

Lipid therapeutics update - going above and beyond statin therapy

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Changing epidemiology of diabetes

Type 1 diabetes

- Autoimmune disease
 - Childhood-onset disease
 - E.g. GAD Ab (+)
 - 'Normal' lipid profile

- Obesity
 - Increased childhood obesity
 - T2DM at age 12-20

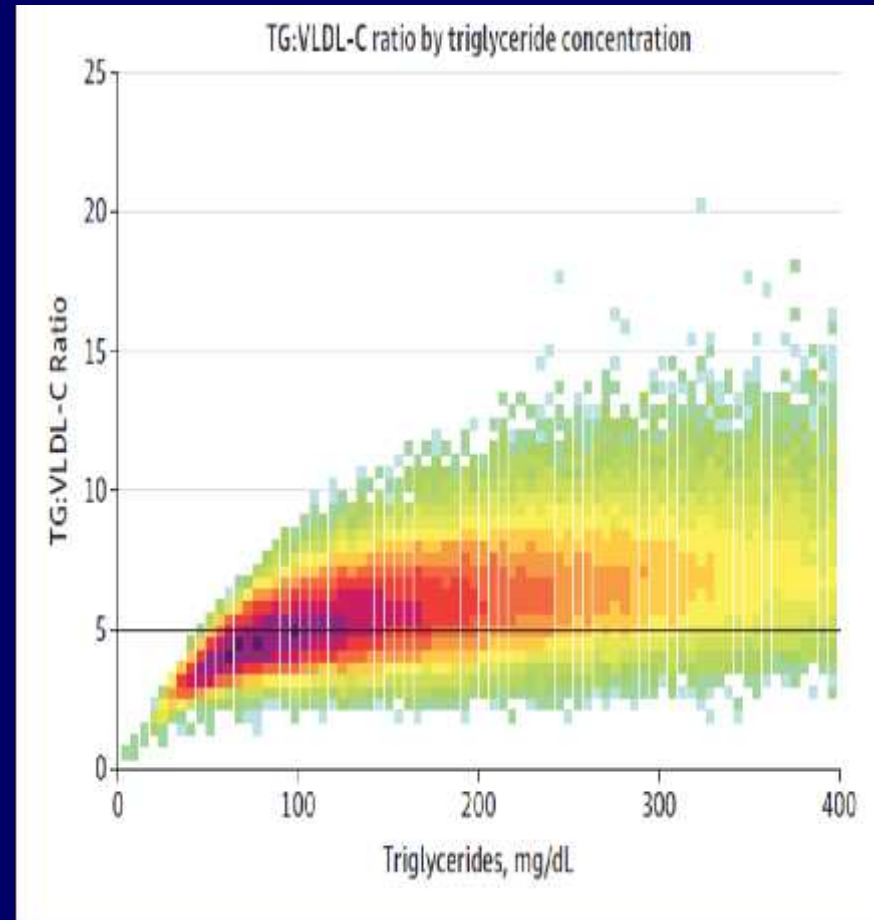
Type 2 diabetes

- Obesity
 - T2DM at age > 40
 - Atherogenic lipid profile
 - Low HDL-C; high TG; sdLDL

- Autoimmune disease
 - Adult-onset disease
 - GAD Ab (+); HLA-DQ group

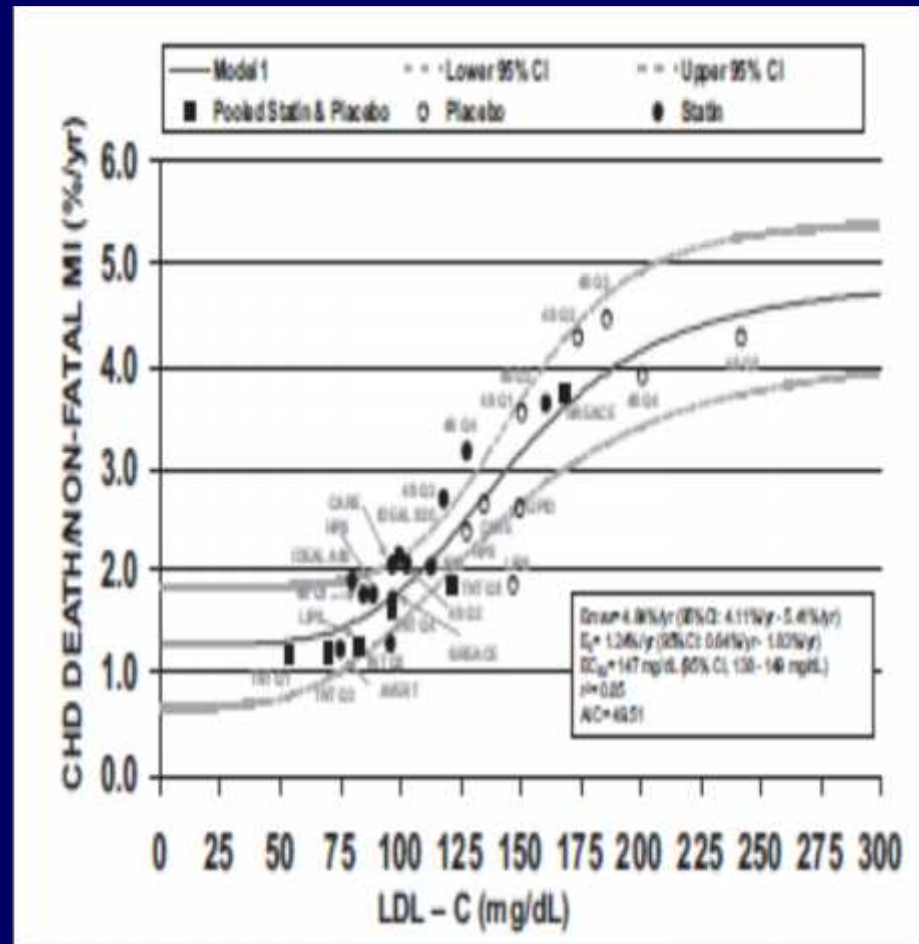
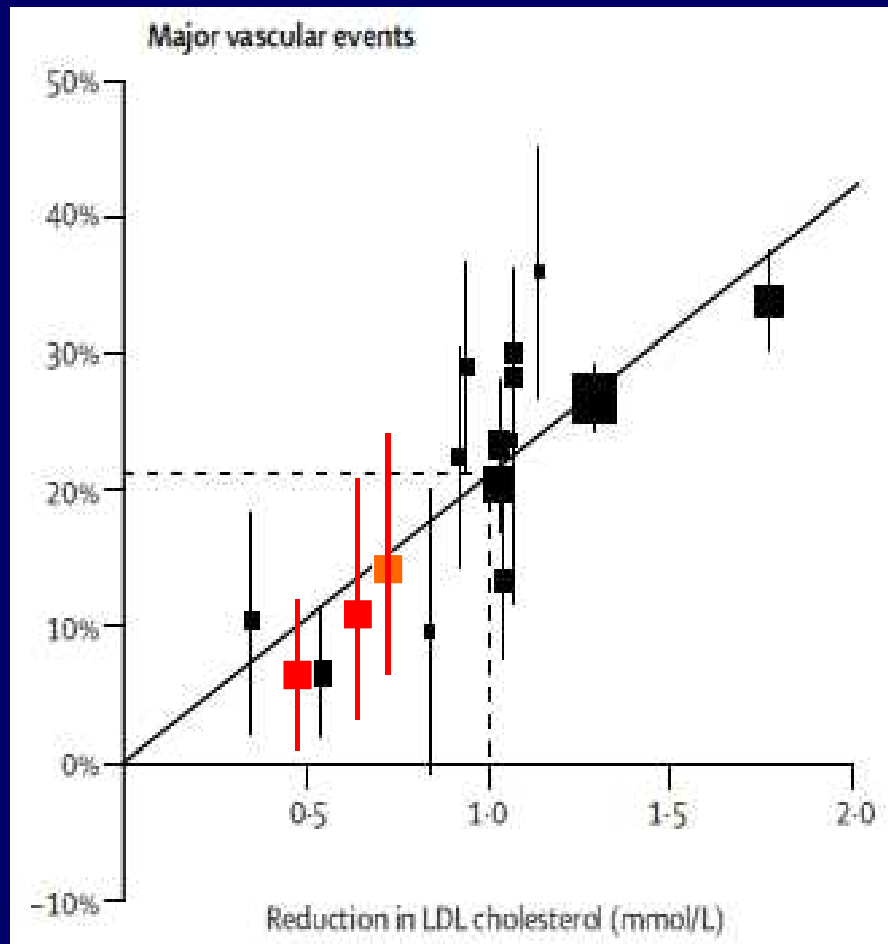
Problems with calculated LDL-C: Lipid efficacy: switch to non-HDL-C

- LDL-C Friedewald
 - Poor calibration
 - Little DM data
- cLDL-C on-treatment error
- Non-HDL-C better for CVD risk
- NHS Health Check
 - Move to HbA_{1c} for DM
- GP workload pressure



N=1,350908

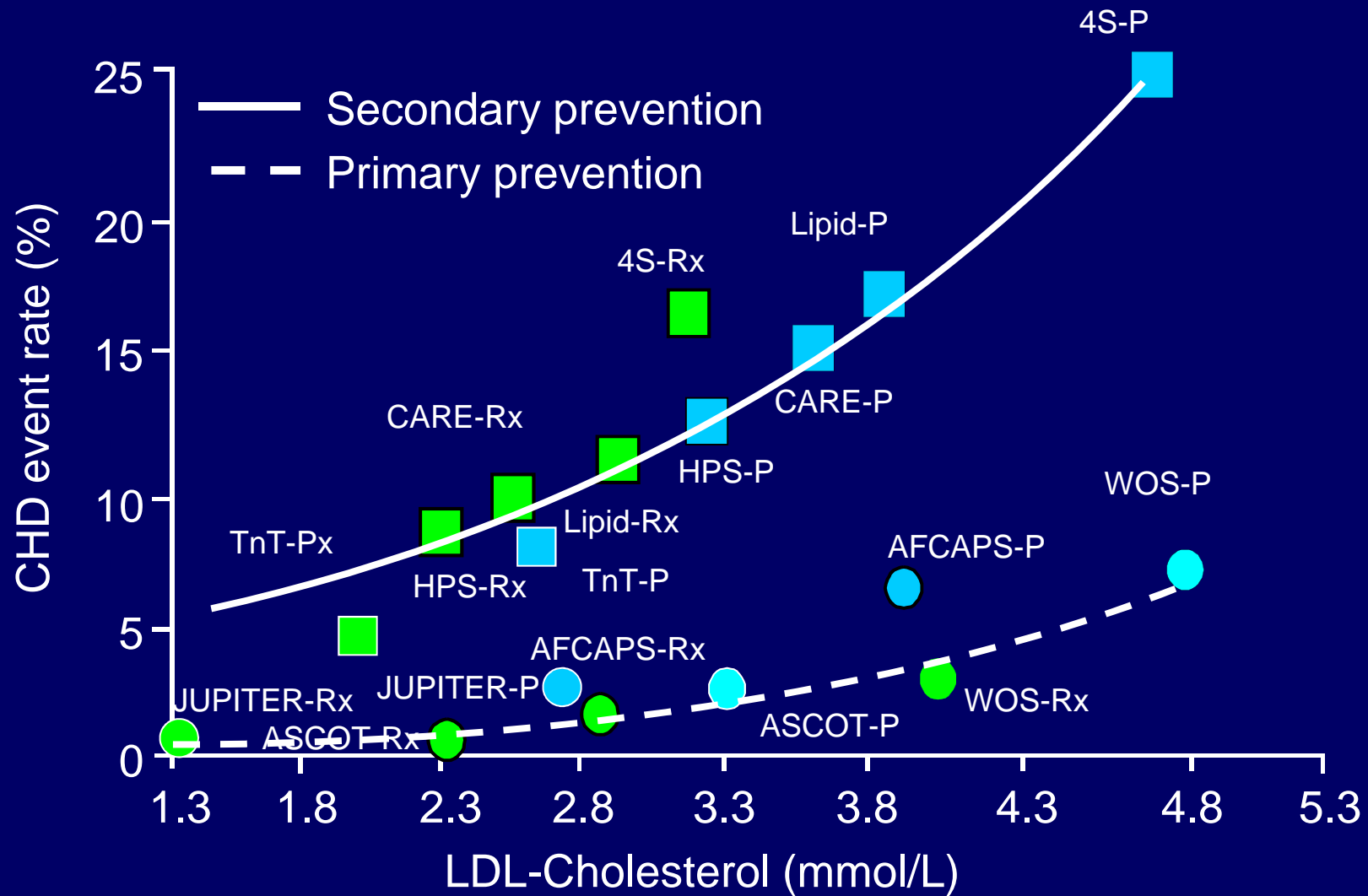
Meta-analyses of CHD vs LDL-C and Incremental effects of lipid drugs



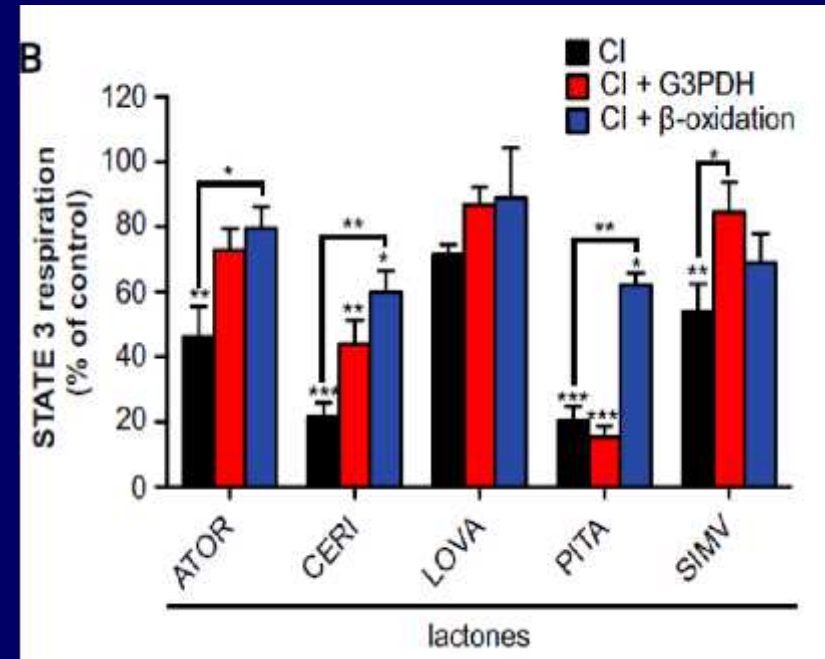
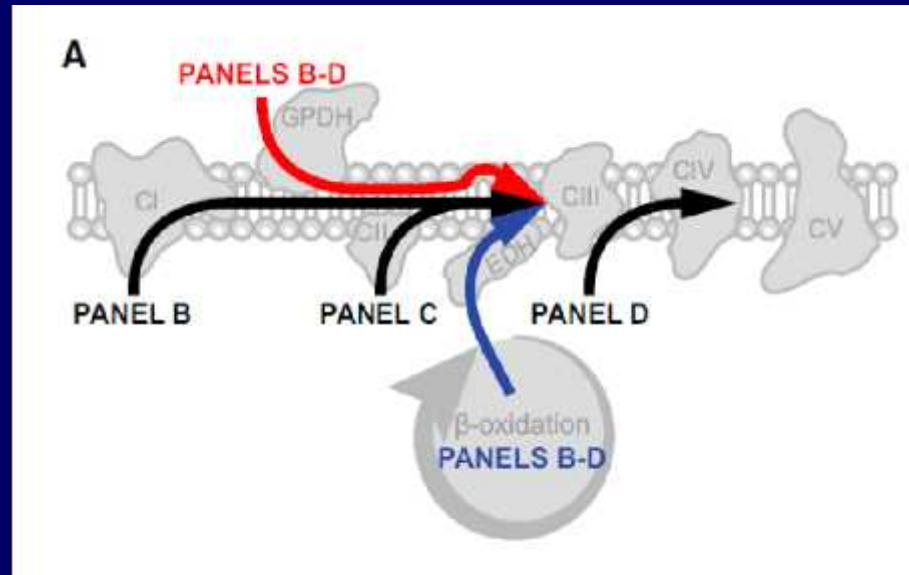
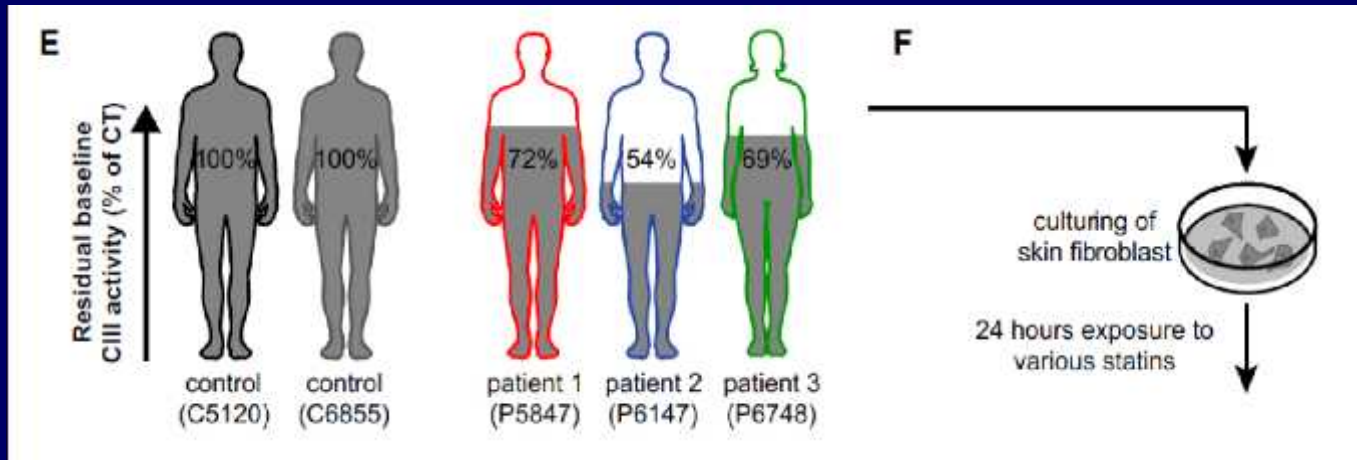
Cholesterol Treatment Trialists; Lancet 2010; 376: 1670

Charland SL & Stanek EJ; Pharmacother 2014; 34 : 452

All Prevention: Is lower better? (in 2009)



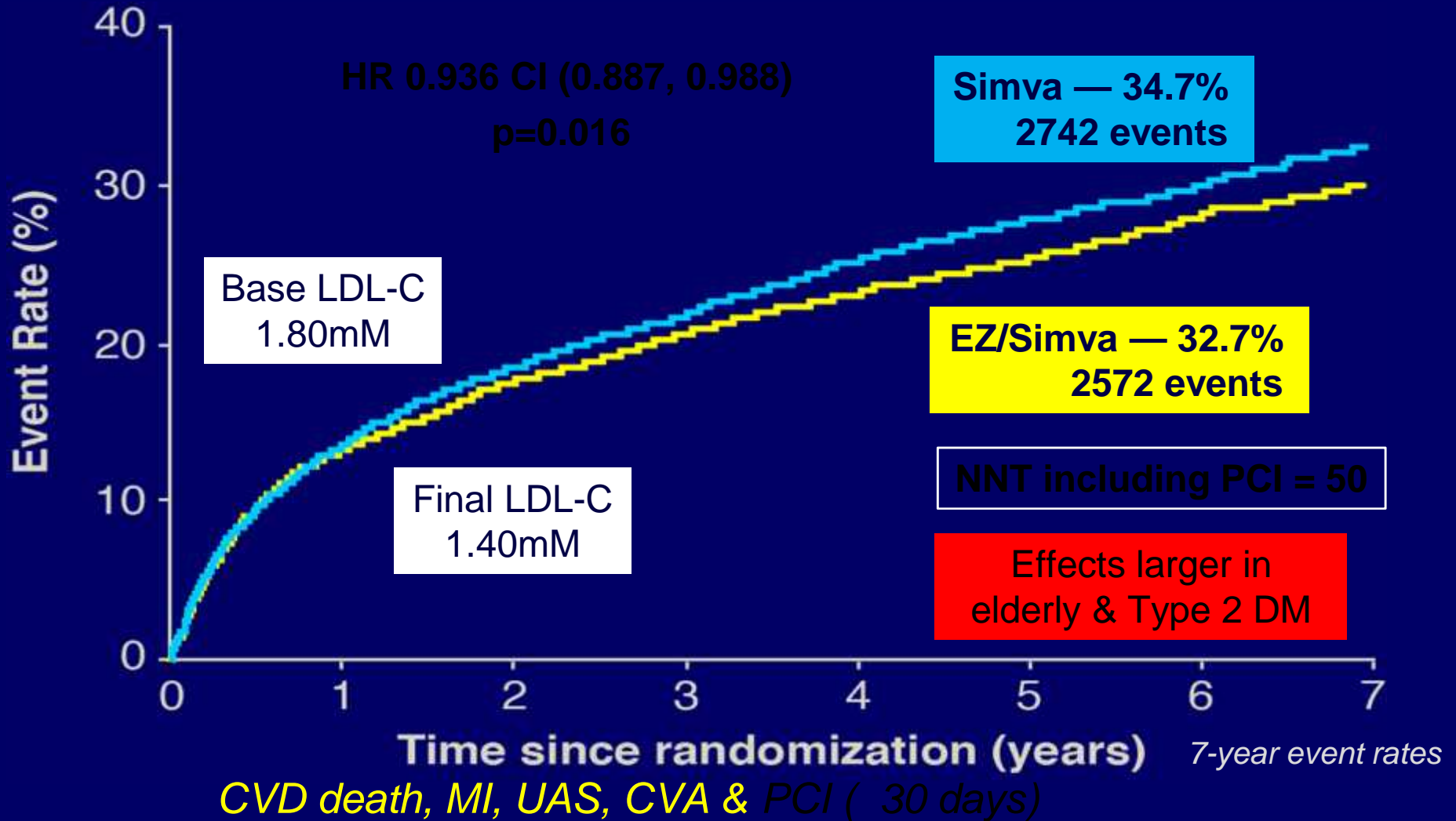
Statin myopathy- a mitochondrial complex 3 problem



New approaches to lowering LDL-C

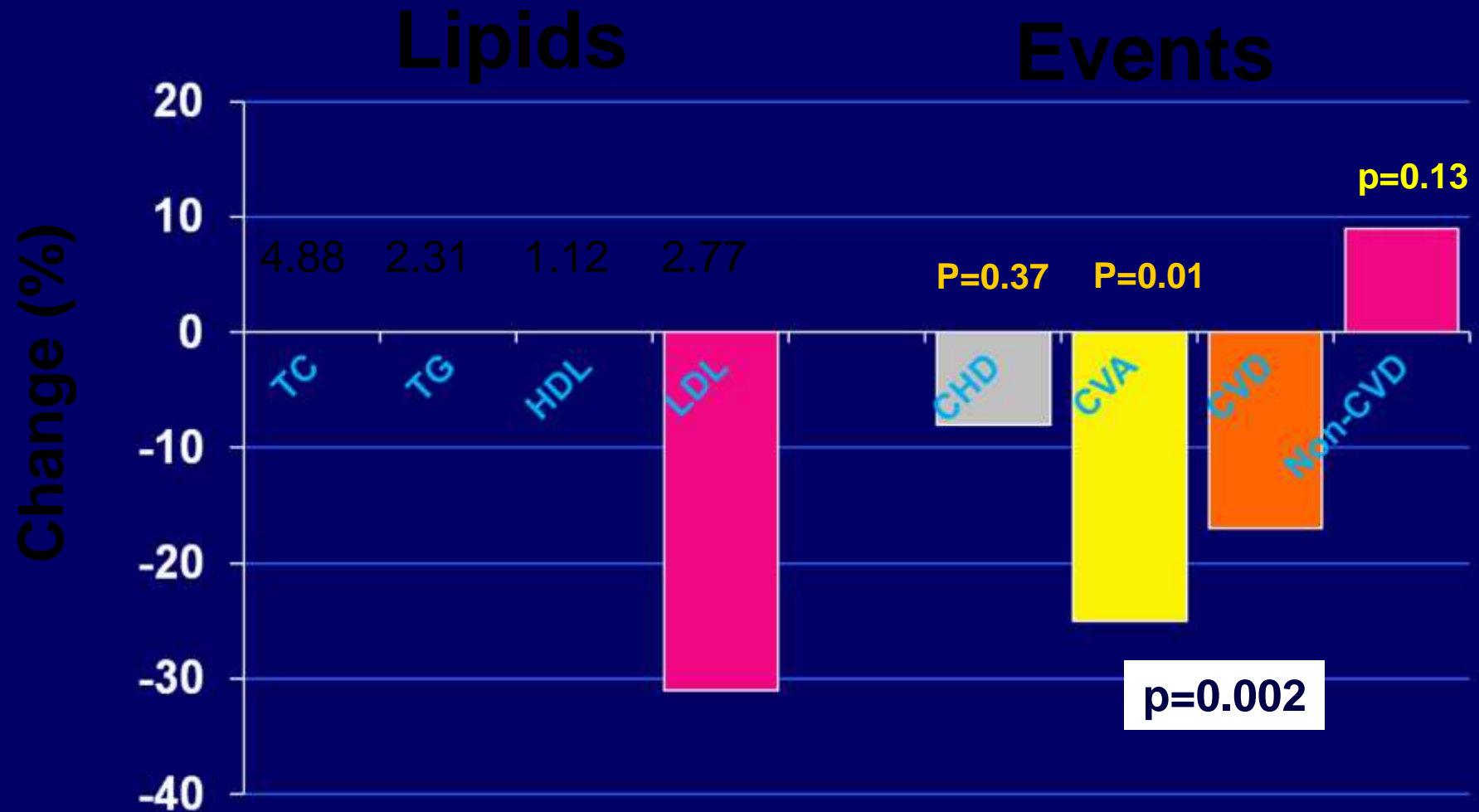
- Inhibiting absorption
 - Bile acid sequestrants
 - Cholestyramine, colestevlam (LRC-PPT)
 - NPC1L1 antagonists
 - Ezetimibe
 - Ileal bile acid transport inhibitors (IBATS)- discontinued
- Inhibiting synthesis (increasing LDL-R expression)
 - Squalene synthase inhibitors
 - Lapaquistat- discontinued
 - Acid citrate lyase inhibitors
 - Bempedoic acid
 - Agents affecting LDLR expression
 - Thyromimetics- Eprotirome; Sobetirome
 - PCSK-9 inhibitors
 - Agents affecting apoB stability
 - Berberine- discontinued
 - Antisense oligonucleotides (ASOs): Mipomersen
 - MTP inhibitors: Lomitapide

IMPROVE-IT: Ezetimibe in ACS Primary Endpoint — ITT

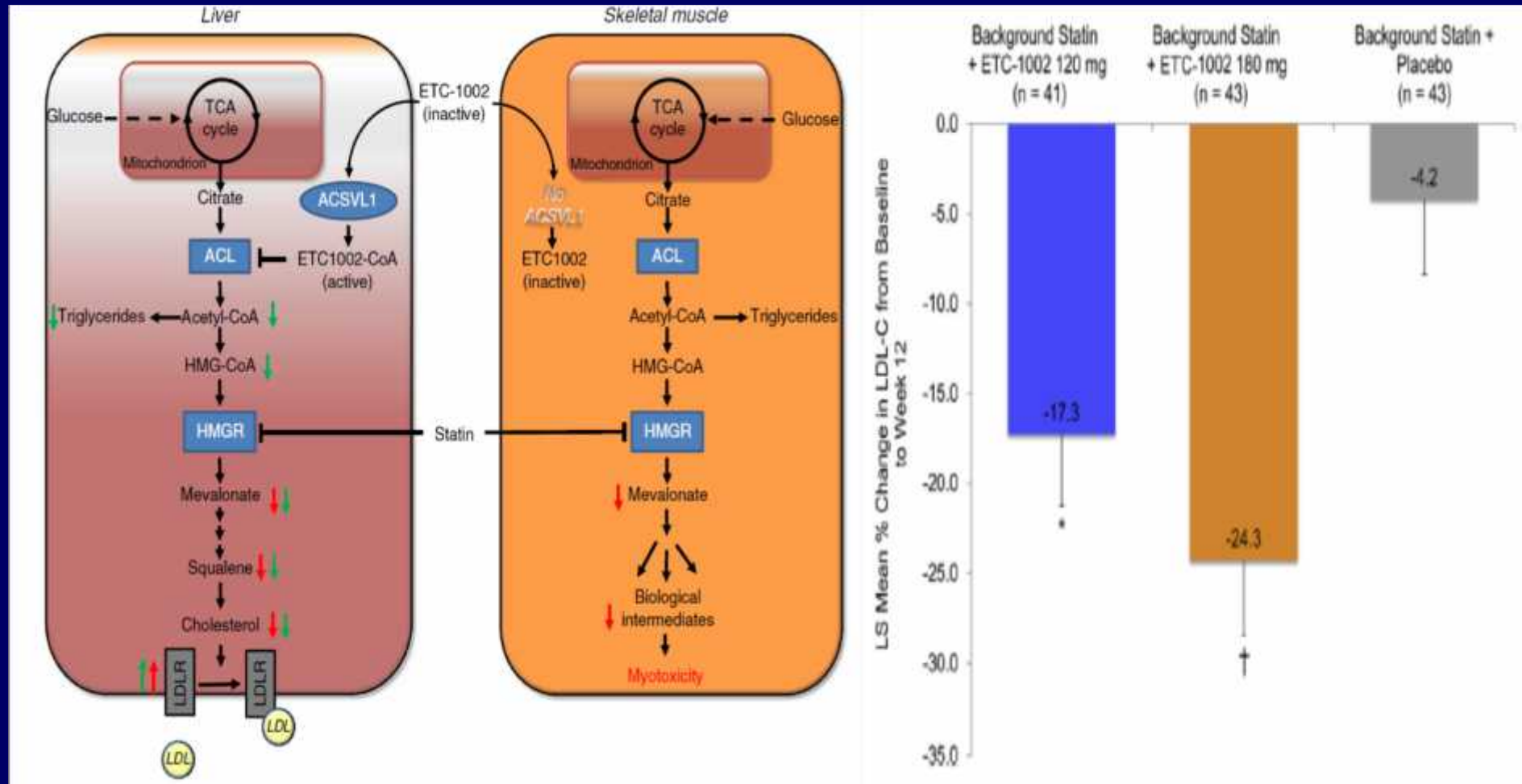


SHARP: (Statin of Heart And Renal Protection)

Principal results: Simvastatin 20mg + Ezetimibe 10mg



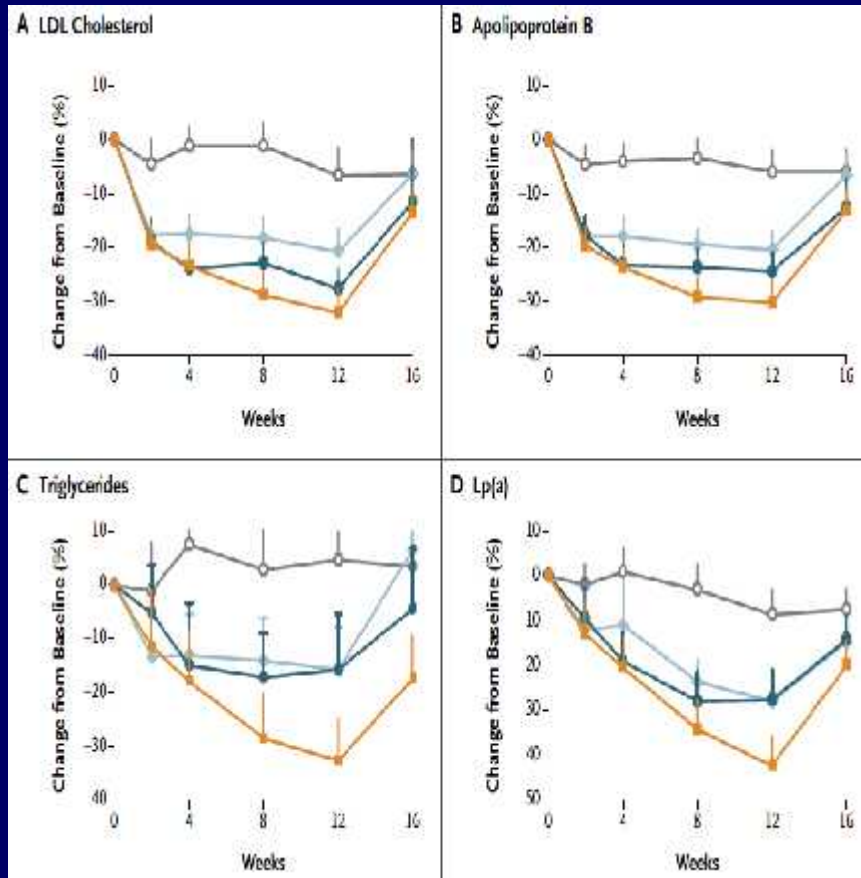
ATP-citrate lyase & bempedoic acid



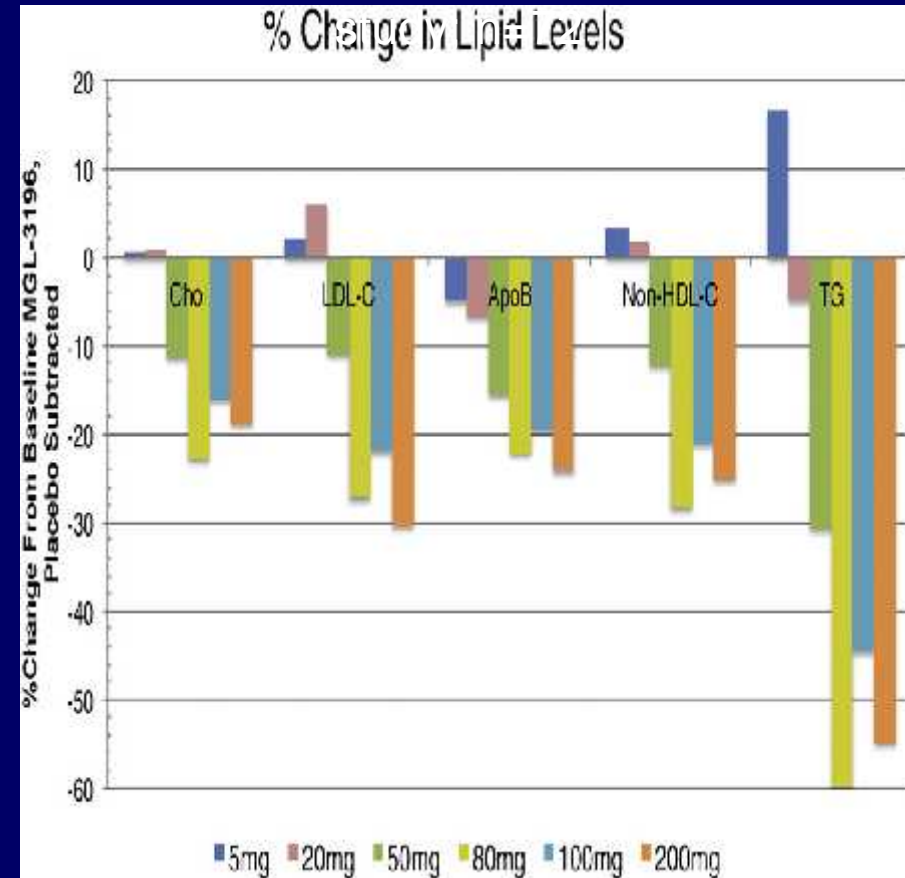
Pinkosky SL et al. Nature Comm 2016; 7: 13457
 Ballantyne CM et al.; Am J Cardiol 117: 1928

Thyromimetics:

Eprotirome phase II; n=329

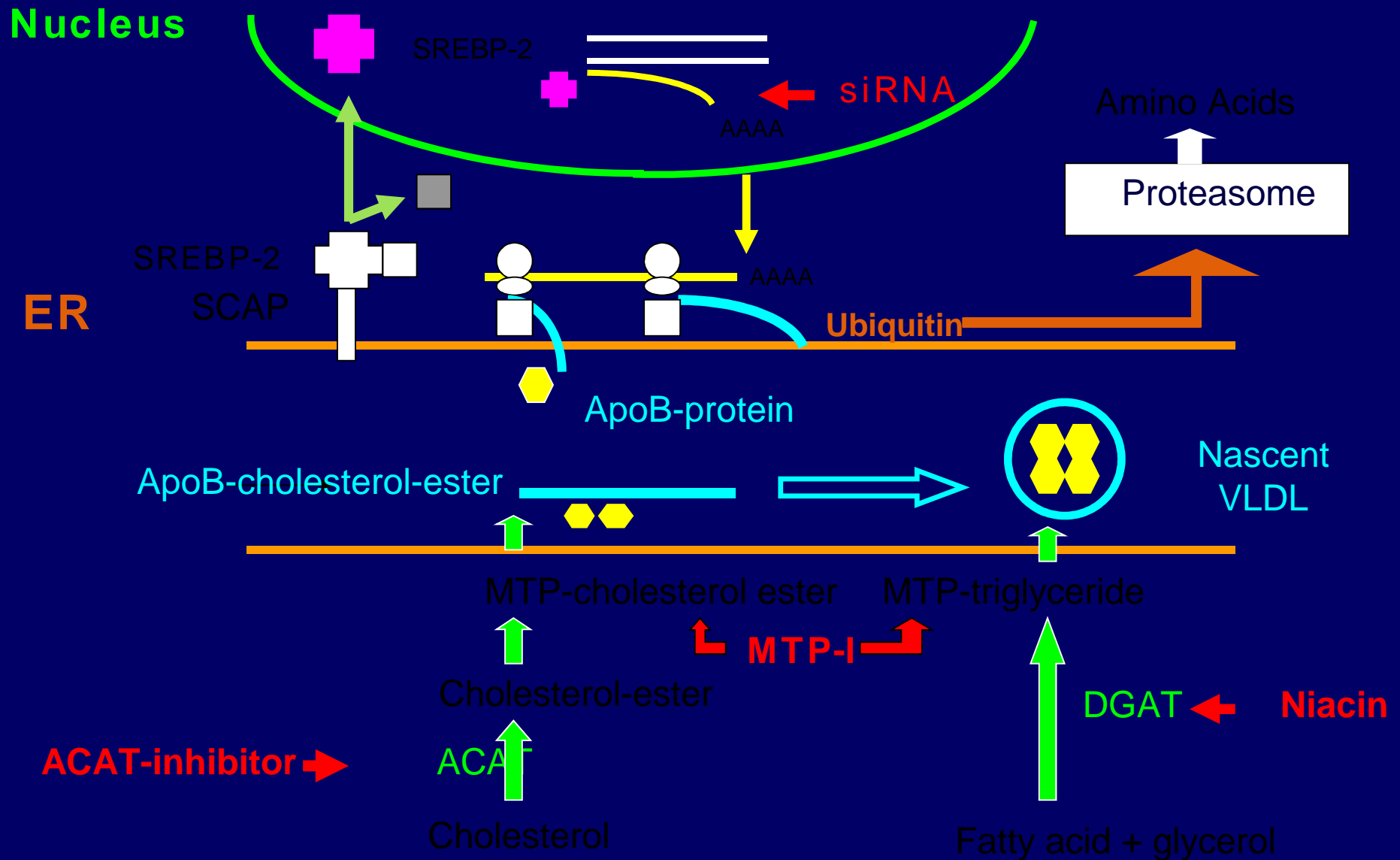


Sobetirome (MGL-3196); Phase I



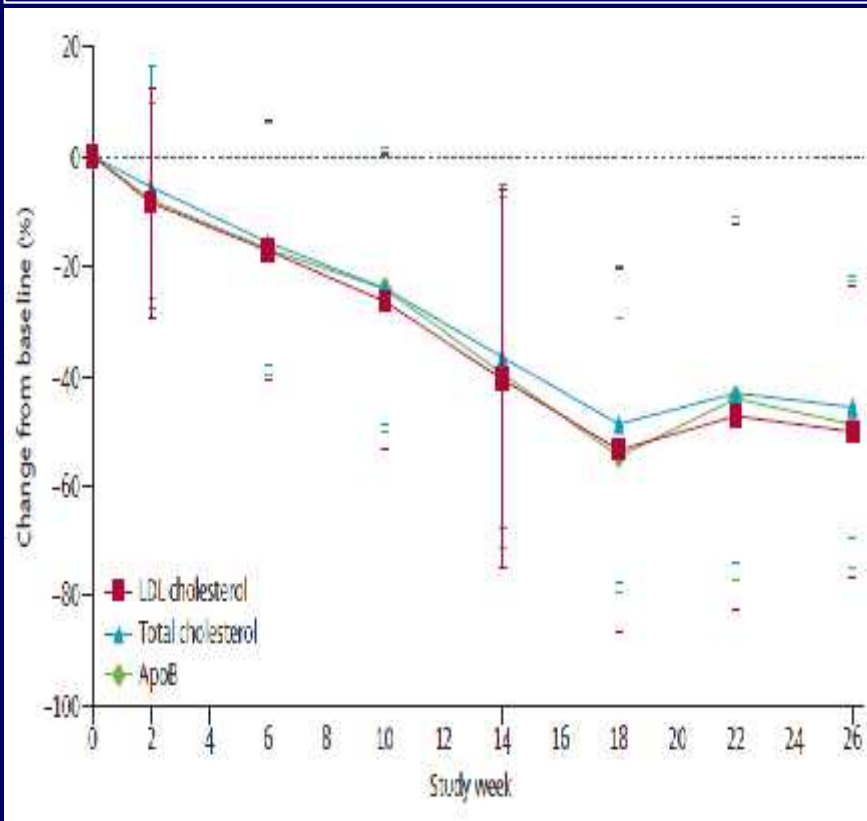
Ladenson PW et al ; NEJM 2010; 362: 906
 Taub R et al; Atherosclerosis 2013; 230 : 373

Synthesis of apoB particles

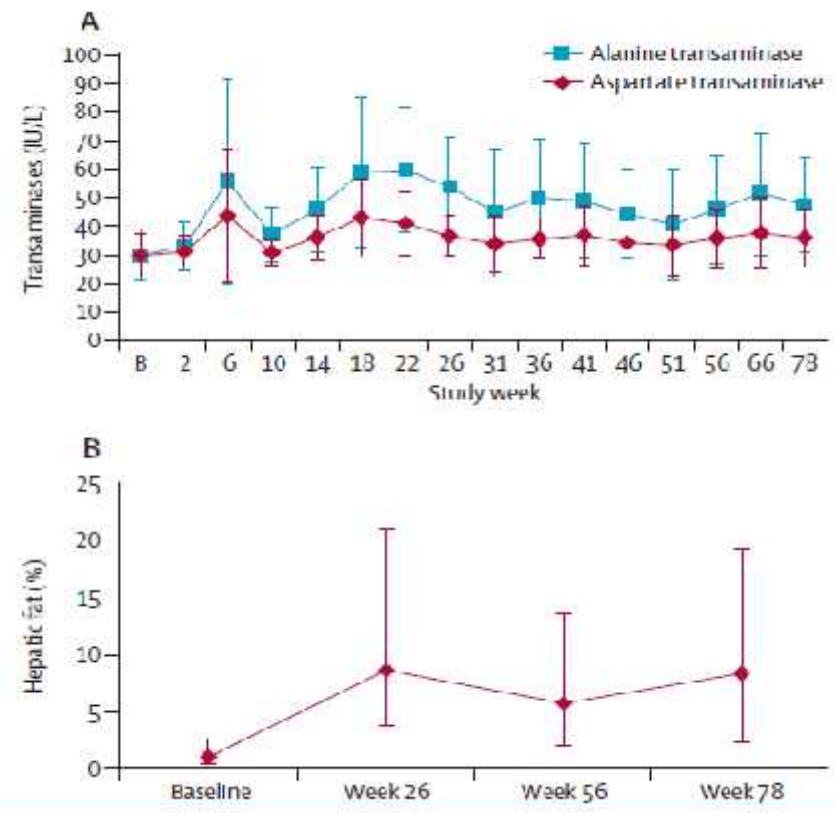


Effect of microsomal transfer protein inhibition with lomitapide in homozygous FH in man

Efficacy in reducing LDL-C

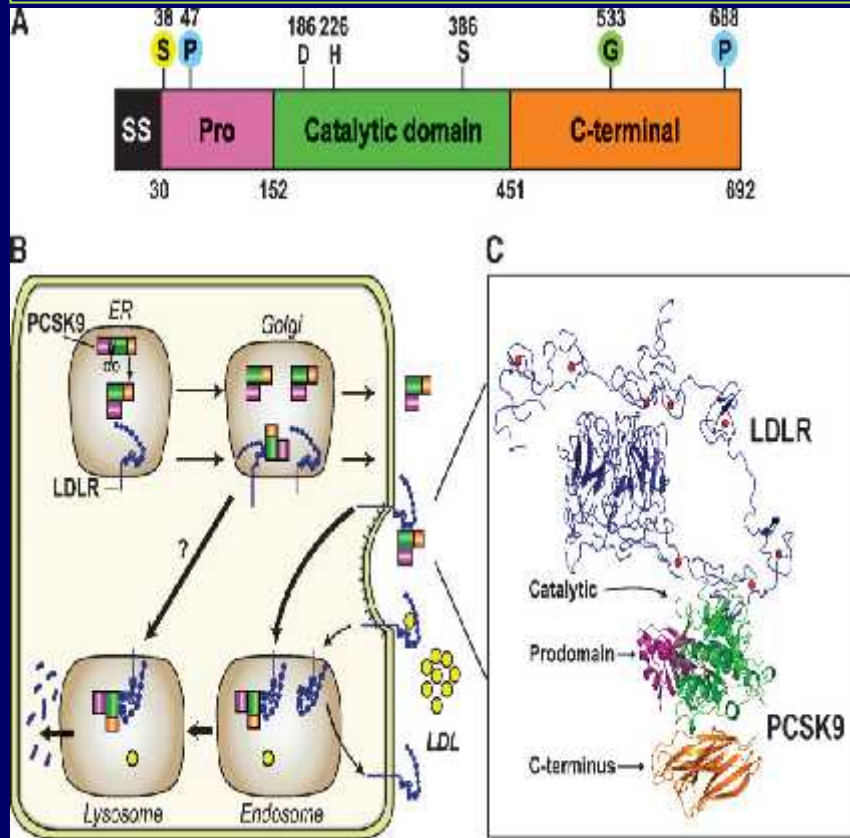


Transaminases & liver fat

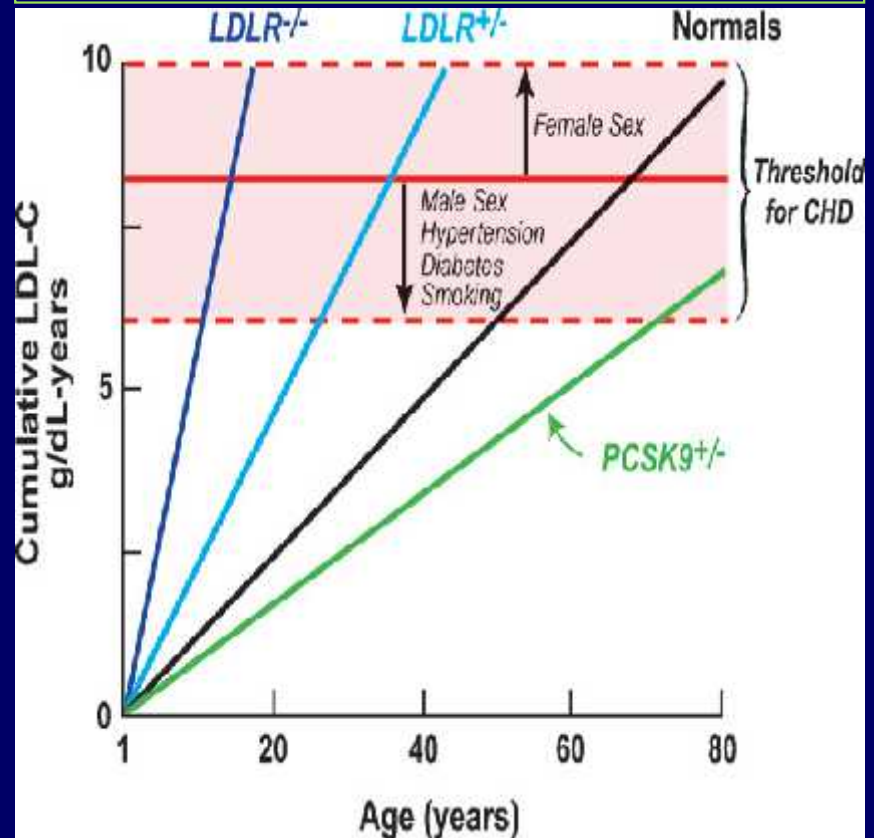


Modulating PCSK-9

PCSK-9 structure & function

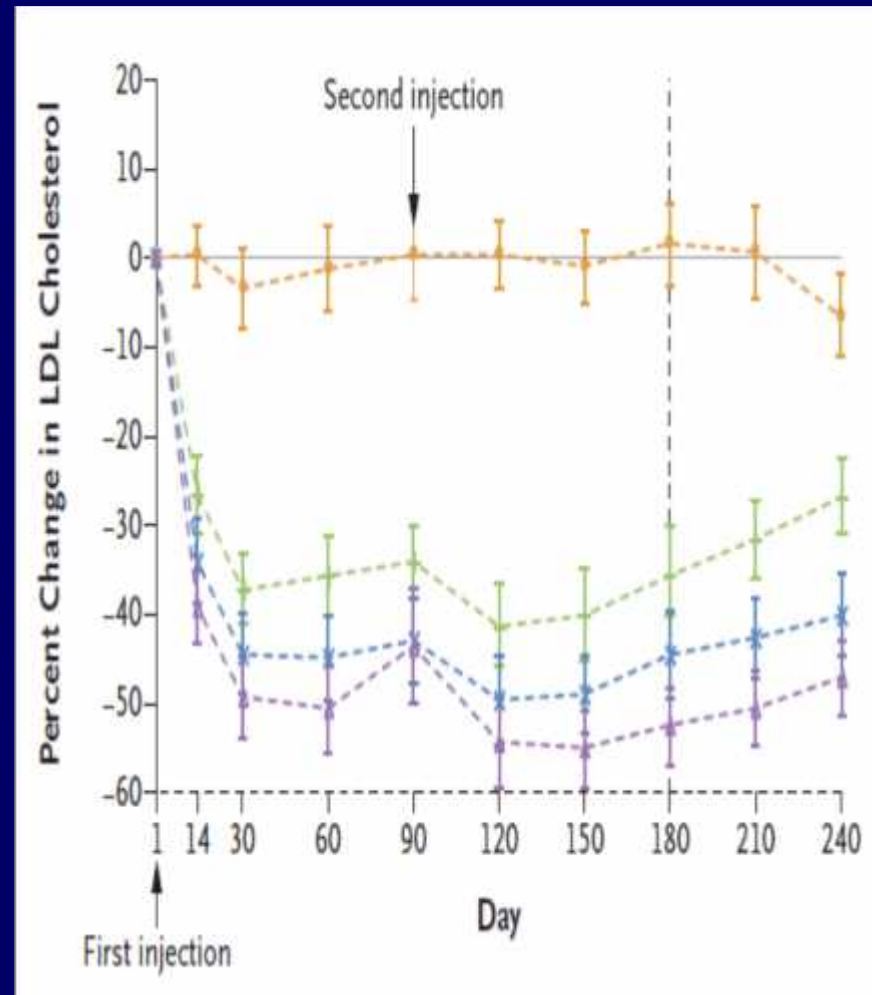


PCSK-9 mutations & CVD



Effects of PCSK-9 inhibition on LDL-C & apoB

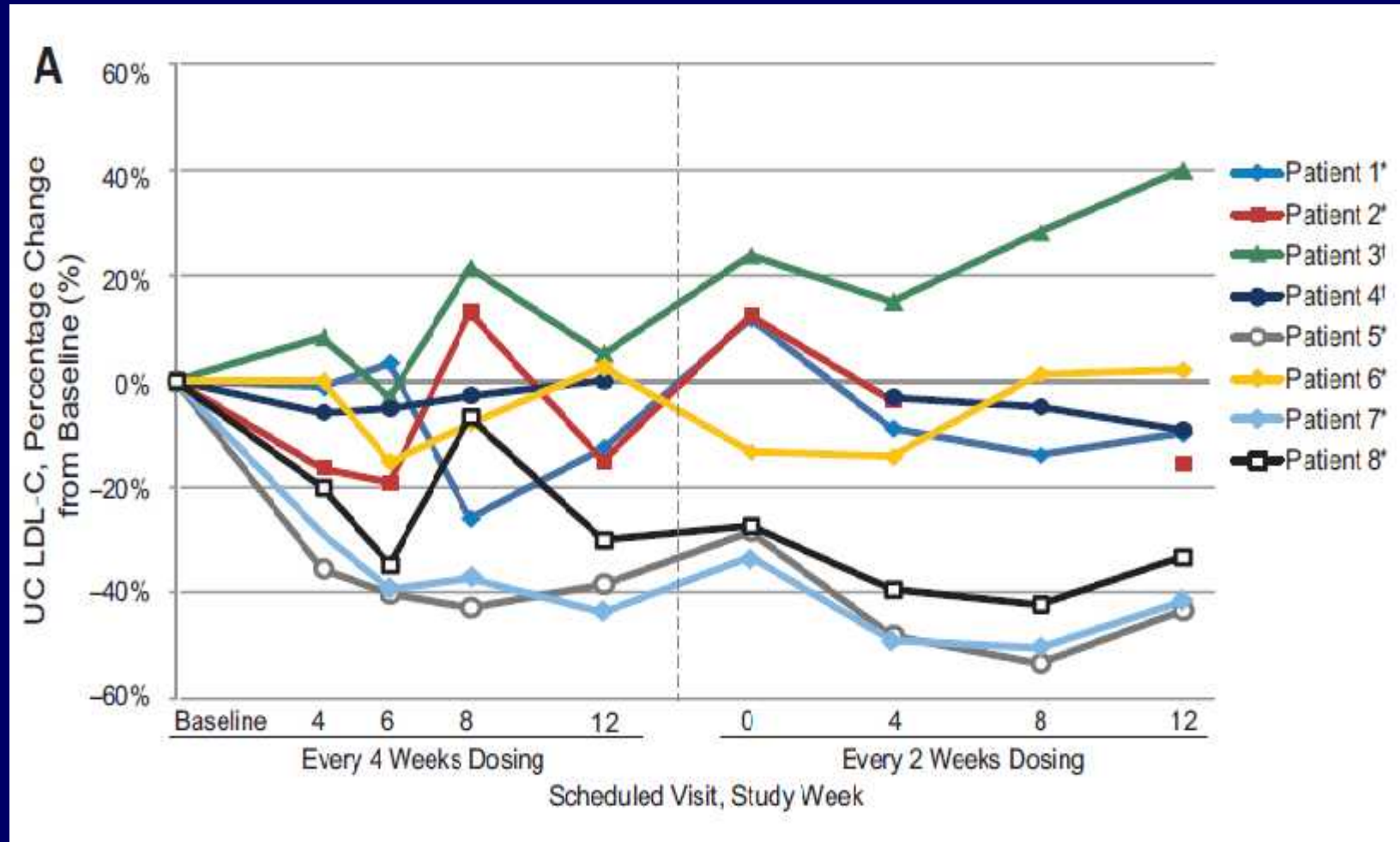
- PCSK-9 inhibitors
 - Small molecule
 - Pre-clinical only
 - Antibody
 - Alirocumab;
 - Evolocumab;
 - Bococizumab- discontinued
 - Antisense oligonucleotide
 - SPC-5001- discontinued
 - Targeted siRNA
 - inclisiran



Stein EA et al; Lancet 2012; 380 : 29
Ray KK et al; NEJM 2017; 376: 1430

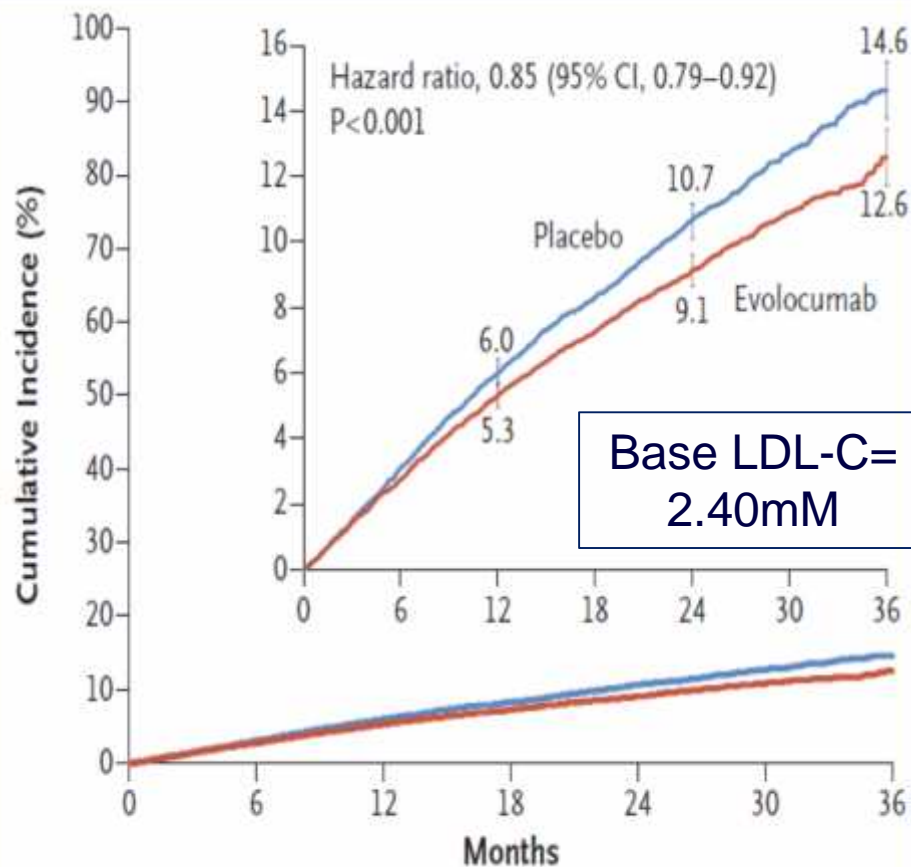
Inclisiran- 2 injections

Evolocumab in Homozygous FH (HoFH)

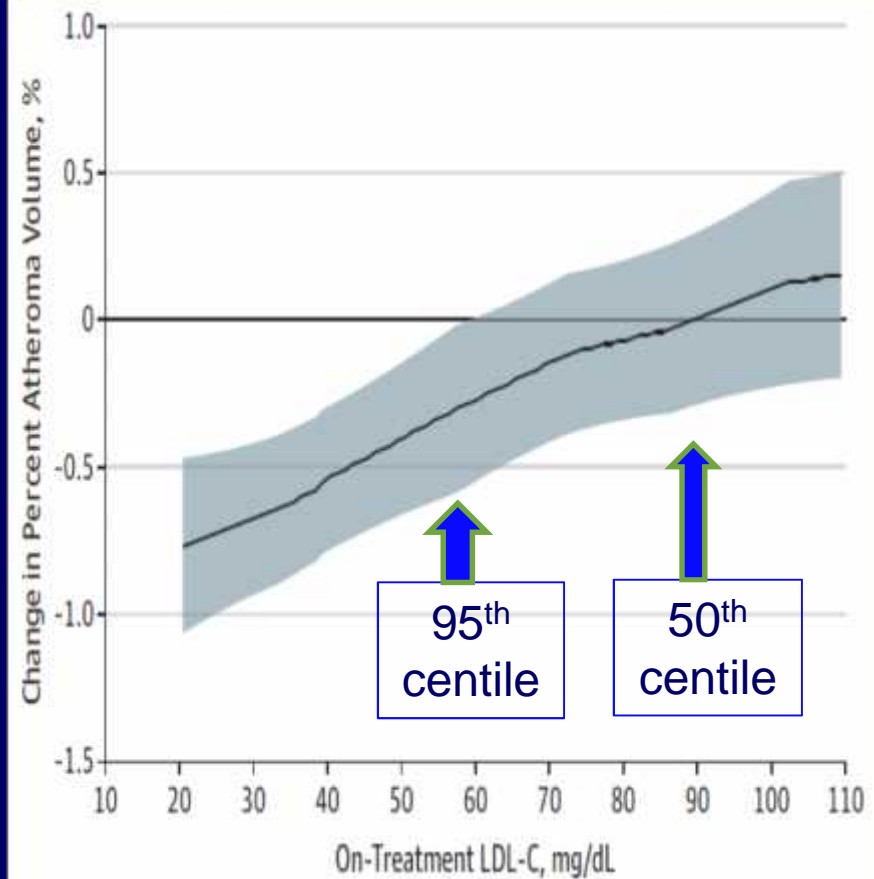


PCSK-9 trials: Evolocumab:

FOURIER ACS & CVD RFs



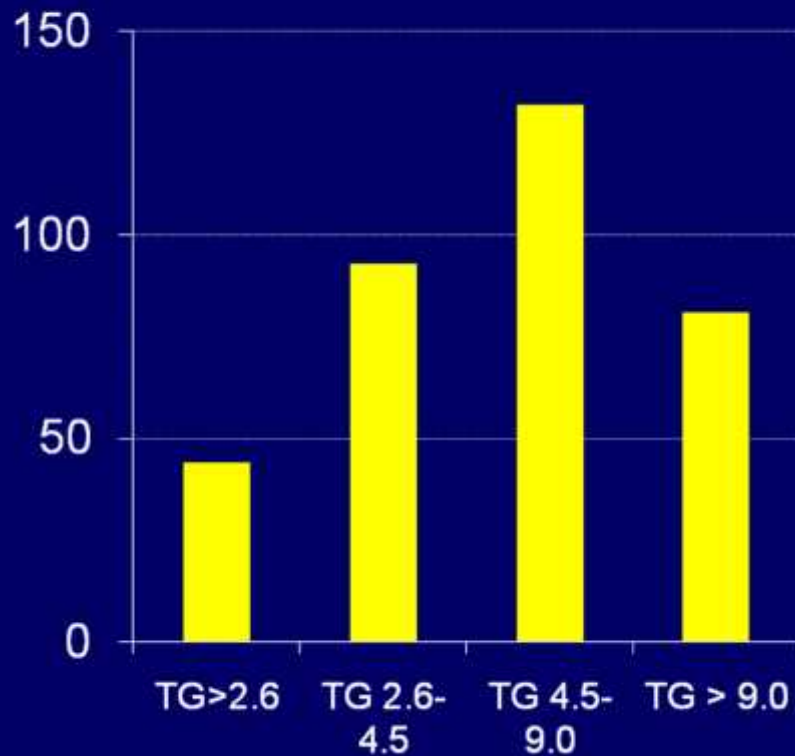
GLAGOV: IVUS analysis



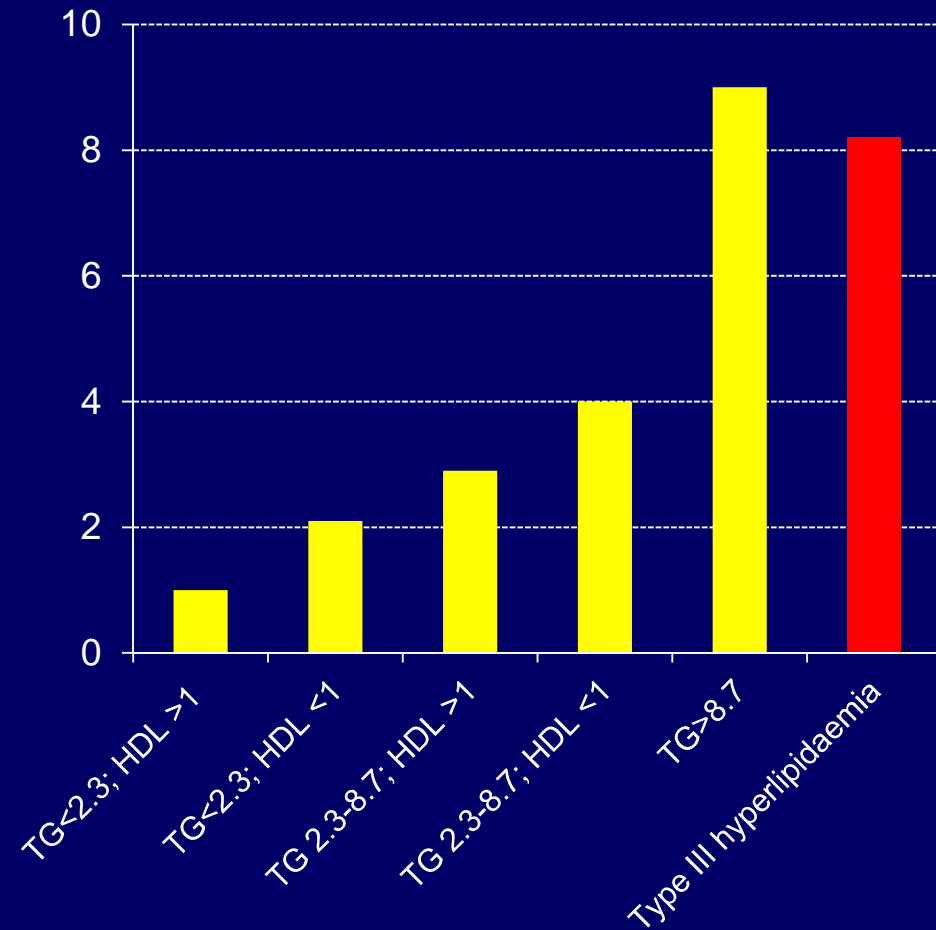
Sabatine M et al; NEJM 2017; 376: 1713
Nicholls SJ et al. JAMA 2016; 316: 2373

Triglycerides & CHD risk

CHD events :
rate/10³/8yrs



Relative risk



Assmann G et al; Am J Cardiol 1996; 77: 1179
Hopkins PN et al; JACC 2005; 45 :1003

New approaches to lowering triglycerides

Inhibiting synthesis

- DGAT-1 inhibitors
 - LCQ-908- discontinued
- MTP inhibitors
 - Lomitapide- single case – liver fibrosis

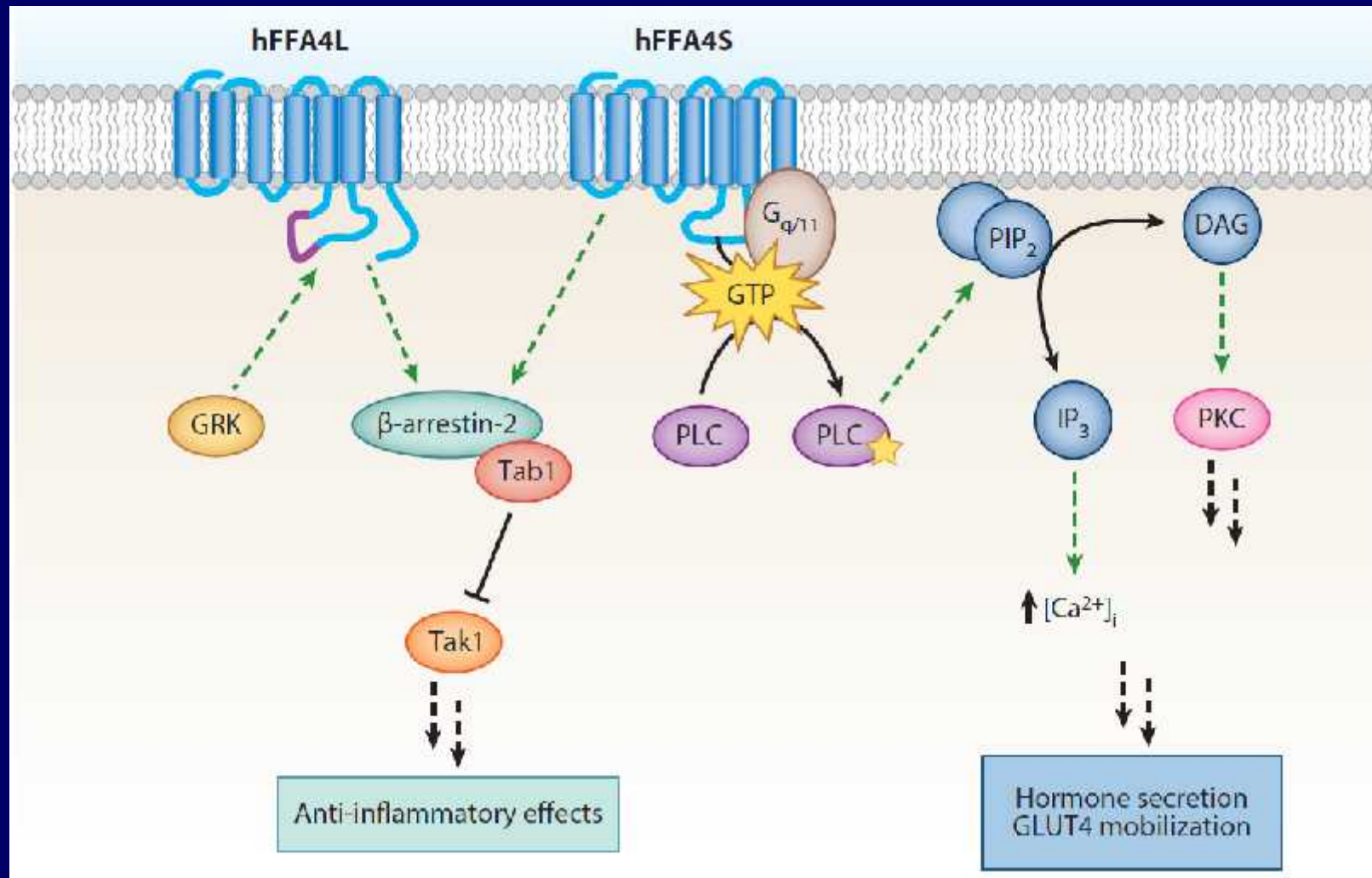
• Increasing clearance

- PPAR- /
 - GFT-505
- PPAR- /
 - Alogliptazar- ALECARDIO trial - discontinued
- PPAR- /
 - DB-959
- Antisense oligonucleotides to apoC3
 - Volanesorsen

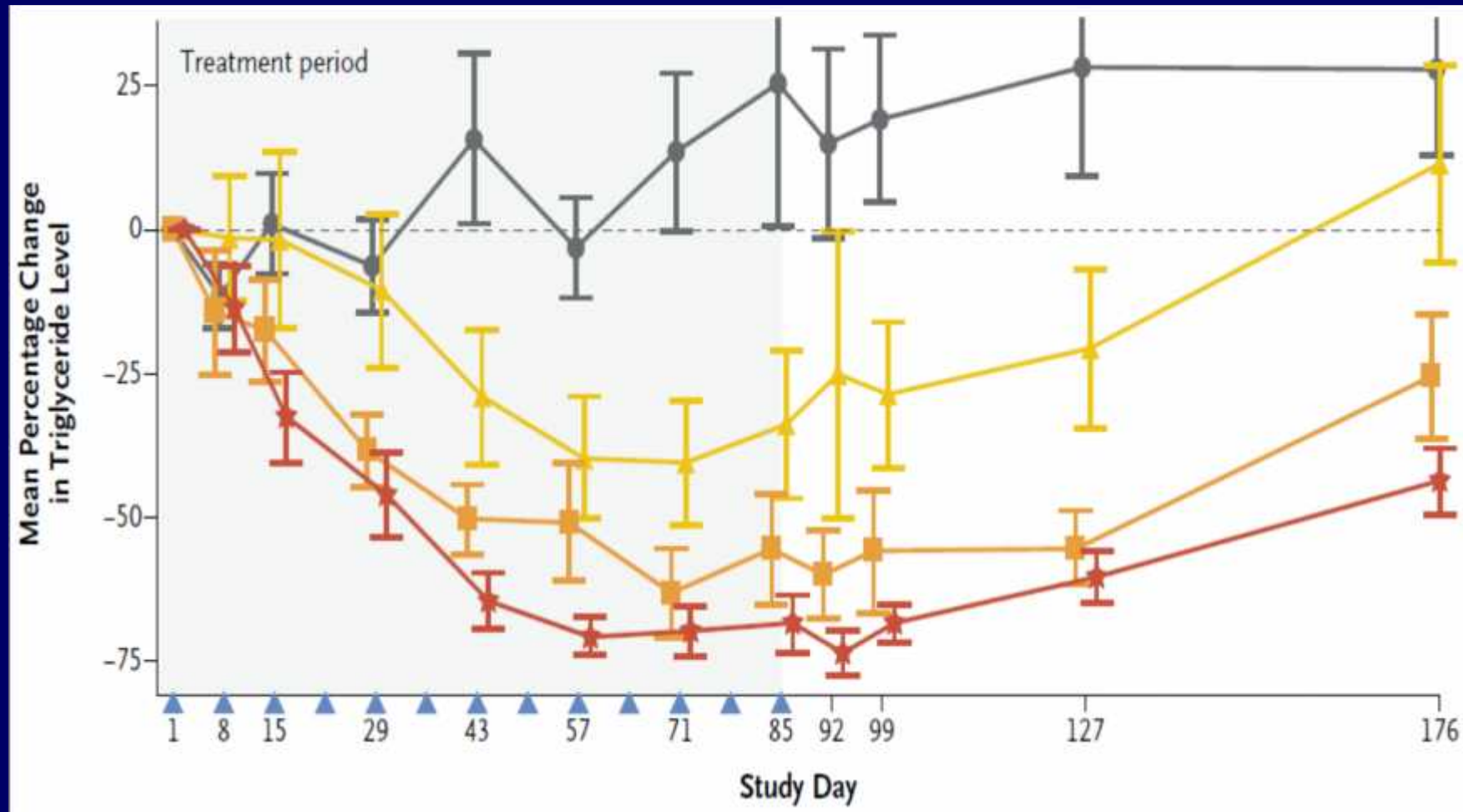
• LPL

- Gene therapy
 - Alipogene tiparvovec- discontinued (commercial)
- ANGPTL3 inhibition
 - Evinacumab

Mechanism of omega-3 FA receptor- FFA-4/GP120

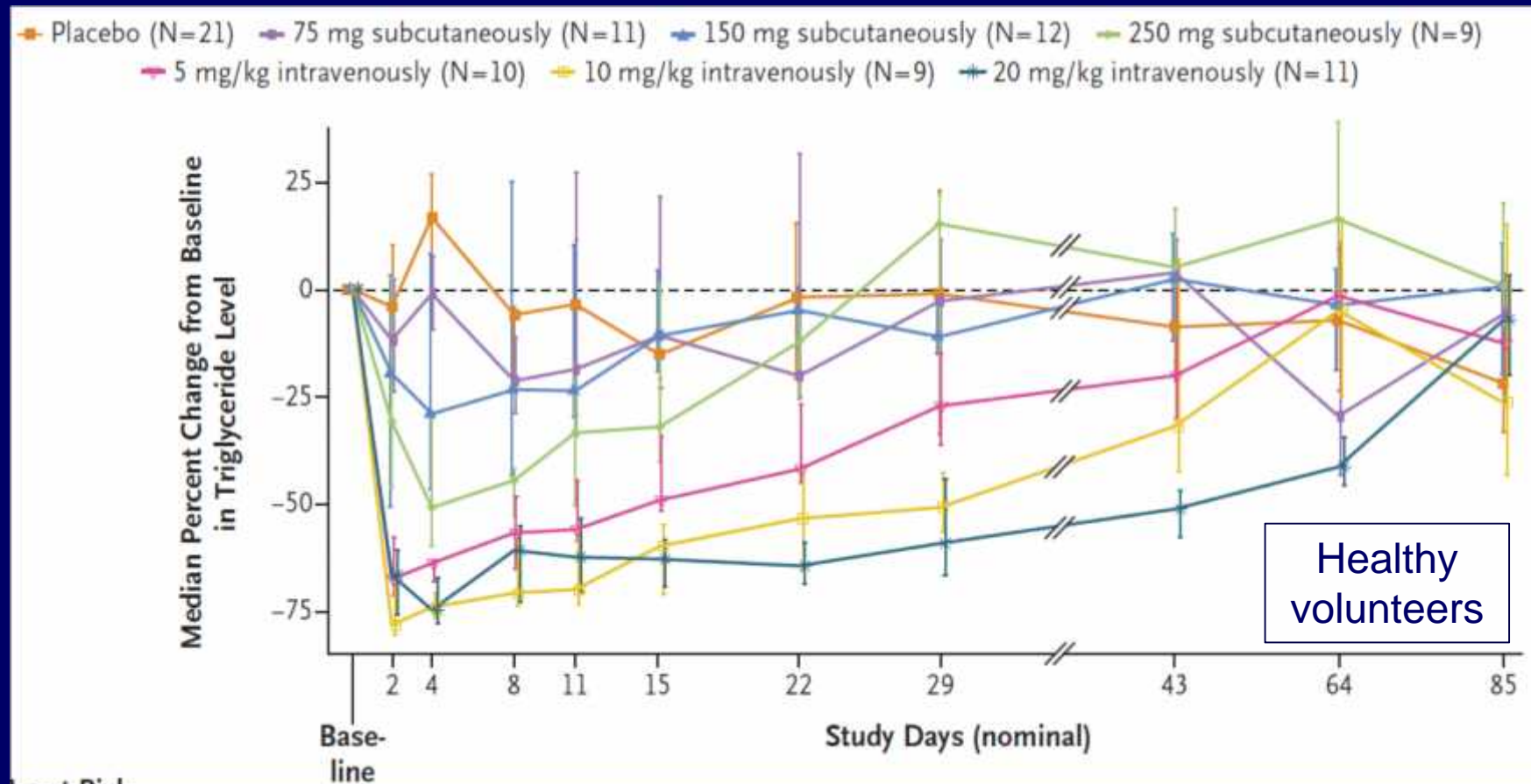


Triglycerides: Volanesorsen- apoC3 inhibition and LPLD/FCS



Gaudet D et al. NEJM 2015; 373 : 438

Triglycerides and ANGPTL3 inhibition: evinacumab



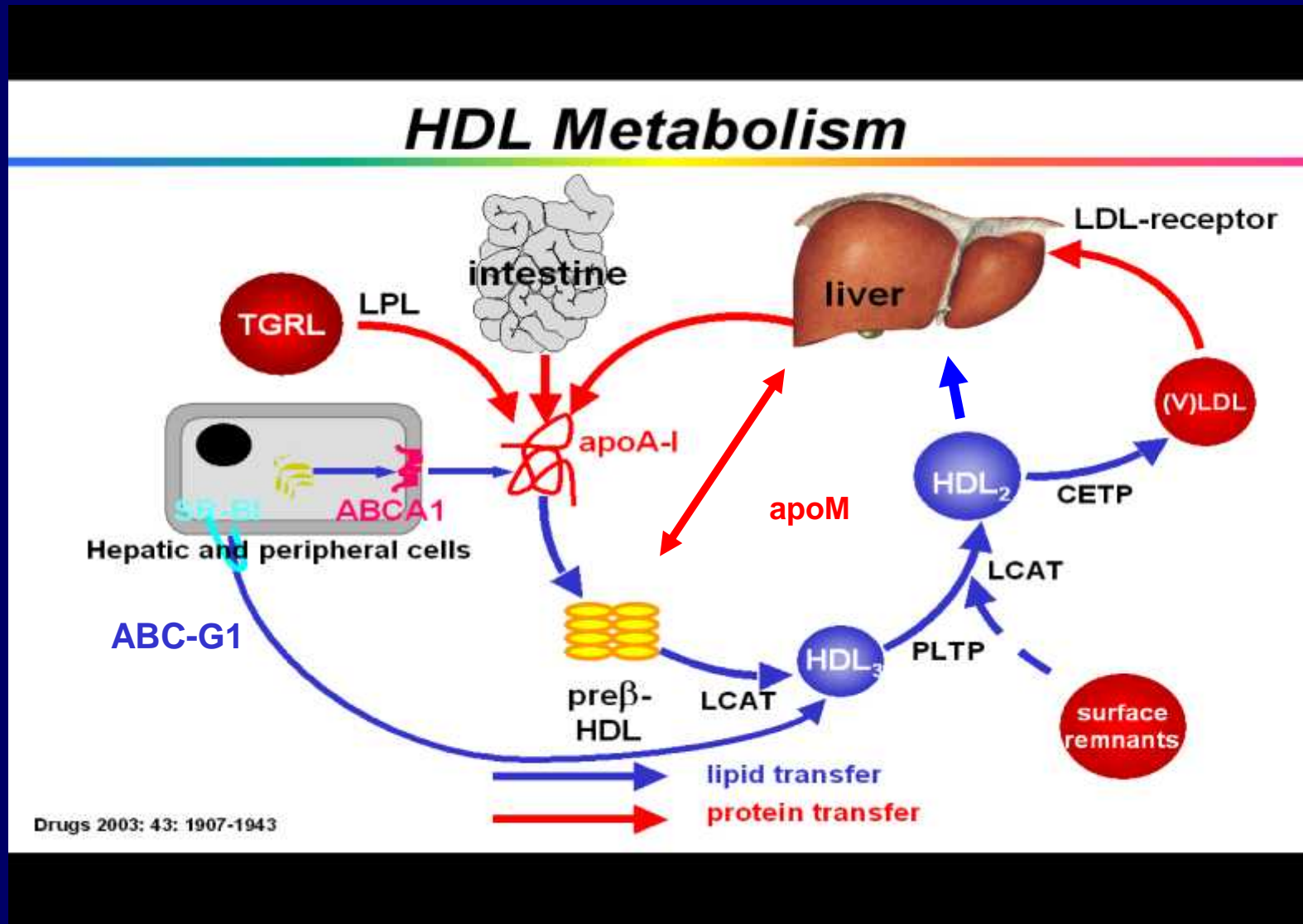
Dewey FE et al; NEJM 2017; 377: 211
Gipe DA et al; NEJM 2017; 377 : 296

NB. LDL-C 49% in HoFH (n=9)

New approaches to raising HDL-C

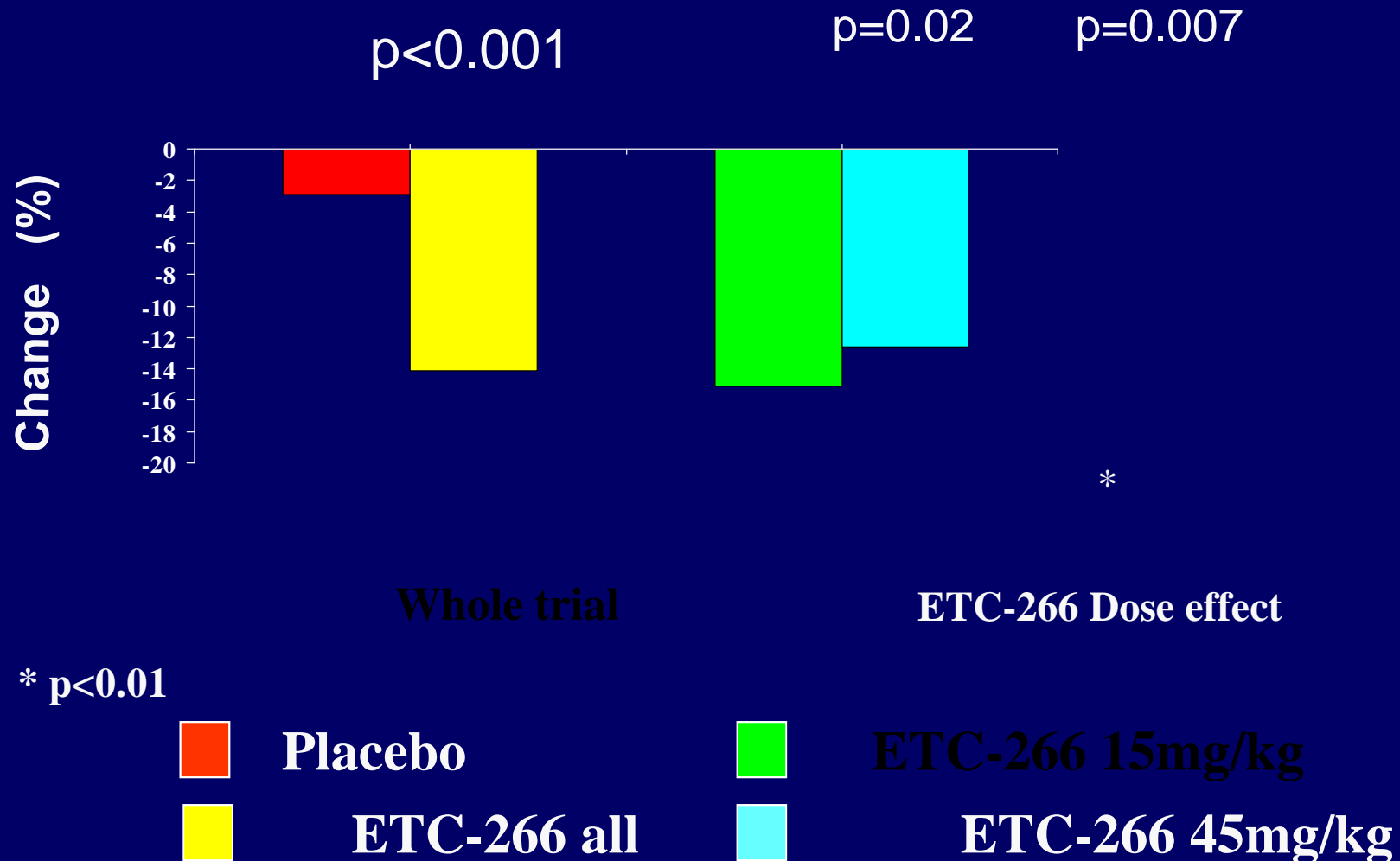
- HDL mimetics
 - Apolipoprotein strategies
 - MOTC/ETC-266- **suspended**
 - rHDL infusion (CSL-112)- **no IVUS benefit**
 - HDL pheresis & re-infusion
 - D4F- **discontinued**
- Increasing synthesis
 - Non-PPAR
 - RVX-208- **ASSURE IVUS negative**
 - Niacin derivatives
 - ARI3037MO
- Redistributing cholesterol towards HDL-C
 - Torcetrapib- **discontinued**
 - Dalcetrapib- **discontinued**
 - Anacetrapib- **REVEAL study- no commercial pursuit**
 - Evacetrapib- **ACCELERATE ACS negative- discontinued**

HDL Metabolism

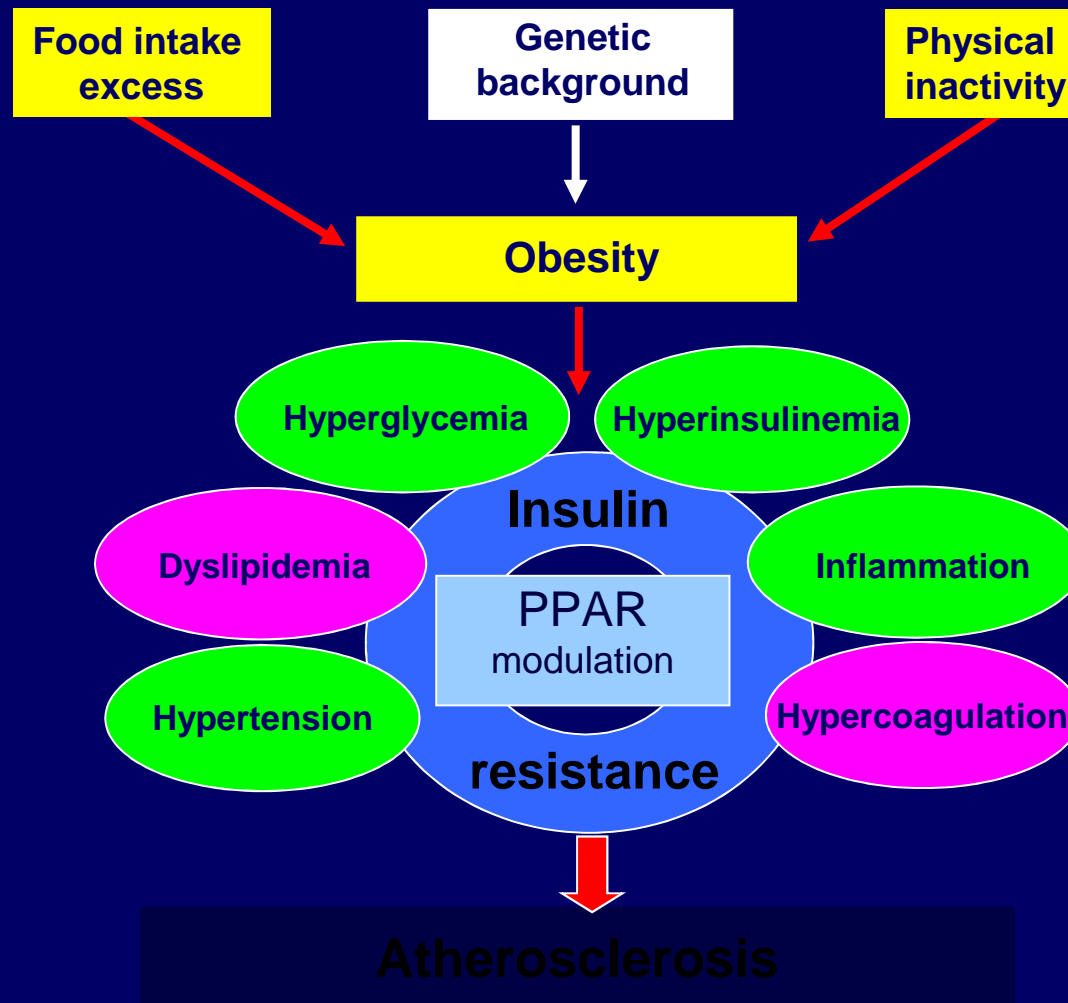


Infusion trial of ETC-266 (ApoA-I_{milano})

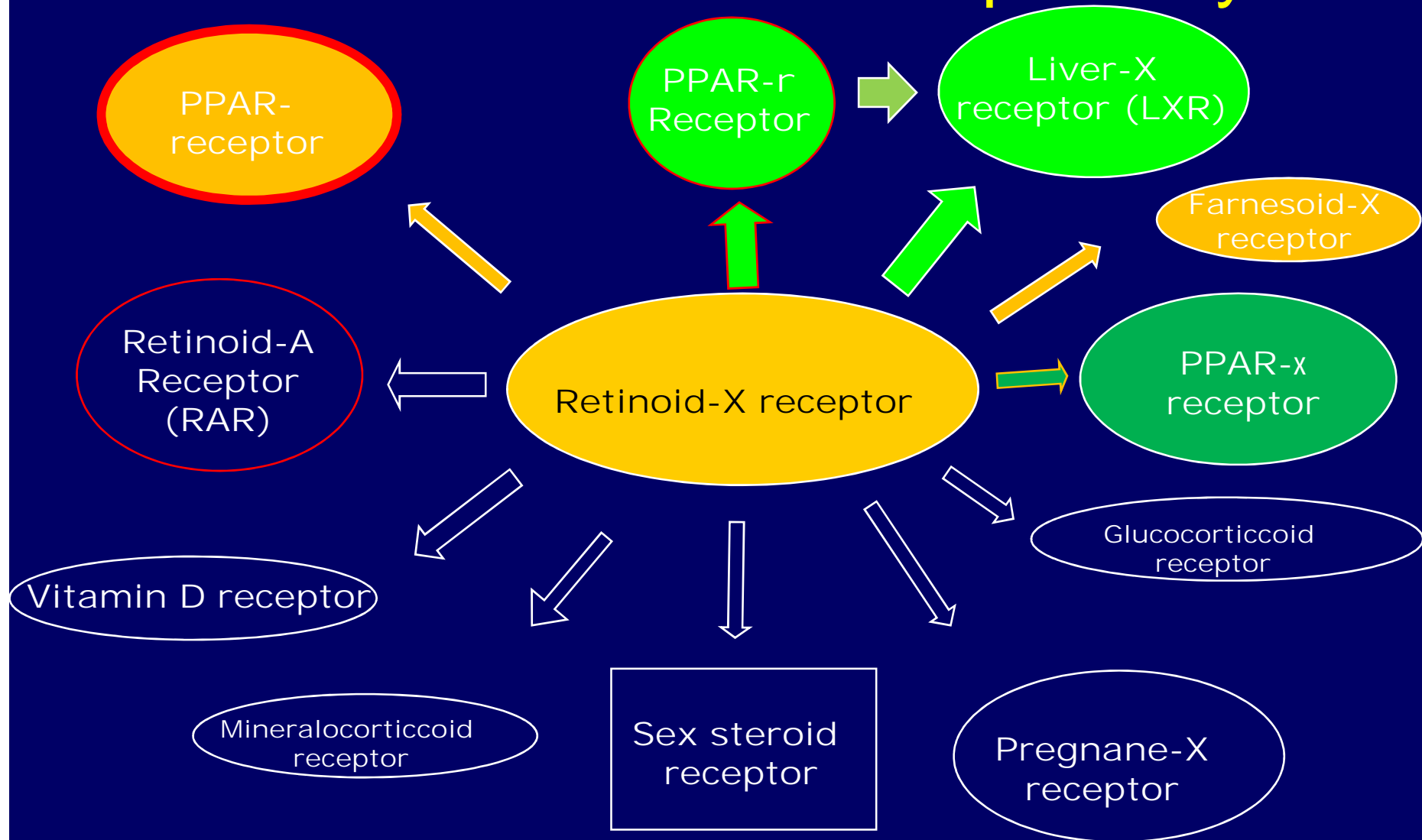
Change in atheroma volume on IVUS



Potential role of PPAR activation in CV risk reduction



The benefits & toxicity of fibrates via the Retinoid -X receptor system

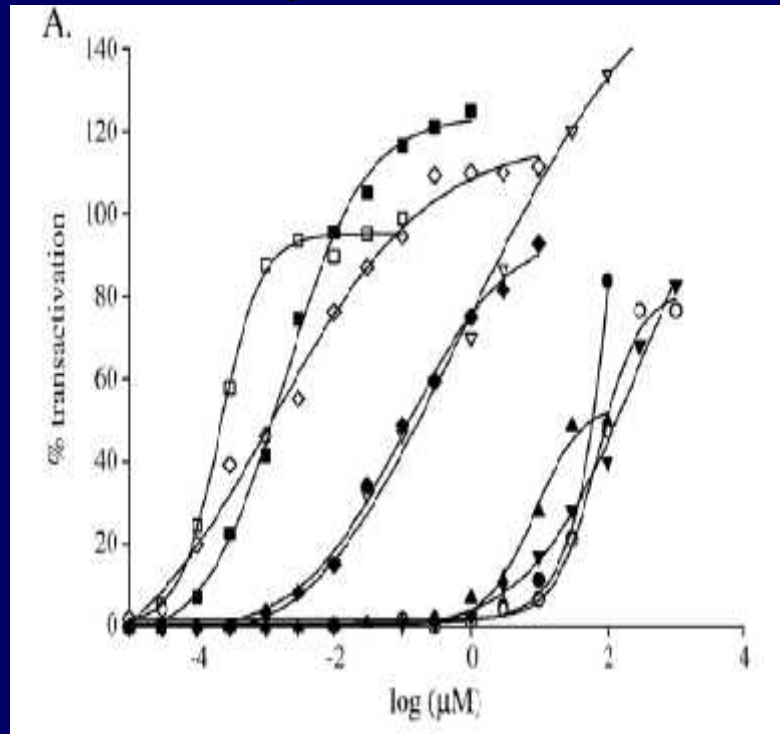


PPAR agents

- PPAR-alpha
 - Traditional fibrates:
 - gemfibrozil; fenofibrate;
 - bezafibrate (pan-PPAR?)
- PPAR-gamma
 - Glitazones: pioglitazone
- PPAR- alpha/delta
 - GFT-505
- PPAR-gamma/delta
 - DB-959

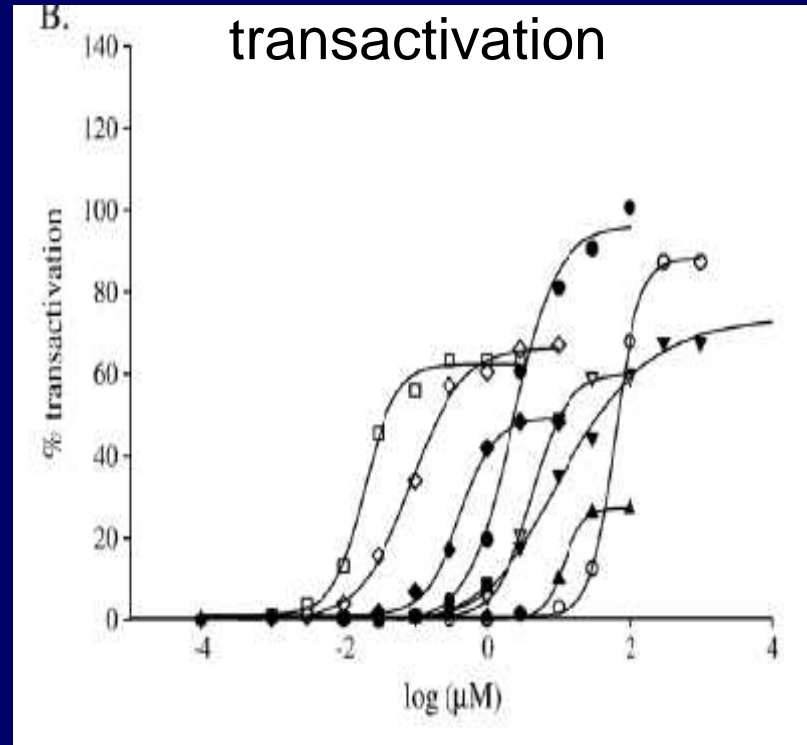
Effects of PPAR agonists on PPAR- & PPAR-

PPAR- γ transactivation



PPAR- α

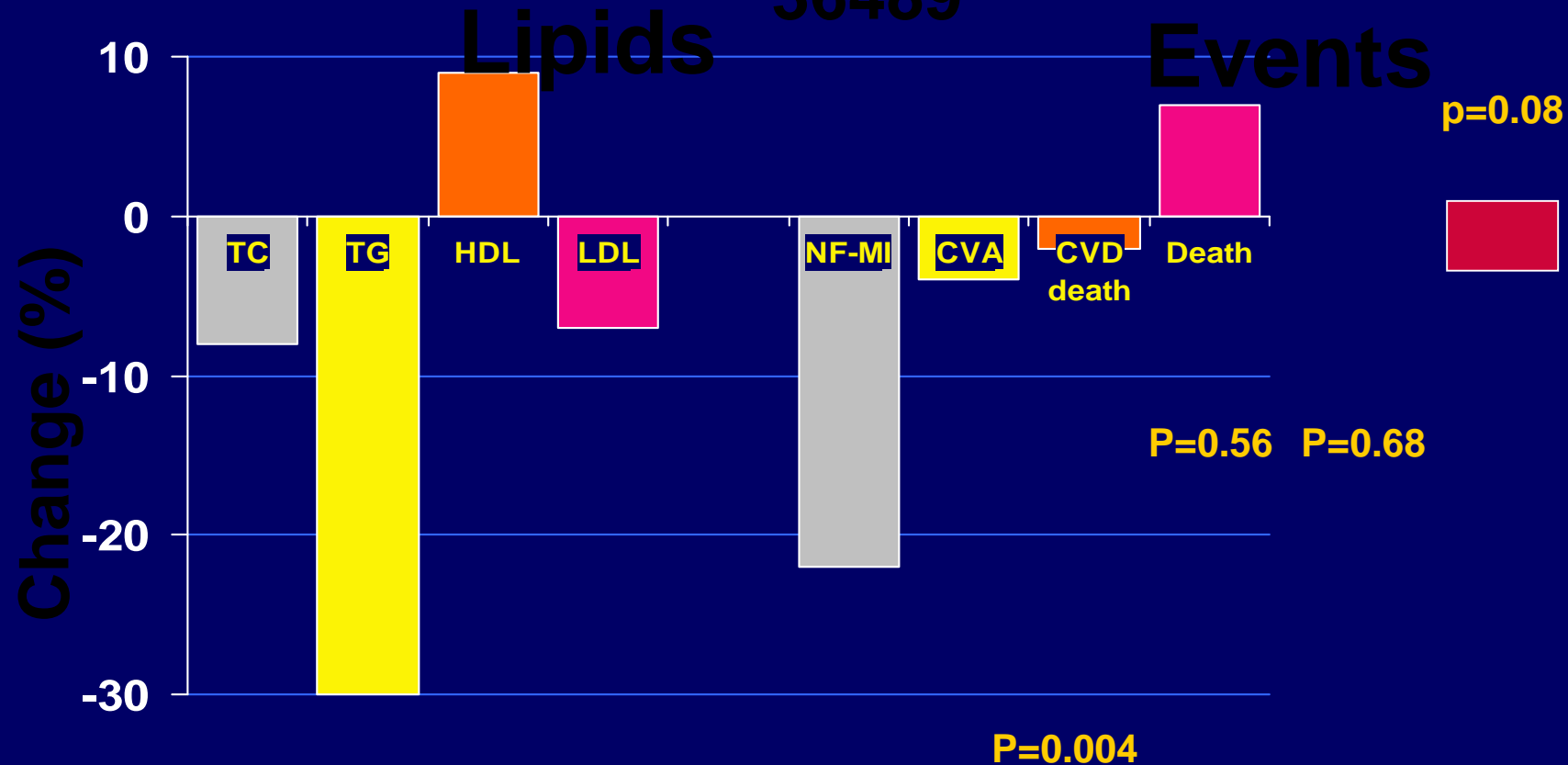
transactivation



- | | |
|-------------------|----------------|
| ● Fenofibric acid | ○ Gemfibrozil |
| ▼ Bezafibrate | ▽ Pioglitazone |
| ■ Rosiglitazone | □ Farglitazar |
| ◆ Tesaglitazar | ◇ Muraglitazar |
| ▲ Metaglidasen | |

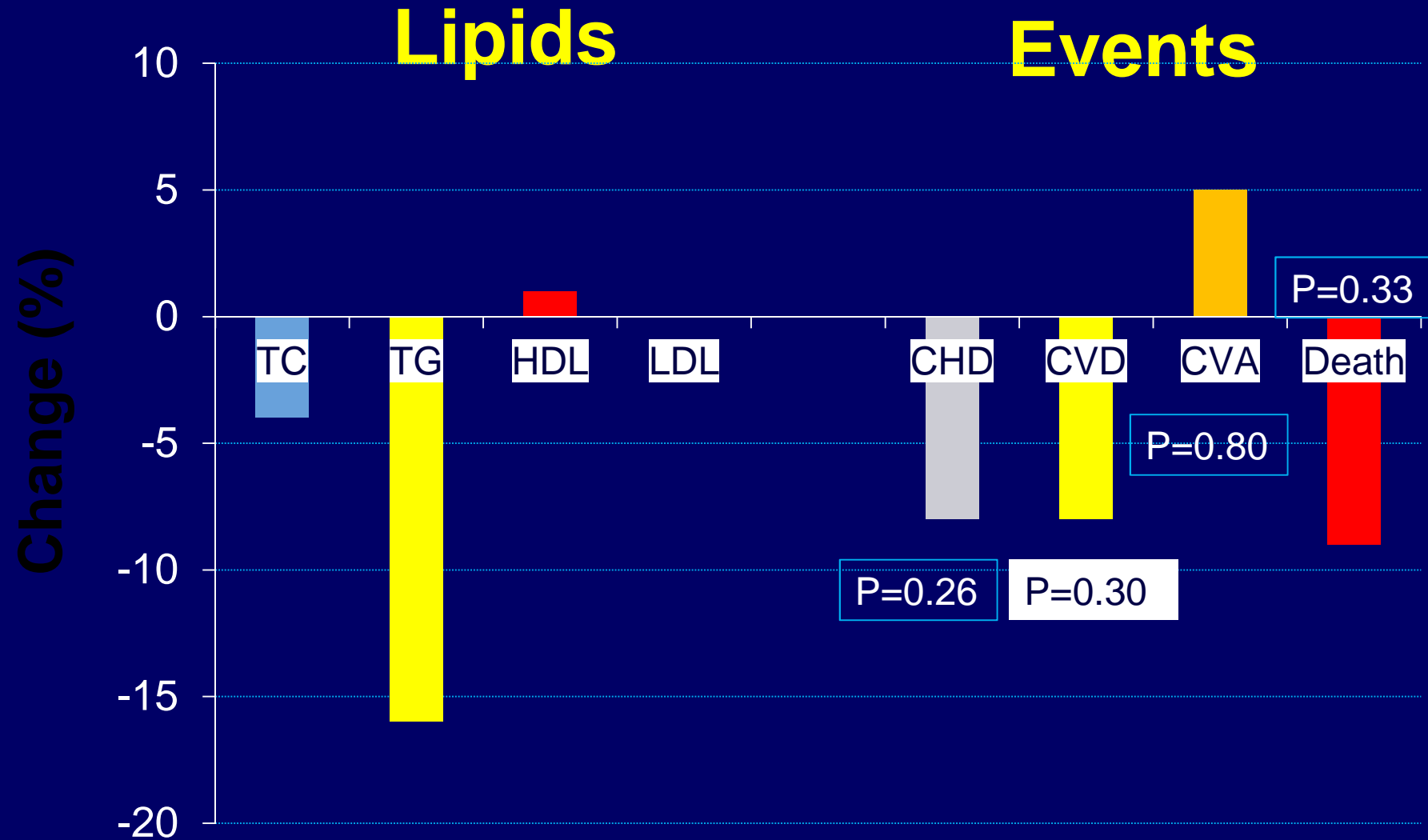
Fibrates : a meta-analysis

Secondary & primary prevention; 10 studies; n=36489



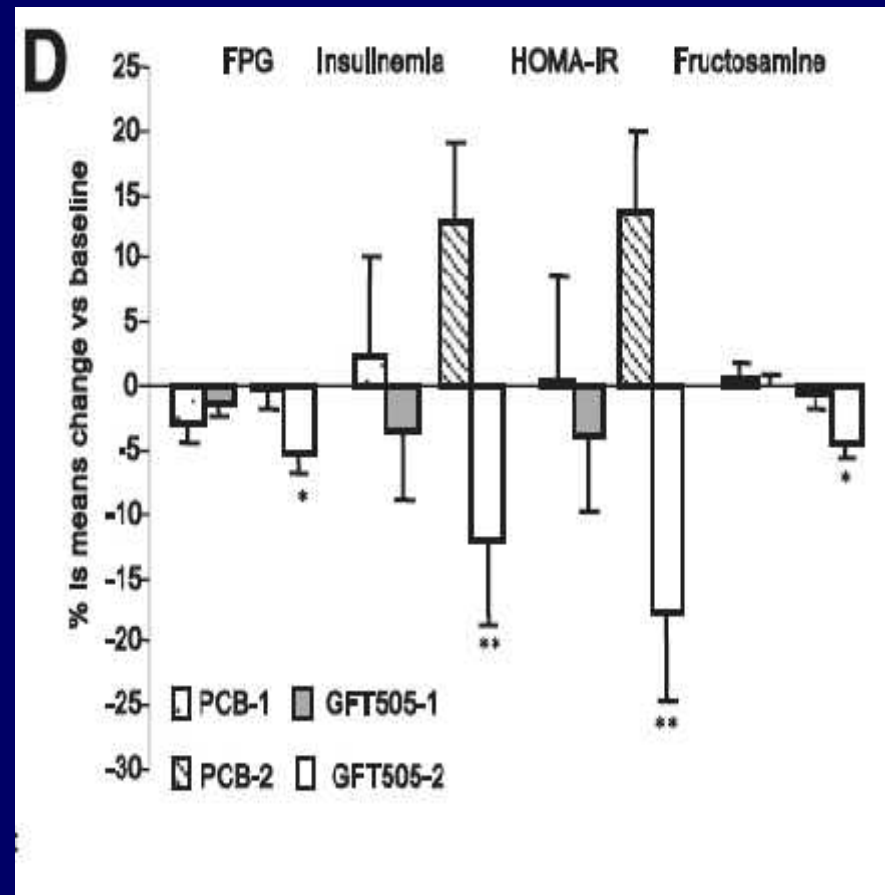
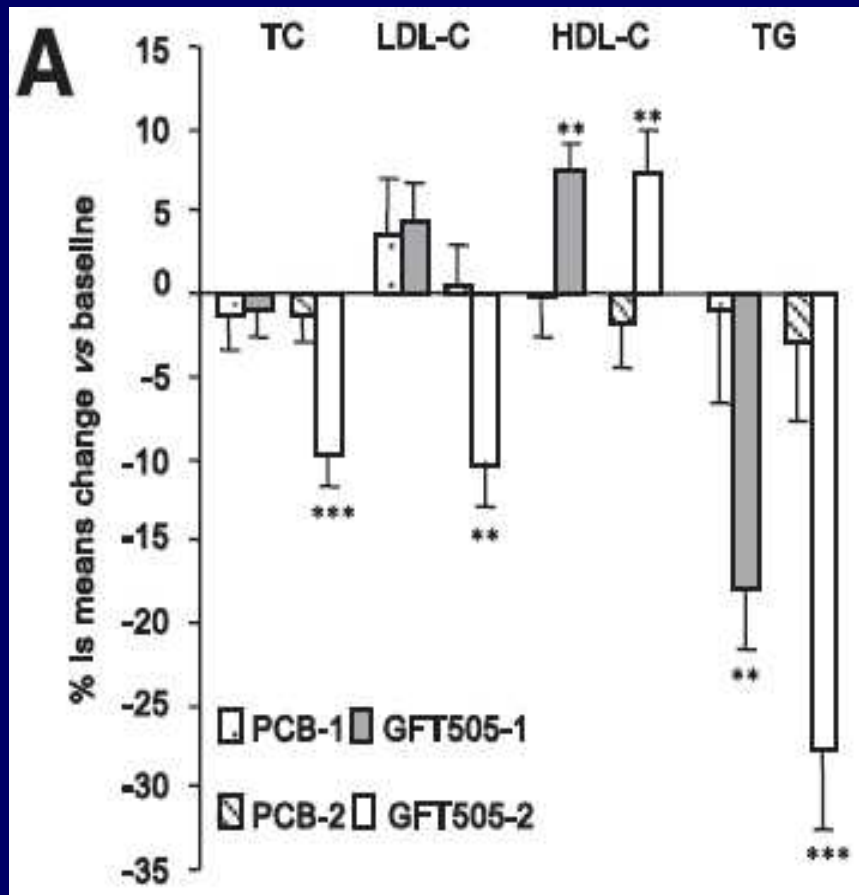
ACCORD: Fibrate on statin in type 2 diabetes

Secondary & primary prevention; n= 5518

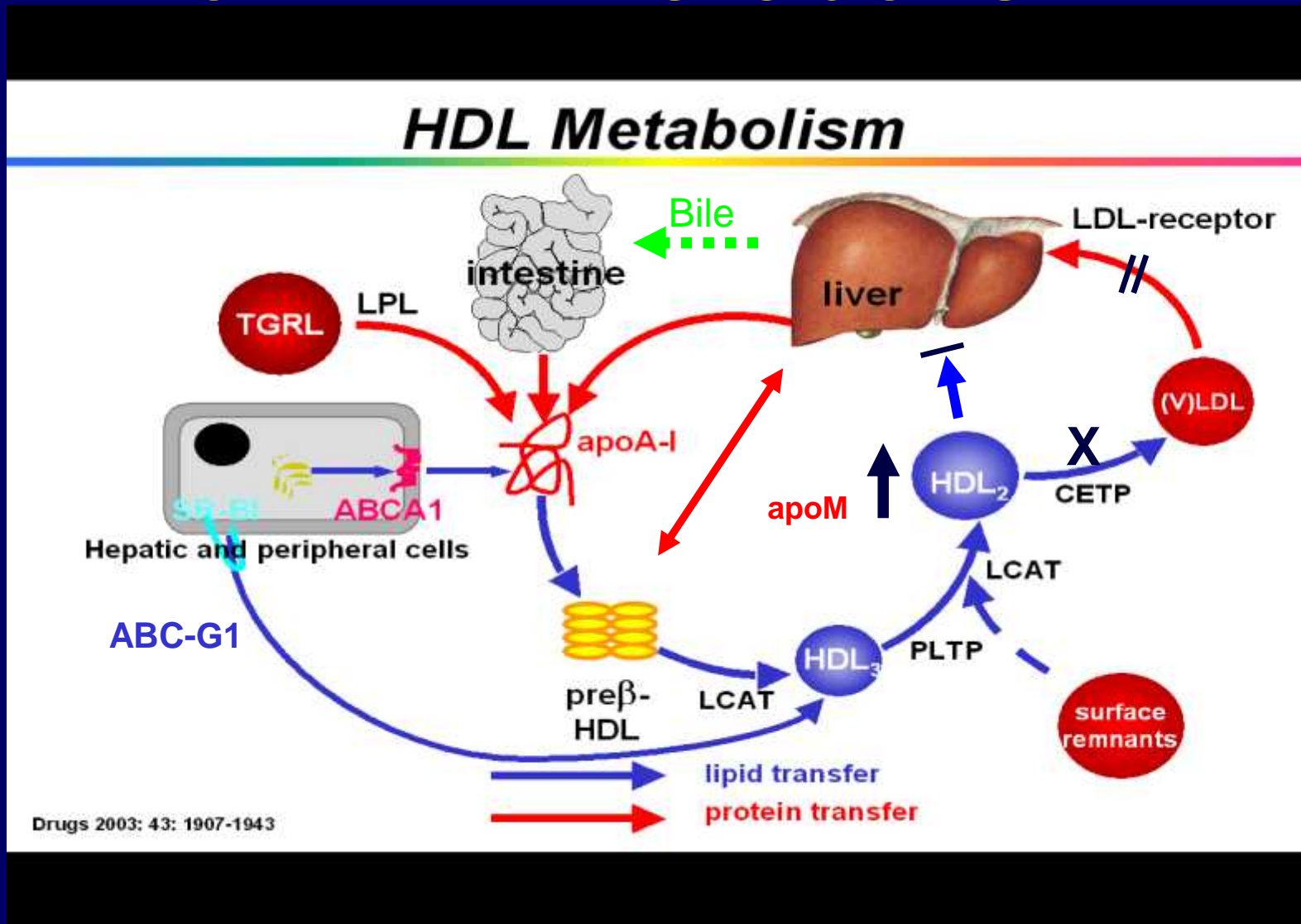


Ginsberg HN et al; NEJM 2010 ; 362 : 1563

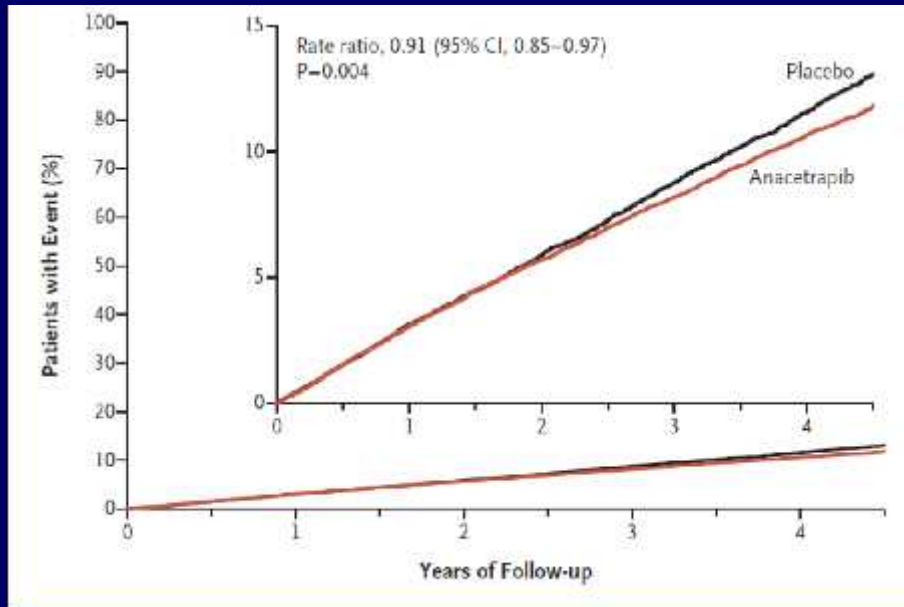
PPAR- / agonist (GFT-505) in mixed hyperlipidaemia



Effect of CETP inhibition on HDL Metabolism



REVEAL: CETP inhibition & CVD



Baseline LDL-C 1.58mM
(nonHDL-C 2.38mM)

LDL-C change

Direct method: -0.67mM; 41%

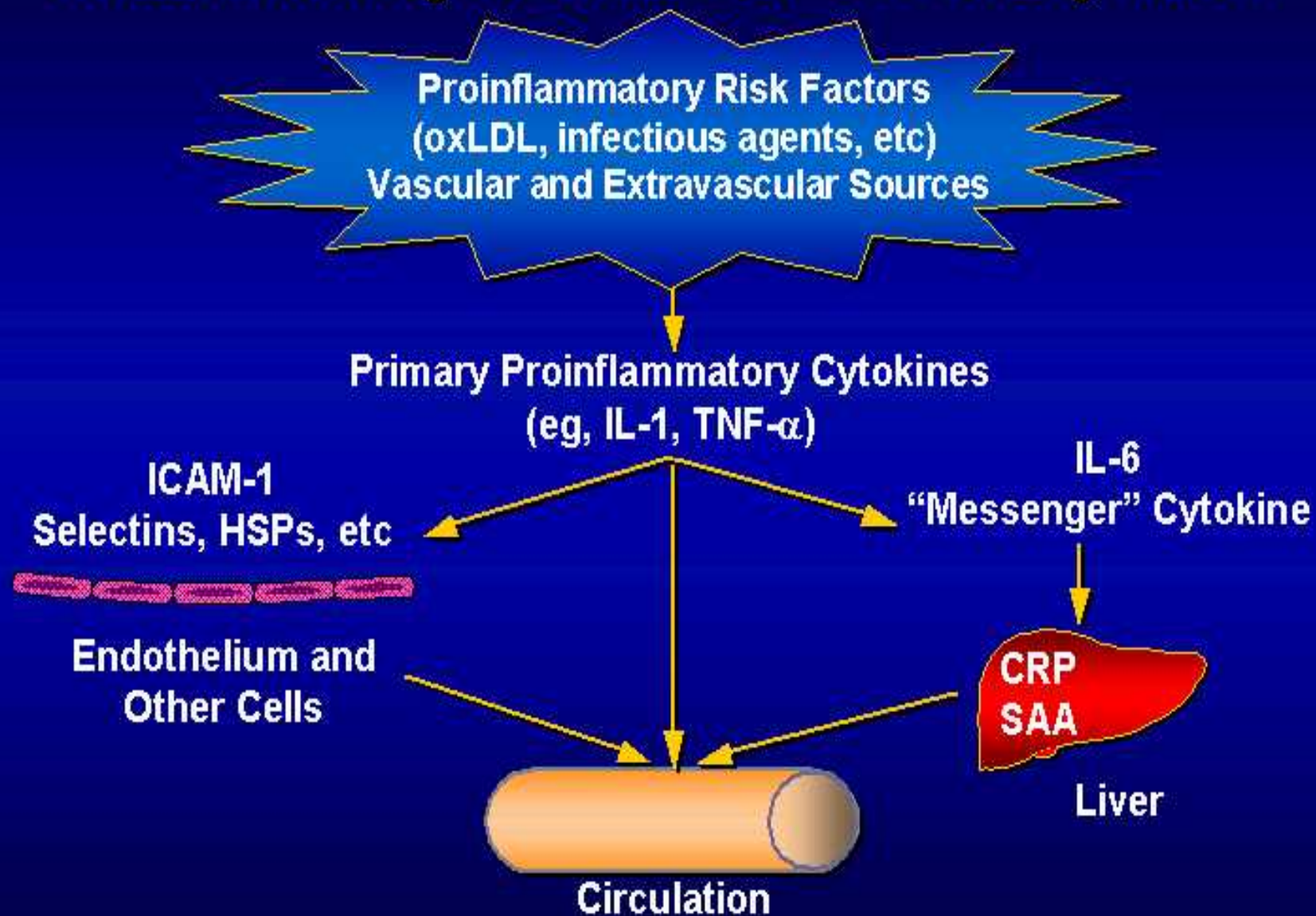
Beta-quant : - 0.3mM; 17%

Non-HDL-C -0.44mM; 18%

ApoB: -12 mg/dL ; 18%

Type of Event	Anacetrapib (N=15,225) <i>no. of patients with event (%)</i>	Placebo (N=15,224) <i>no. of patients with event (%)</i>	Rate Ratio (95% CI)	P Value
Coronary death	388 (2.5)	420 (2.8)	0.92 (0.80-1.06)	0.25
MI	669 (4.4)	769 (5.1)	0.87 (0.78-0.96)	0.007
Coronary death or MI	934 (6.1)	1048 (6.9)	0.89 (0.81-0.97)	0.008
Coronary revascularization	1081 (7.1)	1201 (7.9)	0.90 (0.83-0.97)	0.01
Major coronary event	1640 (10.8)	1803 (11.8)	0.91 (0.85-0.97)	0.004
Presumed ischemic stroke	485 (3.2)	489 (3.2)	0.99 (0.87-1.12)	NA
Major atherosclerotic event	1383 (9.1)	1483 (9.7)	0.93 (0.86-1.00)	0.052
Major vascular event	2068 (13.6)	2214 (14.5)	0.93 (0.88-0.99)	0.02

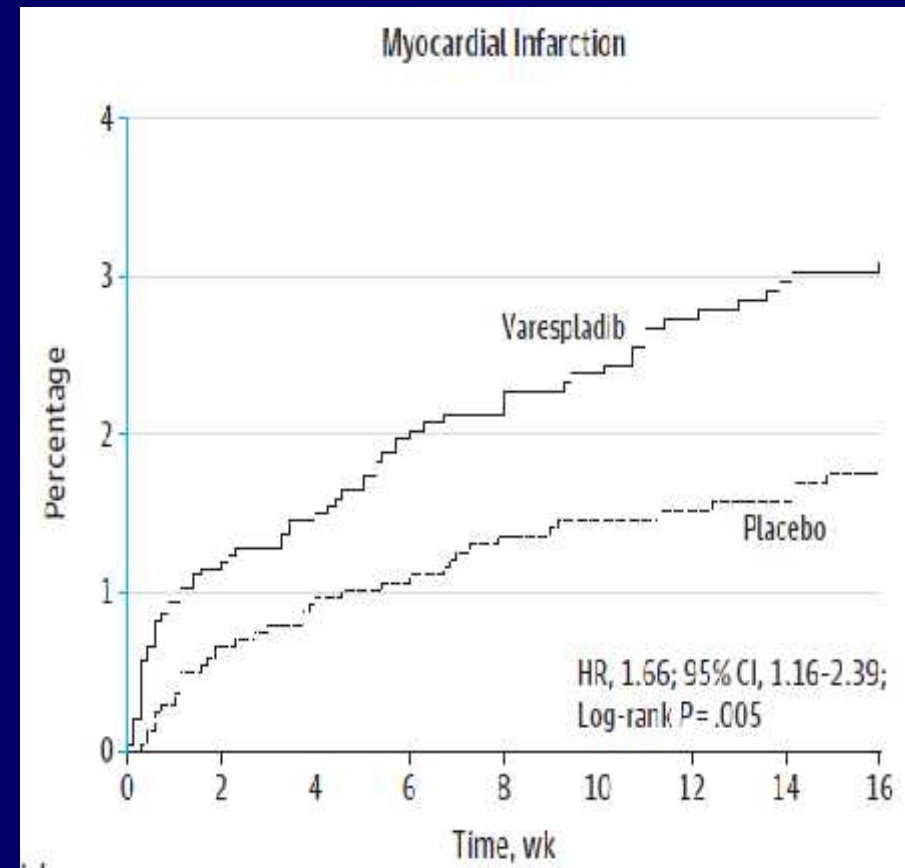
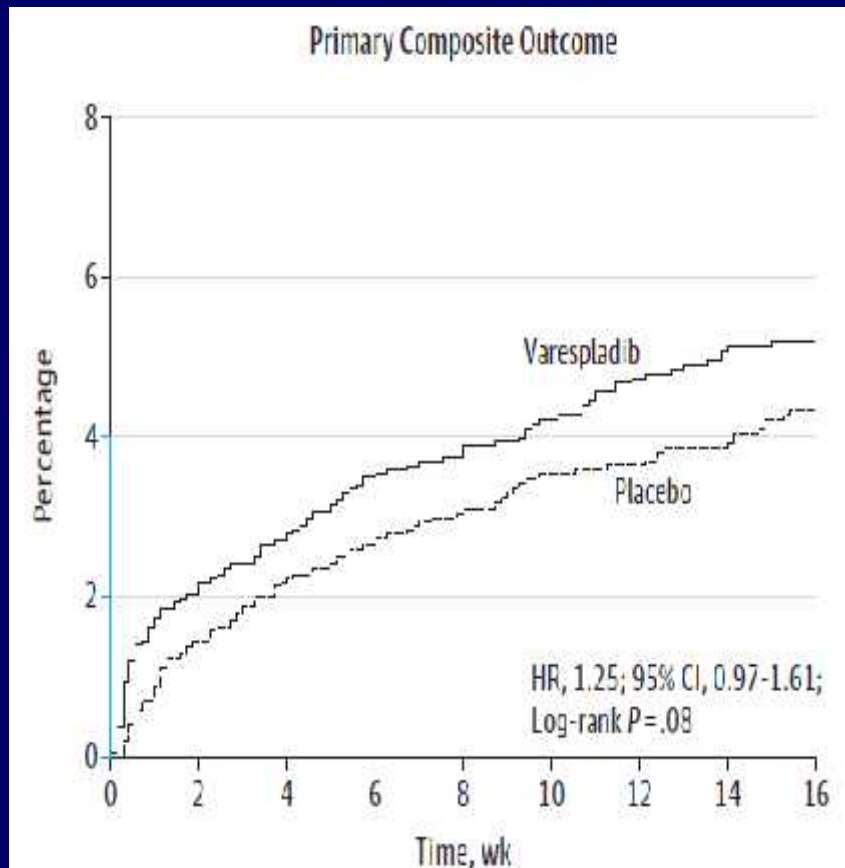
Inflammatory Markers of Coronary Risk



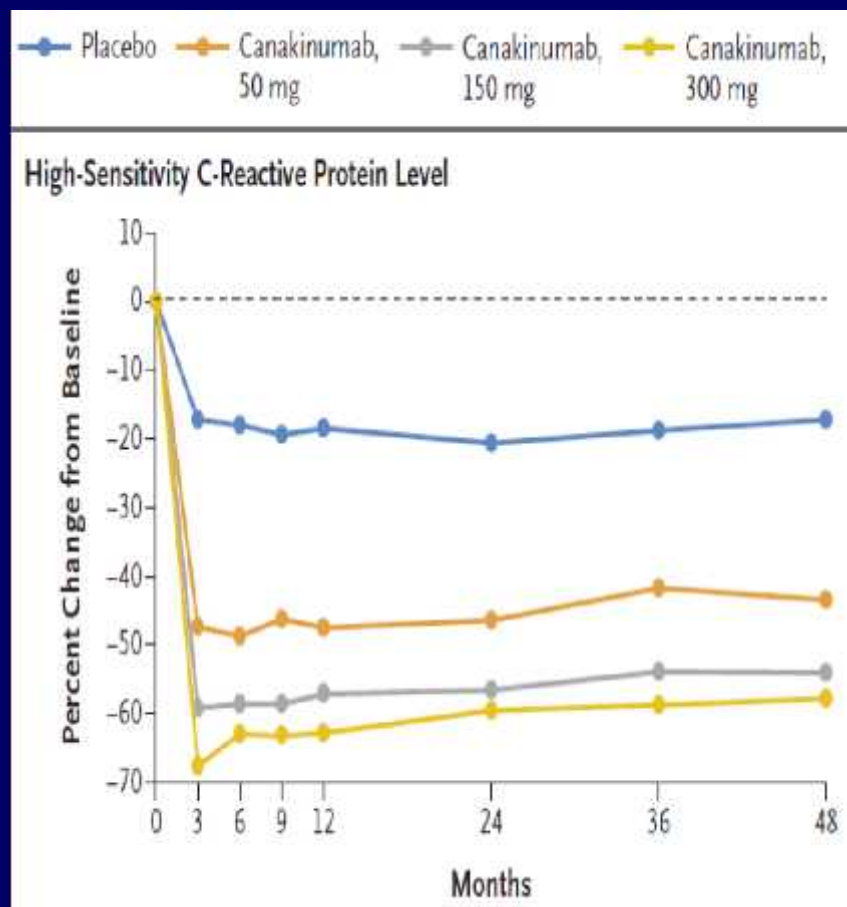
New drugs affecting Lipid-inflammation metabolism

- Anti-inflammatory
 - ACAT inhibitors (macrophage)
 - Avasimibe
 - Pactimibe
 - VCAM-1 uncouplers
 - Probucoi
 - AGI-1067
 - PLA2 inhibitors
 - Daraplabib (LpPLA2)
 - Varespladib (sPLA2)
 - IL-1 inhibitors
 - Canakinumab

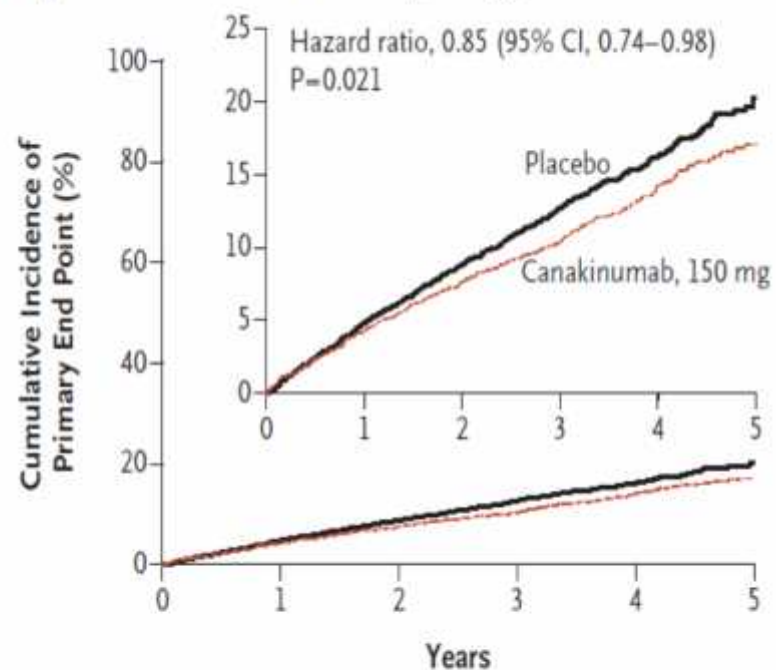
sPLA2 inhibition. Varespladib in ACS: VISTA-16



CANTOS: IL-1 inhibition and CVD: canakinumab



B Primary End Point with Canakinumab, 150 mg, vs. Placebo



No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2284	2151	2057	1849	907	207

Ridker PM et al; NEJM 2017; 377: 1119

Guidelines: Defining recommendations

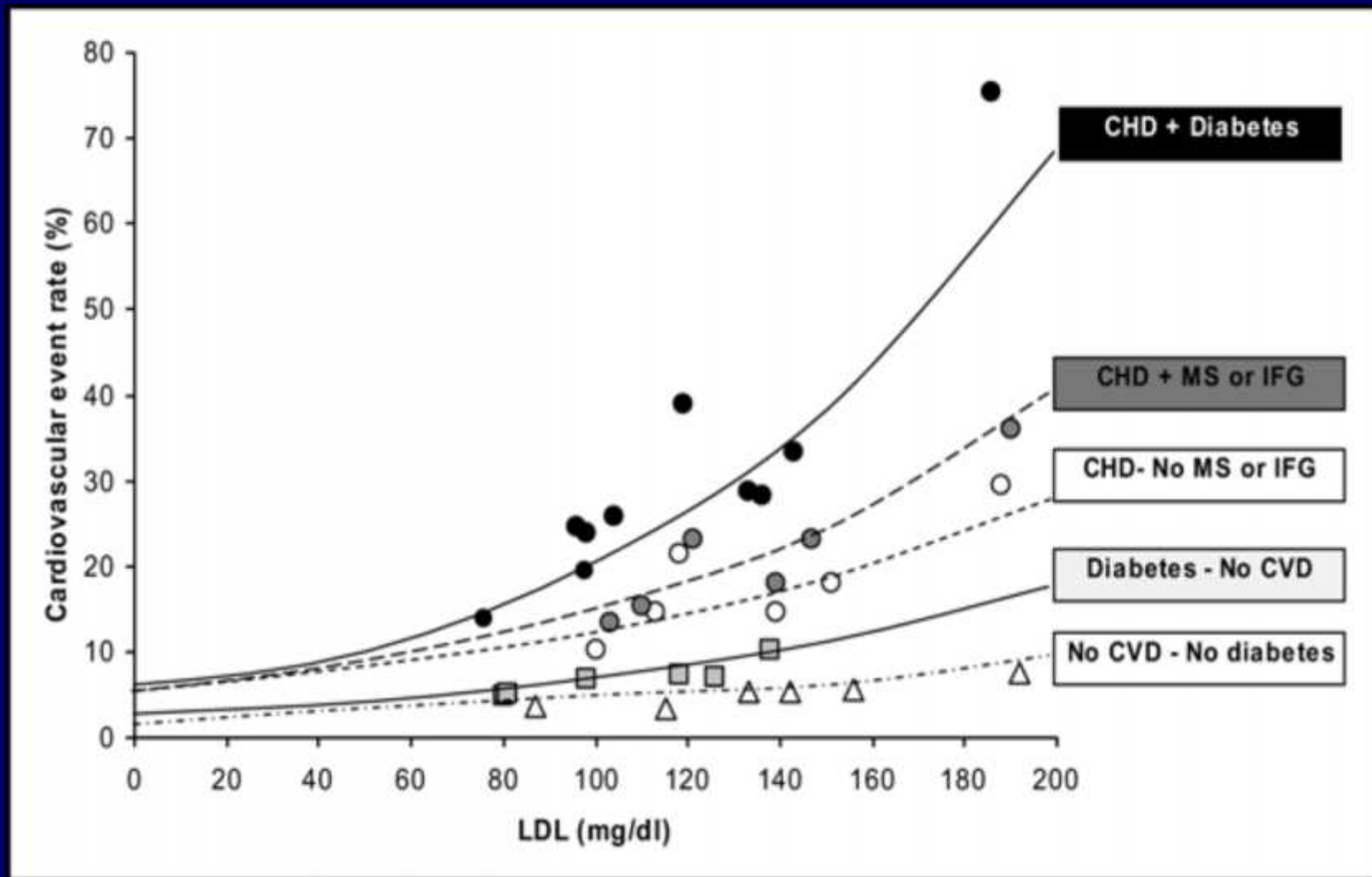
Targets

- Consistent with epidemiology
- Rare in clinical trials
- Traditional output
- Focused on single risk factor
- Set on 50th centile
- Requires multiple monitoring

Drug-based

- Consistent with trials
 - Exception limits defined
- Common trial design
- Novel output
- Focused on overall risk
- Centile-independent
- Minimal monitoring required

CVD risk for different groups



Conclusions

- Additional therapies are required because
 - Statins only reduce risk by 50%
 - 1-2% patients cannot tolerate statins
 - Ezetimibe adds only 17-21% LDL-C reduction
 - LDL-C targets are falling towards 1.50 mmol/L (60 mg/dL)
- Novel approaches are required in high-risk groups
 - e.g. diabetes; FH
- New compounds for orphan lipid disorders
 - Familial hylomicronaemia; homozygous FH
- Other mechanisms may accelerate atherosclerosis & CVD
 - Compounds targeting inflammation
 - Compounds with added benefits e.g. GLP-1 agonists; SGLT-2 inhibitors