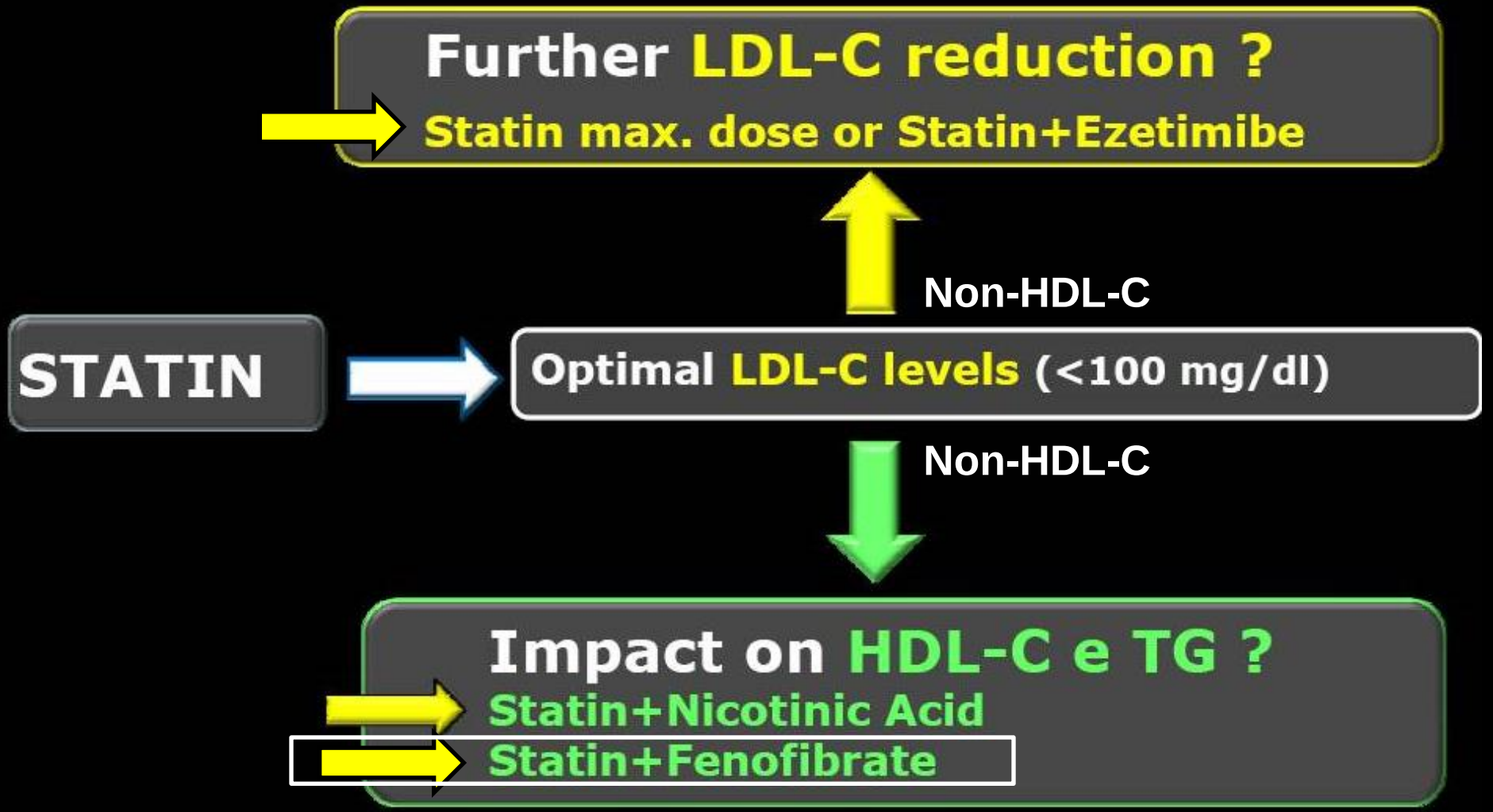
Fenofibrate case subjects (n = 321, ≧20% increase after 3 months of therapy); fenofibrate control subjects (n = 175, ≦2% increase); and placebo control subjects (n = 565).

Diabetes Care 35:1008–1014, 2012

Possible risk of statins?

- **Statin related myopathy.**
- **Liver injury.**
- **Statin related cognitive adverse event.**
- **Development of T2DM.**

Current Approach for Mixed Dyslipidemia



原給付規定

2.6. 降血脂藥物 Drugs used for dyslipidemia

2.6.1.全民健康保險降血脂藥物給付規定表（86/1/1、87/4/1、87/7/1、91/9/1、93/9/1、97/7/1）

治療起步準則	血脂異常之	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）	有下列情況之一時，應給予三至六個月非藥物治療	TC	≧200mg/dL	V	×	< 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	V	×	< 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)		×	V	< 200mg/dL (87/4/1)	
有心血管疾病或糖尿病患者	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)		×	V	< 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)							

Statin

2.6. 降血脂藥物 Drugs used for dyslipidemia

2.6.1.全民健康保險降血脂藥物給付規定表（86/1/1、87/4/1、87/7/1、91/9/1、93/9/1、97/7/1、102/8/1）

全民健康保險降膽固醇藥物給付規定表

	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患者	與藥物治療可並行	TC≧160mg/dL 或 LDL-C≧100mg/dL	TC＜160mg/dL 或 LDL-C＜100mg/dL	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≧200mg/dL 或 LDL-C≧130mg/dL	TC＜200mg/dL 或 LDL-C＜130mg/dL	
1 個危險因子	給藥前應有 3-6 個月非藥物治療	TC≧240mg/dL 或 LDL-C≧160mg/dL	TC＜240mg/dL 或 LDL-C＜160mg/dL	
0 個危險因子	給藥前應有 3-6 個月非藥物治療	LDL-C≧190mg/dL	LDL-C＜190mg/dL	

- 心血管疾病定義：
  (一) 冠狀動脈粥狀硬化病人：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包含：
  1.腦梗塞。
  2.暫時性腦缺血患者(TIA)。(診斷須由神經科醫師確立)
  3.有症狀之頸動脈狹窄。(診斷須由神經科醫師確立)
- 危險因子定義：
  1.高血壓
  2.男性≧45 歲，女性≧55 歲或停經者
  3.有早發性冠心病家族史(男性≦55 歲，女性≦65 歲)
  4.HDL-C<40mg/dL
  5.吸菸(因吸菸而符合起步治療準則之個案，若未戒菸而要求藥物治療，應以自費治療)。

Fibrate

全民健康保險降三酸甘油酯藥物給付規定表

	非藥物治療	起始藥物治療三酸甘油酯值	三酸甘油酯目標值	處方規定
心血管疾病或糖尿病病人	與藥物治療可並行	TG≧200mg/dL 且 (TC/HDL-C>5 或 HDL-C<40mg/dL)	TG＜200mg/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。
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)	TG＜200mg/dL	
無心血管疾病病人	與藥物治療可並行	TG≧500mg/dL	TG＜500mg/dL	

Conclusions

- In patients with TG≥500 mg/dl, lipanthyl first to prevent pancreatitis.
- In patients with mixed dyslipidemia
  - Statin first to achieve LDLC goal, if persist high levels of TG adding lipanthyl is an option.
  - In high risk patients, initial combination therapy with statin and lipanthyl is an option.

Thank you for your attention !