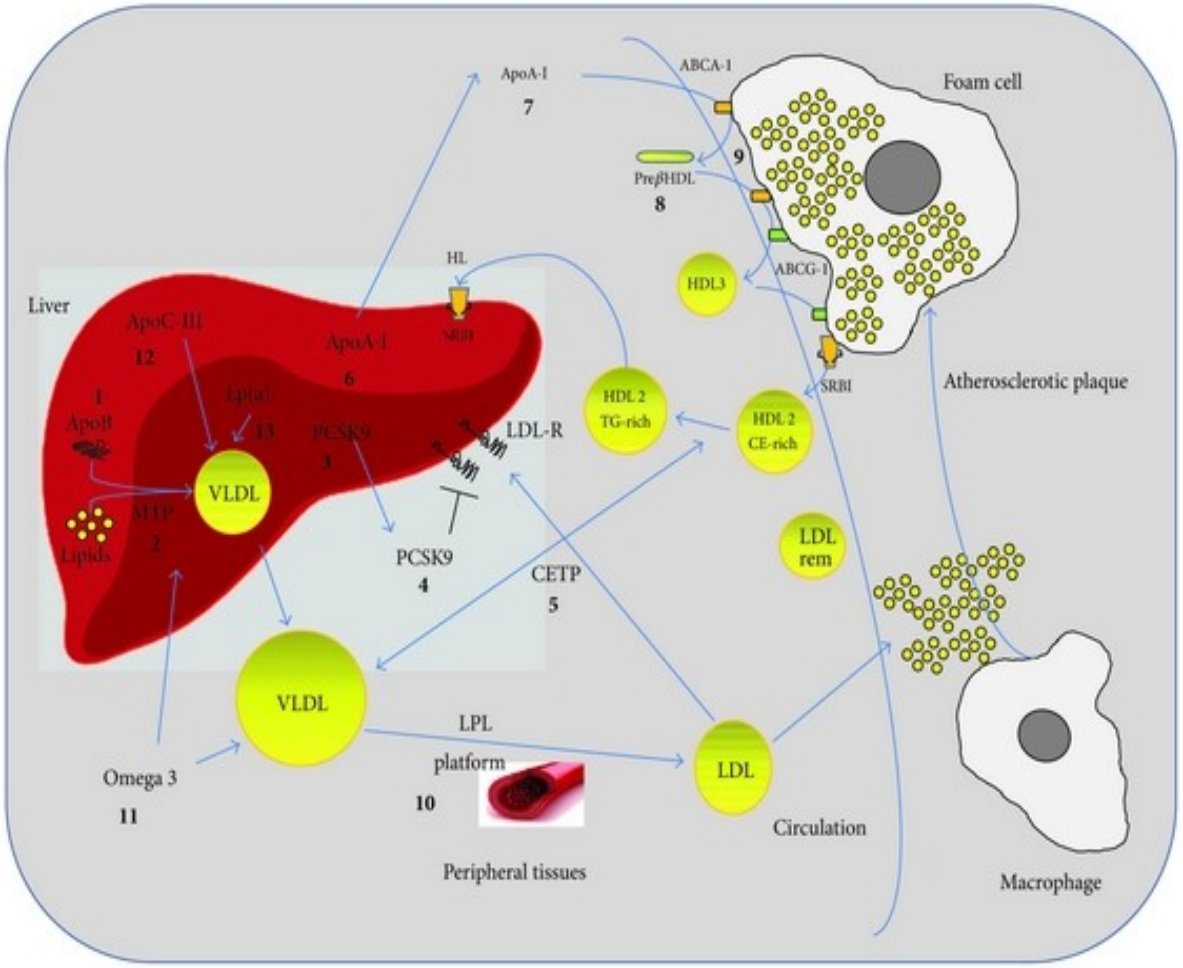
Да очакваме ли нови медикаменти при лечение на дислипидемията?

Проф. Д-р А.Гудев, FESC, FACC

УМБАЛ “Царица Йоанна – ИСУЛ”

- Механизми на лечение на дислипидемията
- Намаляване на LDL холестерола – терапия със статини
- Повлияване на HDL холестерола
- Повлияване на възпалението

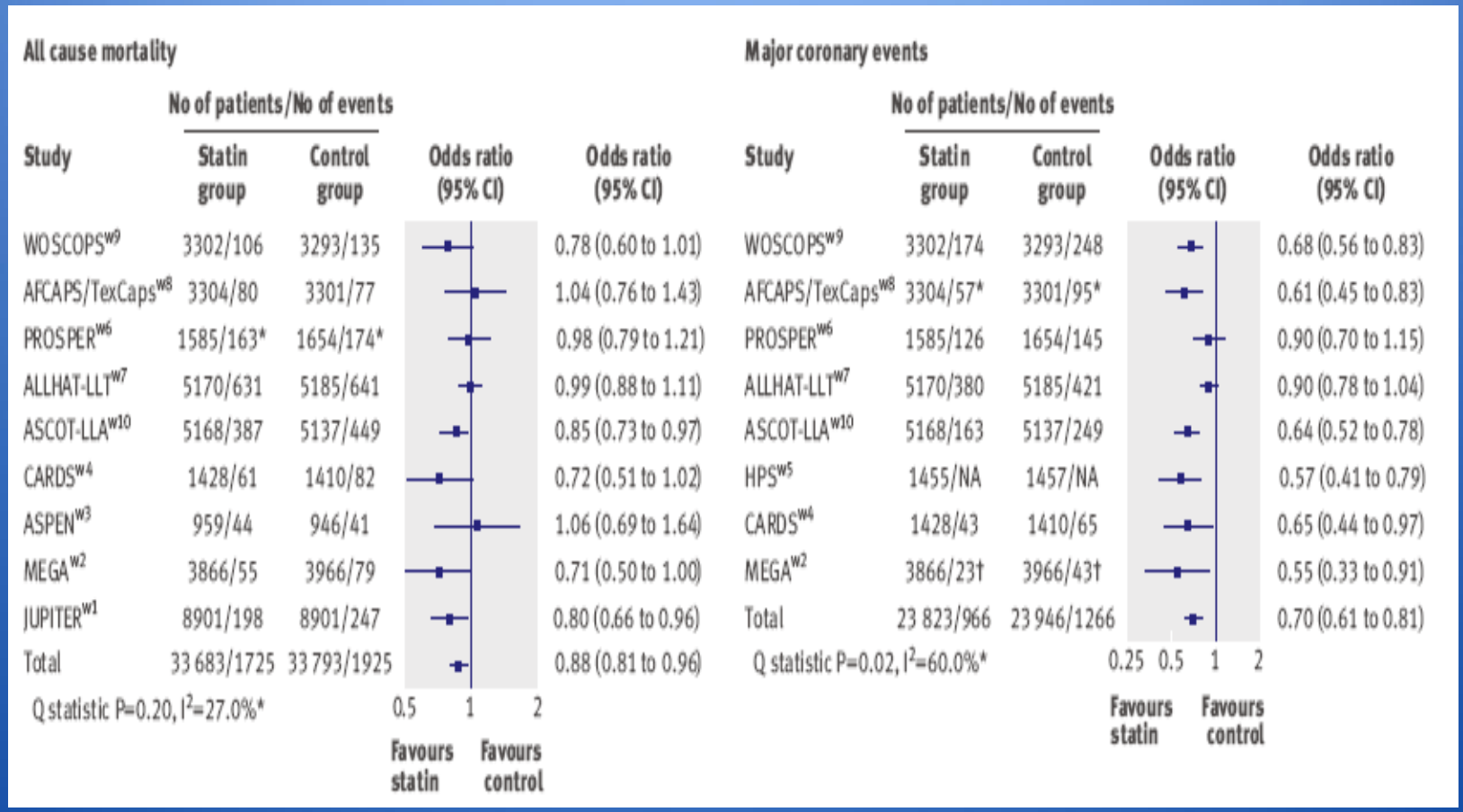
Основни механизми на лечение на дислипидемията



- ***Намаляване на LDL холестерола***
- ***Увеличаване на HDL холестерола***
- ***Повлияване на възпалението***

Намаляване на LDL холестерола – терапия със статини

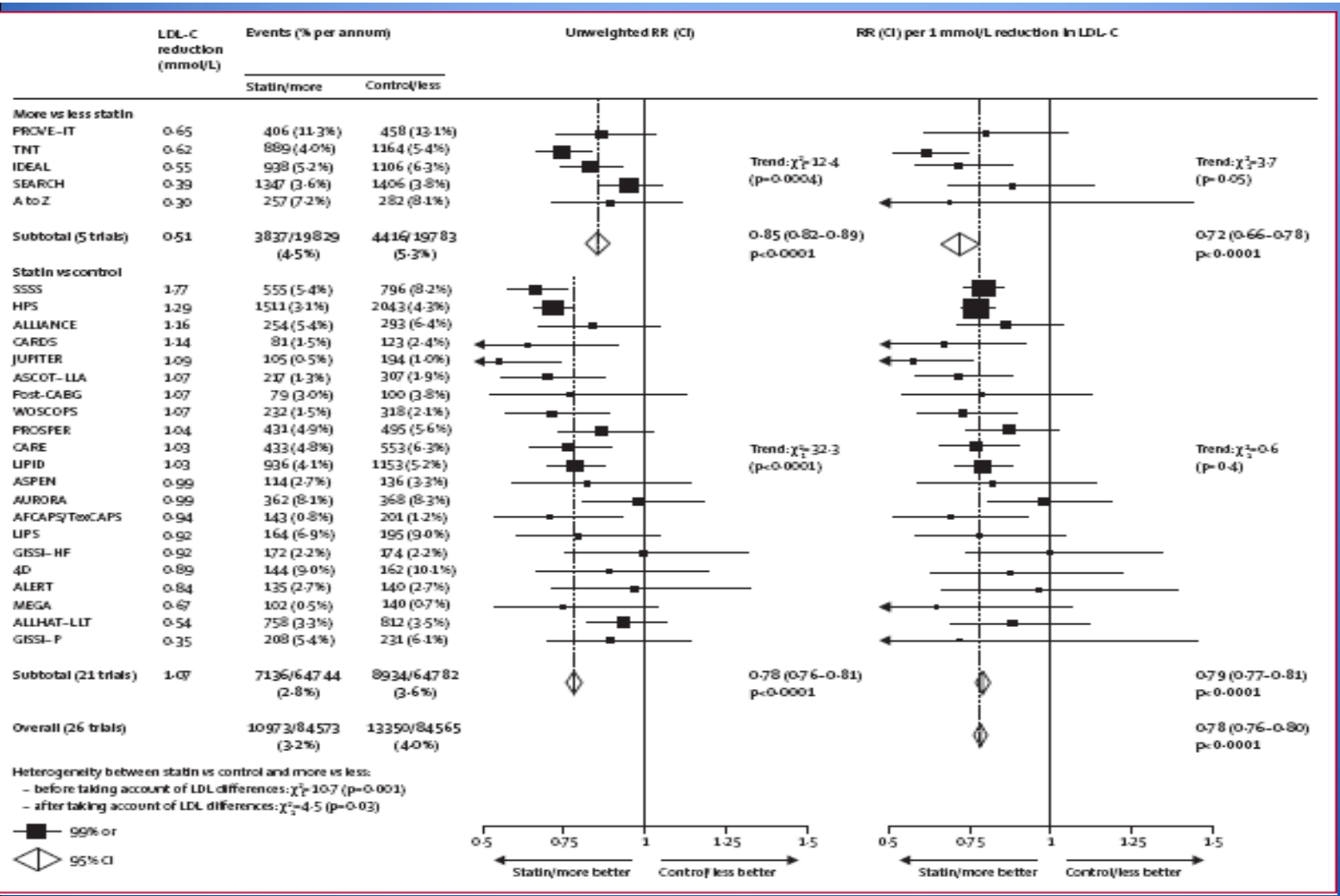
The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials



BMJ 2009;338:b2376

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**



Lancet 2010; 376: 1670–8

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

The NEW ENGLAND JOURNAL of MEDICINE

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

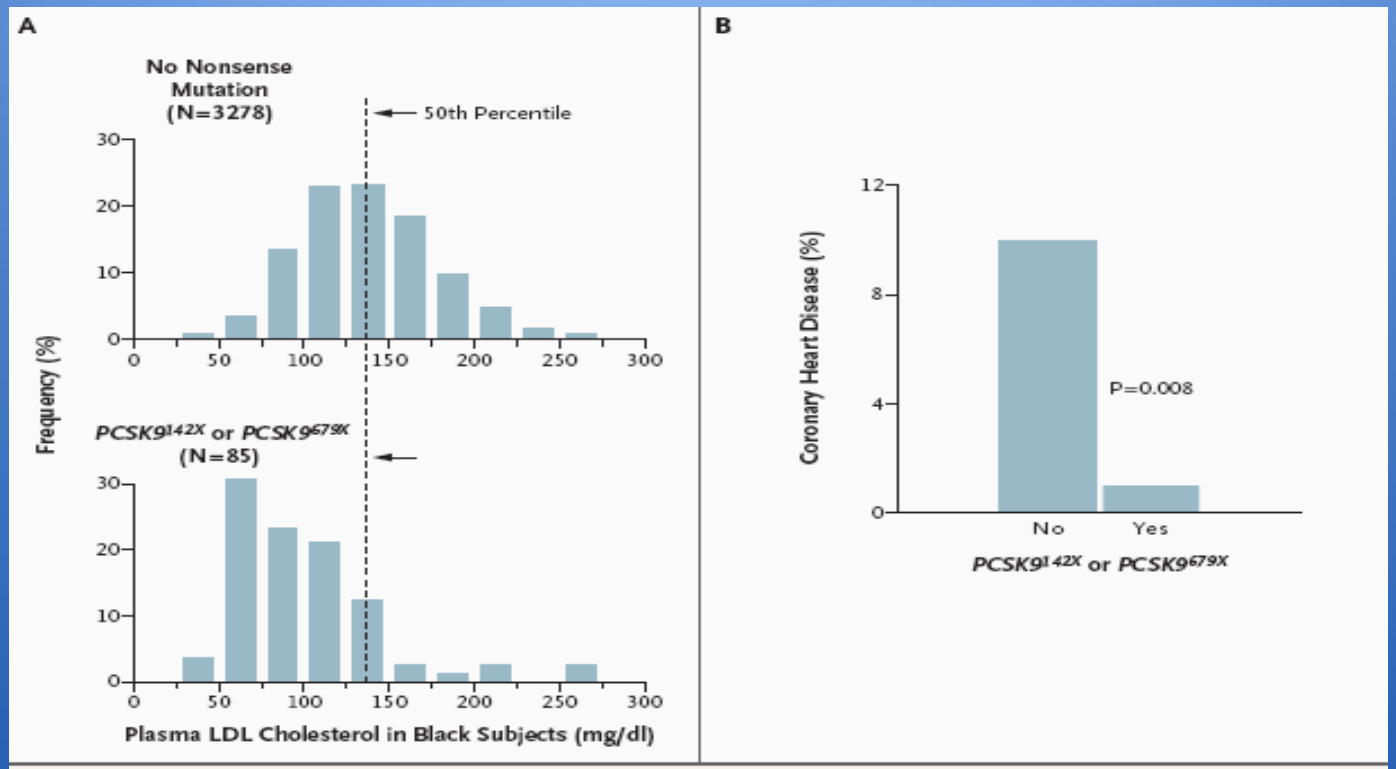


Figure 1. Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a *PCSK9*^{142X} or *PCSK9*^{679X} Allele.

In Panel A, the distribution of plasma LDL cholesterol levels at baseline among 3278 black subjects who did not have a *PCSK9*^{142X} or *PCSK9*^{679X} allele (top) is compared with the distribution of levels among the 85 black subjects who had one of these two alleles (bottom). Panel B shows the percentage of participants from these two groups who had no evidence of coronary heart disease at baseline and in whom coronary heart disease developed during the 15-year follow-up period. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

N Engl J Med 2006;354:1264-72

The Severe Hypercholesterolemia Phenotype

Clinical Diagnosis, Management, and Emerging Therapies

Allan D. Sniderman, MD,* Sotirios Tsimikas, MD,† Sergio Fazio, MD, PhD‡

Montreal, Quebec, Canada; La Jolla, California; and Nashville, Tennessee

Journal of the American College of Cardiology

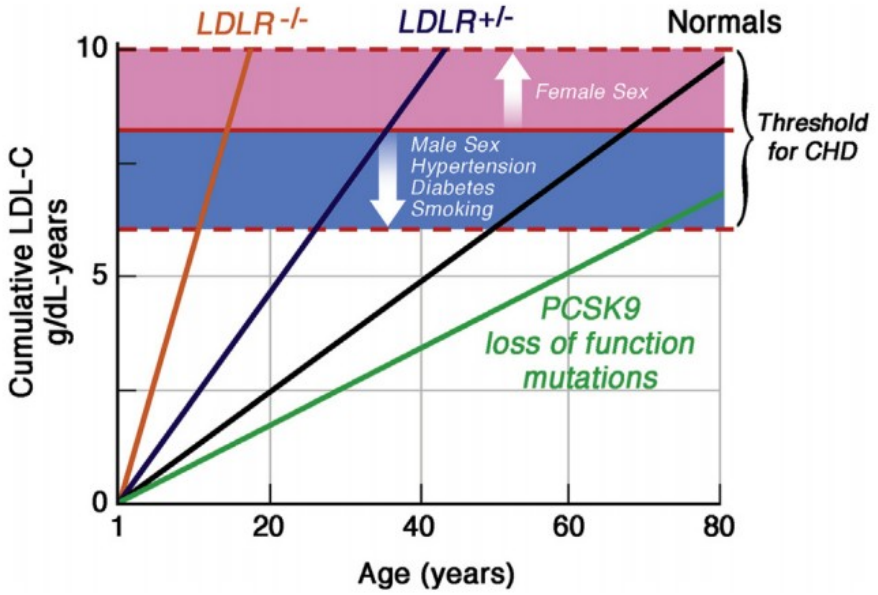
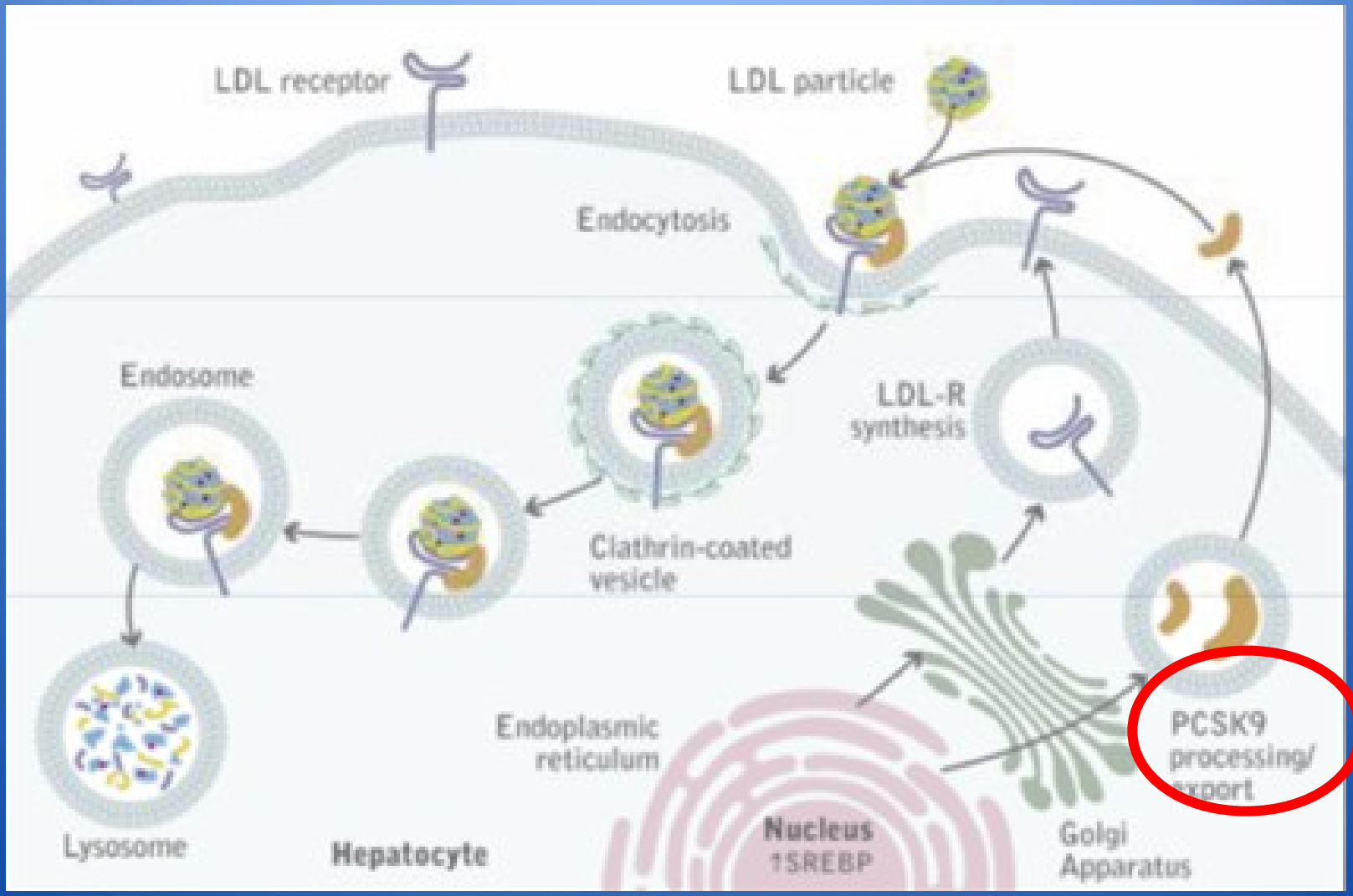


Figure 1 **Relationship Between Age and Cumulative LDL-C Exposure**

Coronary heart disease (CHD) risk is estimated for homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), and age-adjusted low-density lipoprotein cholesterol (LDL-C) levels in normal individuals. The **horizontal red line** represents a theoretical threshold of the cumulative LDL-C exposure required for development of CHD. The **height of the red line** will be lower in the presence of additional CHD risk factors. Reprinted with permission from Horton et al. (7).

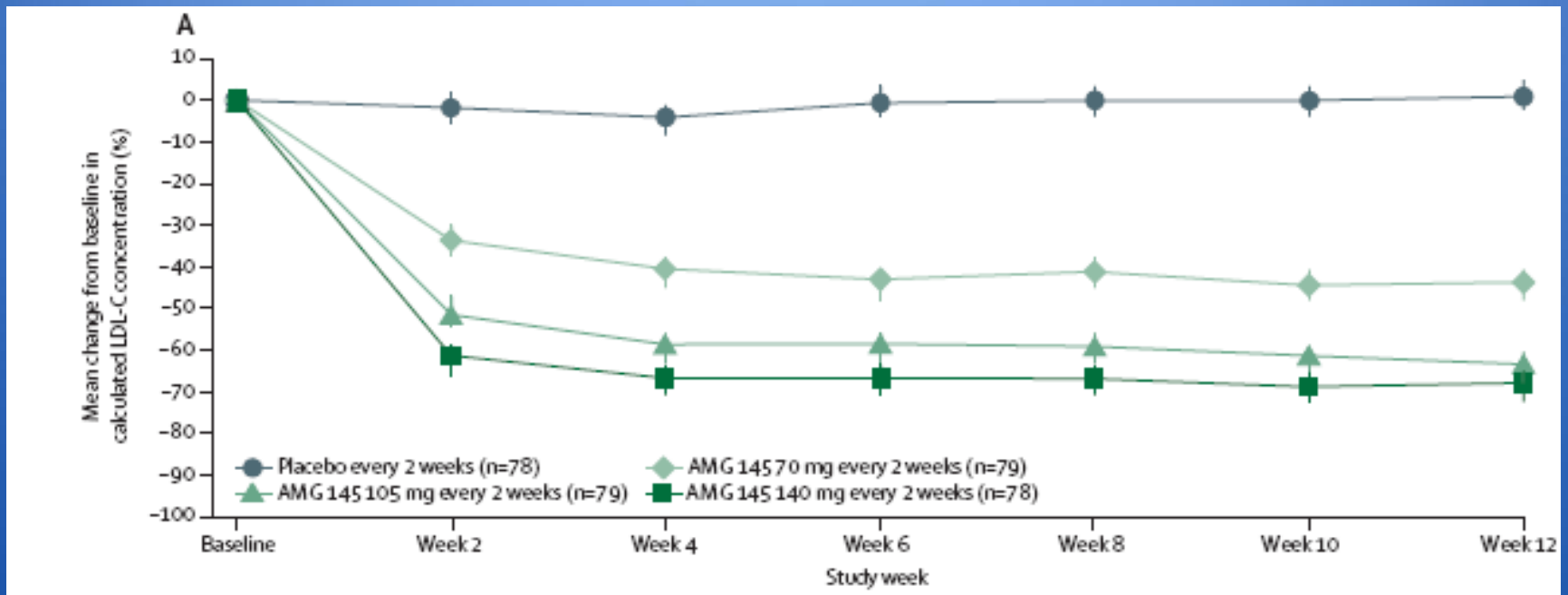
Vol. 63, No. 19, 2014

Повлияване на PCSK9



Lambert, at al. J Lipid Res. 201

Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study



Number of patients							
Placebo	78	74	77	78	76	77	74
AMG 145 70 mg	79	78	77	75	76	76	76
AMG 145 105 mg	79	76	76	77	73	77	74
AMG 145 140 mg	78	77	76	77	75	76	73

B

Lancet 2012; 380: 2007–17

Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER)

- A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy In Patients With Clinically Evident Cardiovascular Disease

www.amgen.com

ODYSSEY OUTCOMES Study

- Effect of SAR236553/REGN727 on the occurrence of cardiovascular events (composite endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients who have recently experienced an acute coronary event.

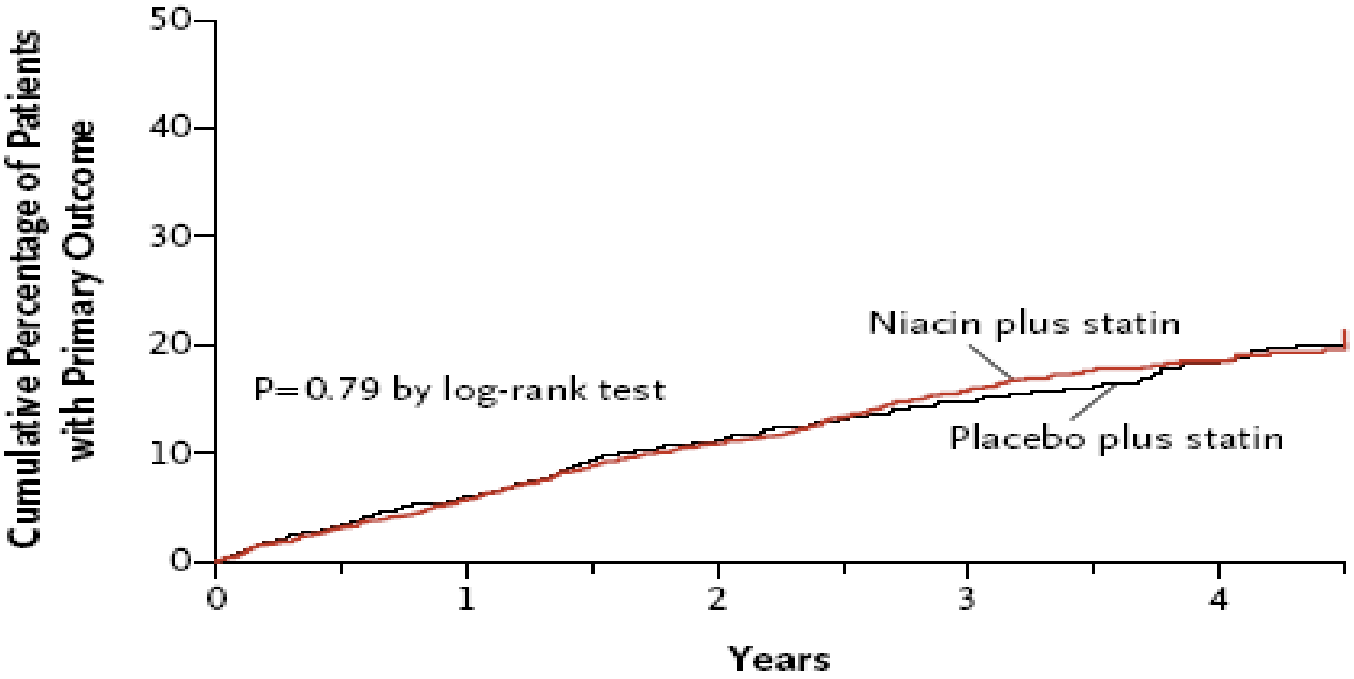
www.odysseytrials.com

Повлияване на HDL холестерола

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

The AIM-HIGH Investigators*

The NEW ENGLAND JOURNAL of MEDICINE



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.

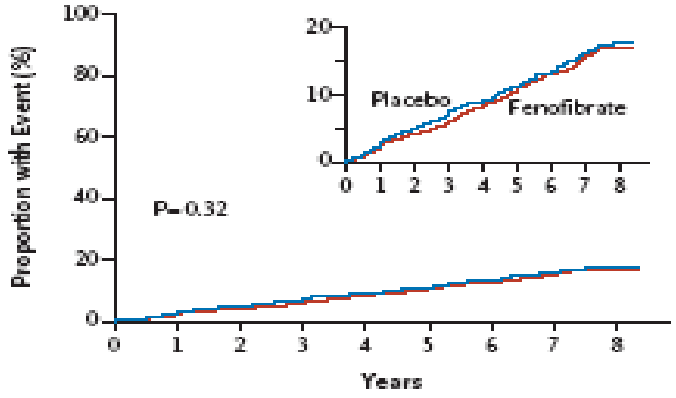
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial. N Eng J Med 2011; 365 : 2255-67

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*

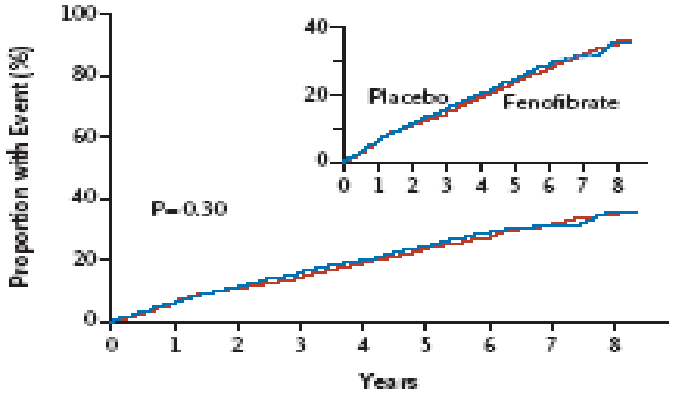
The NEW ENGLAND JOURNAL of MEDICINE

A Primary Outcome



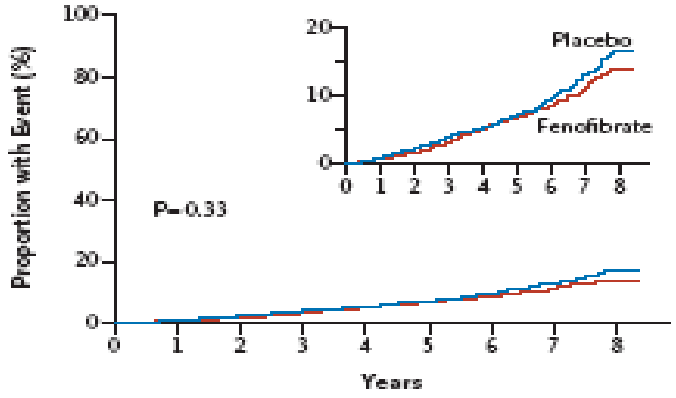
No. at Risk									
Fenofibrate	2765	2644	2565	2485	1981	1160	412	249	137
Placebo	2753	2634	2528	2442	1979	1161	395	245	131

B Expanded Macrovascular Outcome



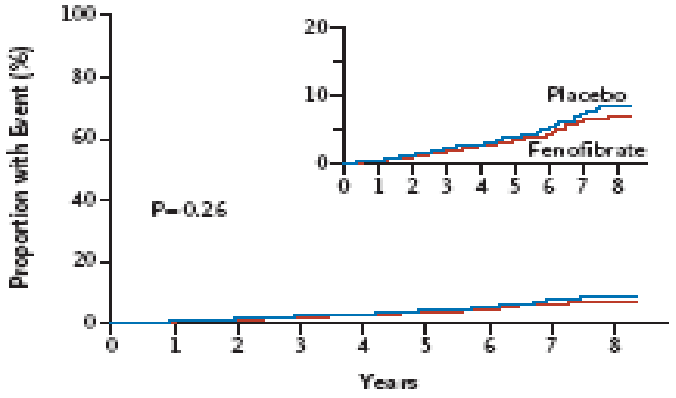
No. at Risk									
Fenofibrate	2765	2538	2390	2262	1751	999	354	211	112
Placebo	2753	2531	2357	2207	1732	992	316	201	104

C Death from Any Cause



No. at Risk									
Fenofibrate	2765	2737	2704	2646	2147	1271	469	285	157
Placebo	2753	2723	2680	2615	2164	1293	450	274	157

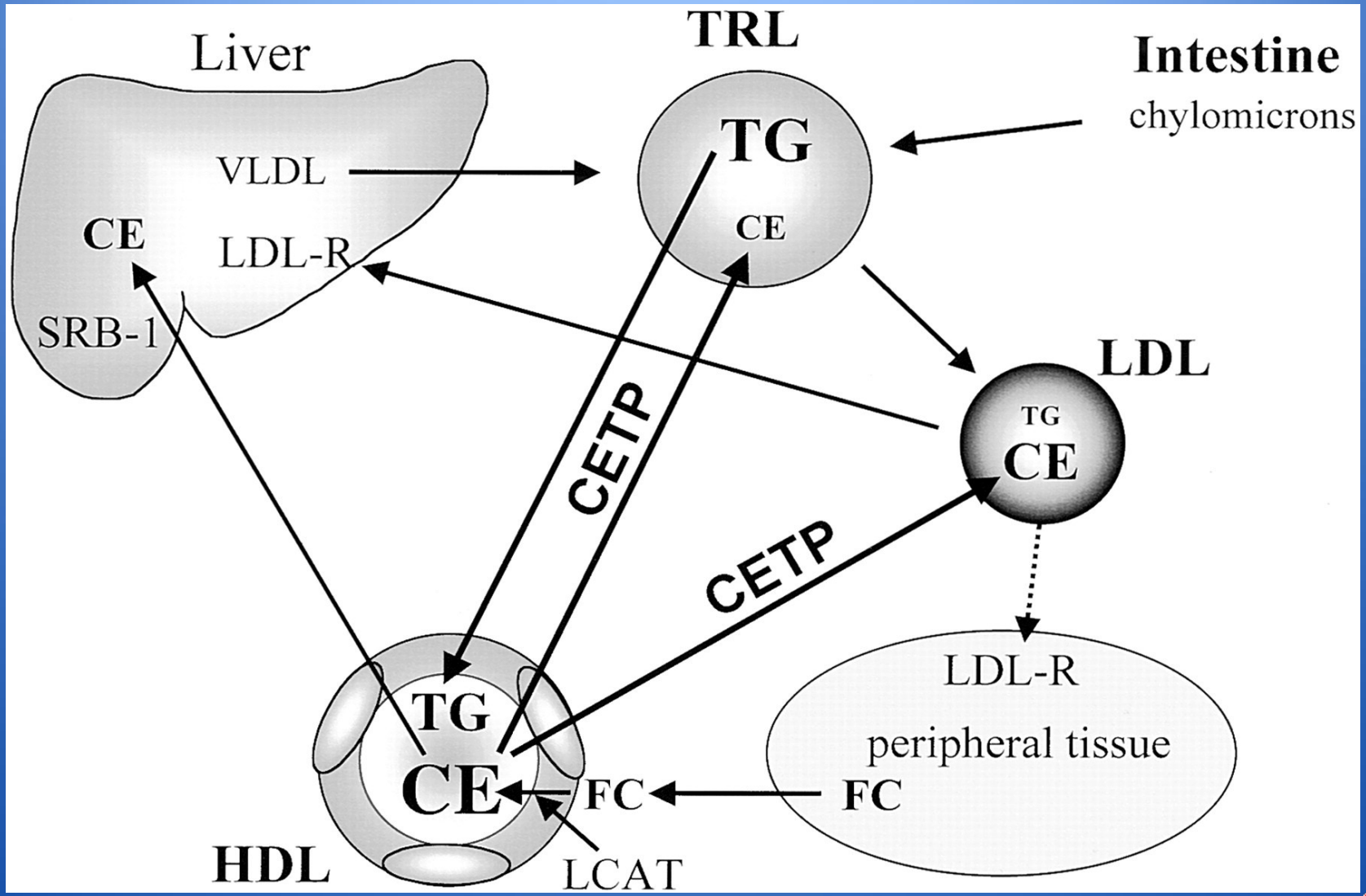
D Death from Cardiovascular Causes



No. at Risk									
Fenofibrate	2765	2700	2660	2606	2114	1255	457	285	155
Placebo	2753	2689	2633	2574	2128	1270	437	271	153

Action to control Cardiovasculr Risk in Diabetes (ACCORD) study group. N Eng J Med 2007; 356 : 1304-16

Role of CETP in plasma lipid transport



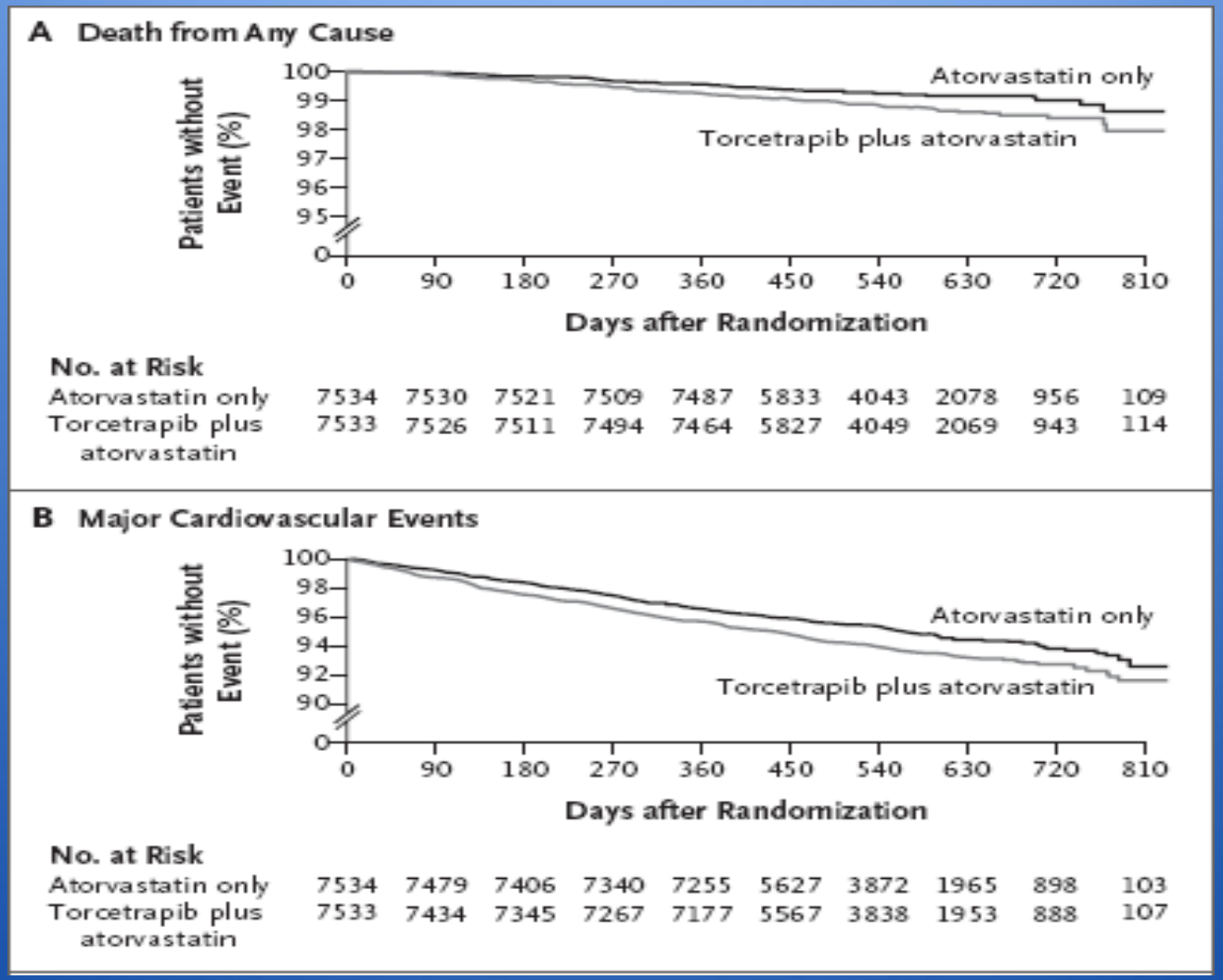
American Heart Association
Learn and Live

Barter P J et al. Arterioscler Thromb Vasc Biol 2003;23:160-167

Effects of Torcetrapib in Patients at High Risk for Coronary Events

The NEW ENGLAND JOURNAL of MEDICINE

ILLUMINATE TRIAL

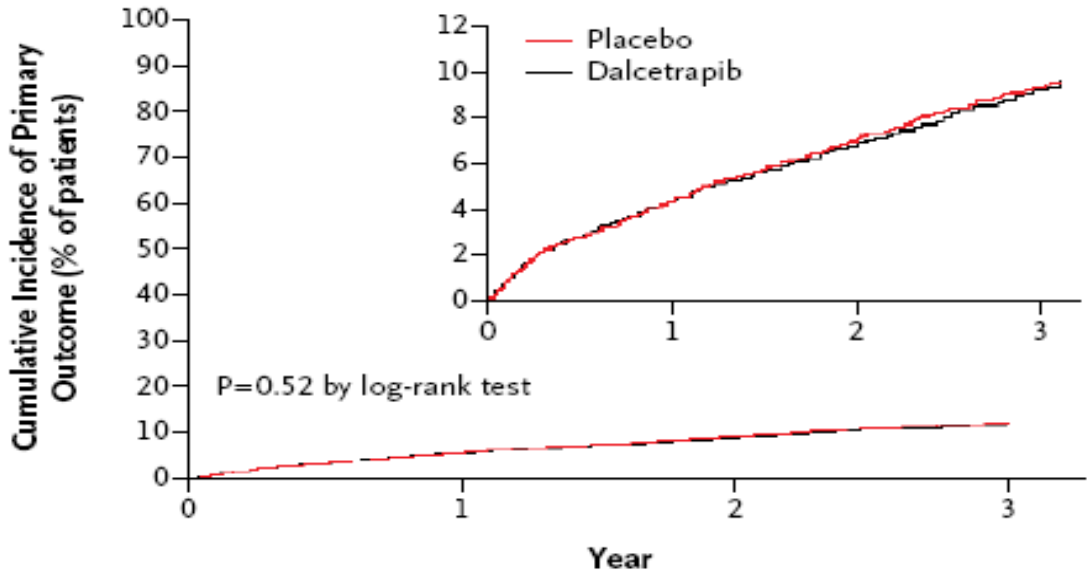


Barter P J et al. N Eng J Med 2007; 357 : 2109-22

The NEW ENGLAND JOURNAL of MEDICINE

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

dal-OUTCOMES Investigators*



No. at Risk

Placebo	7933	7386	6551	1743
Dalcetrapib	7938	7372	6495	1736

Figure 2. Incidence of the Primary Efficacy End Point.

Shown is the cumulative incidence in the two study groups of the composite primary end point of death from coronary heart disease, a major nonfatal coronary event (myocardial infarction, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or resuscitation after cardiac arrest), or stroke of presumed atherothrombotic cause. The inset shows the same data on an enlarged y axis.

N Eng J Med367;22

ACCELERATE

A Study of Evacetrapib in High-Risk Vascular Disease (ACCELERATE)

The purpose of the ACCELERATE study is to evaluate the efficacy and safety of evacetrapib in participants with high-risk vascular disease (HRVD). Evacetrapib has been shown to increase HDL significantly and lower LDL.

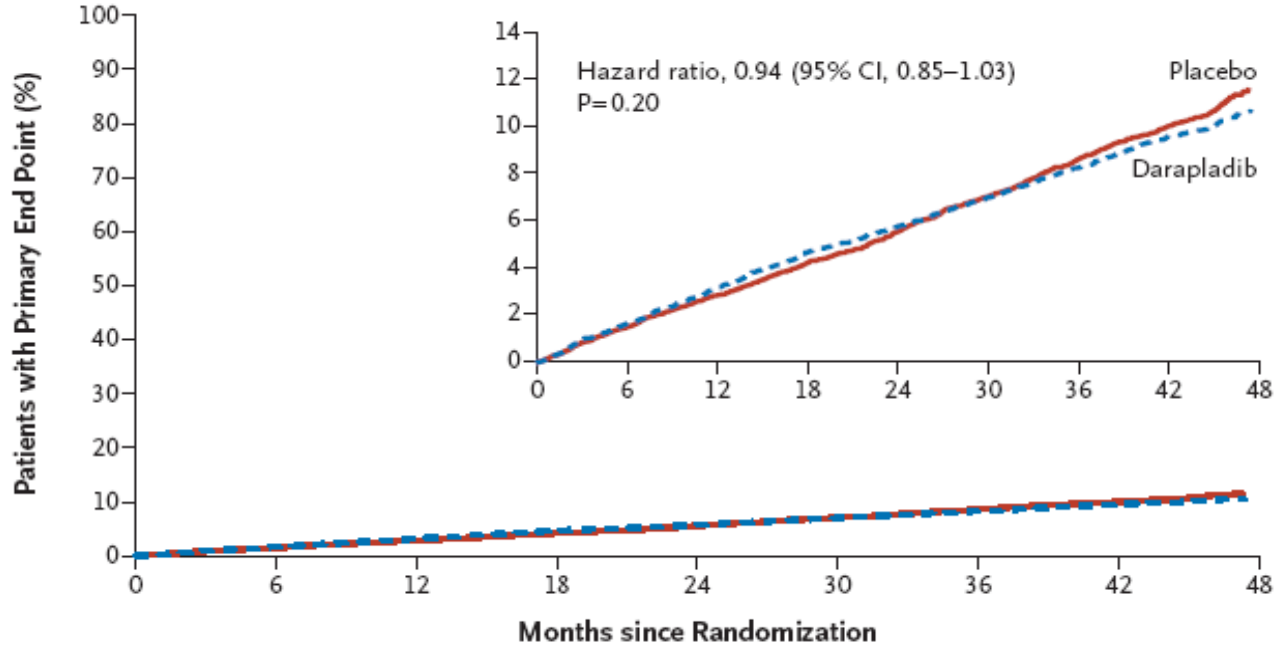
?

Повлияване на възпалението

The NEW ENGLAND JOURNAL of MEDICINE

Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease

The STABILITY Investigators*



No. at Risk									
Placebo	7904	7683	7523	7380	7226	7065	6871	5691	598
Darapladib	7924	7694	7518	7355	7218	7078	6907	5716	566

Figure 2. Kaplan–Meier Curves for the Primary End Point of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke.

The inset shows the same data on an enlarged y axis.

N Engl J Med 2014;370:1702-

GSK announces phase III study with darapladib did not meet primary endpoint in patients following an acute coronary syndrome

In the study, darapladib did not achieve the primary endpoint of a reduction of major coronary events versus placebo when added to standard of care. The overall safety profile for darapladib showed no major safety concerns and was generally consistent with the safety data seen in the previously reported phase III study, STABILITY. Further analysis of the data is ongoing. Darapladib is not approved for use anywhere in the world.

Tuesday 13 May 2014, London UK – LSE announcement

CANTOS

Canakinumab **An**ti-inflammatory **T**hrombosis **O**utcomes **S**tudy

Specific Aims

The primary goal of the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) is to determine whether long-term treatment with canakinumab (50 mg, 150 mg or 300 mg subcutaneous every three months) as compared to placebo will reduce rates of recurrent cardiovascular events among stable post-myocardial infarction patients who remain at elevated vascular risk as gauged by increased levels of hsCRP (≥2mg/L) despite usual care, including statin therapy.

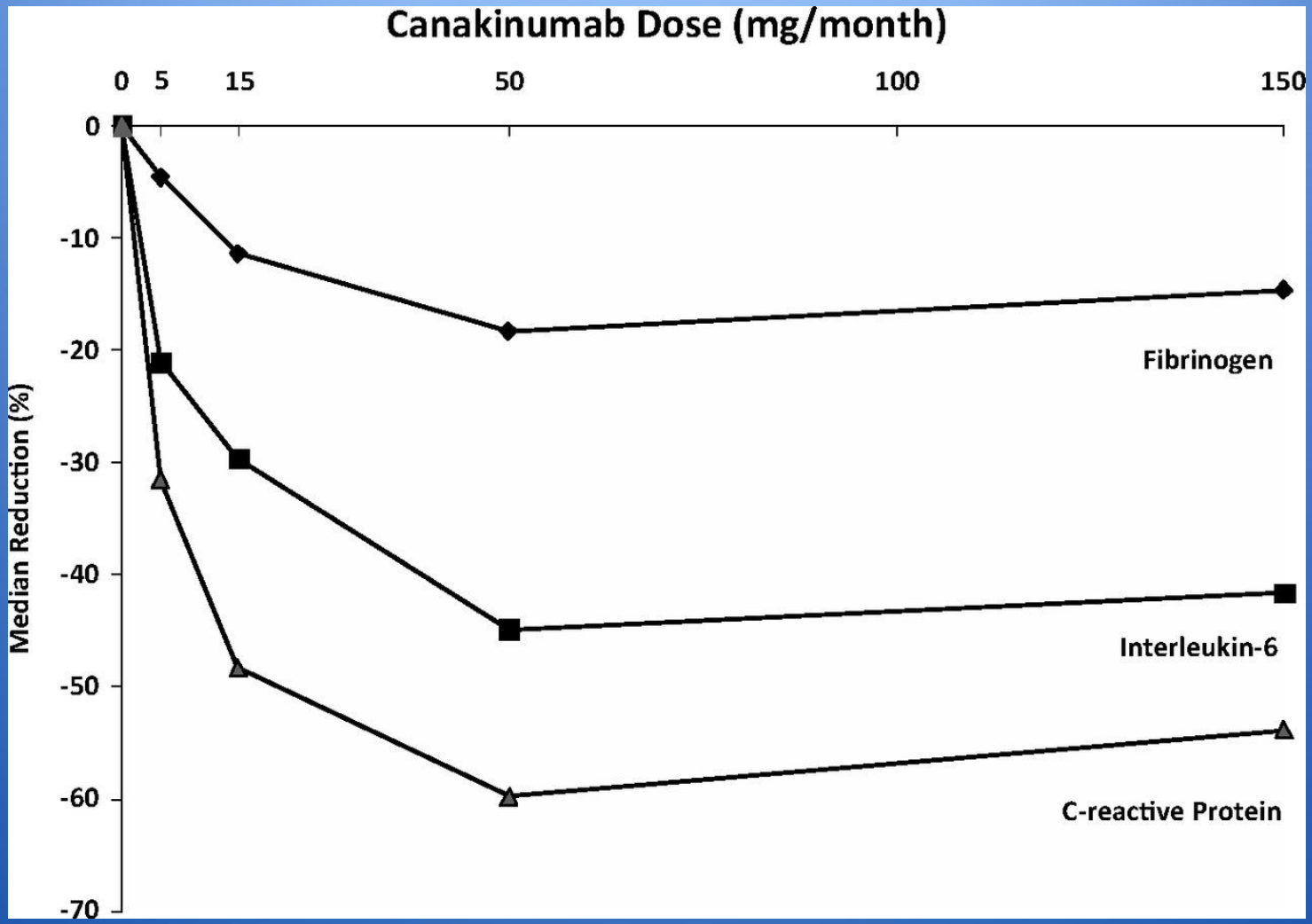
Study Population: Major Inclusion Criteria

CANTOS will enroll 17,200 men and women 18 years of age and over who:

- Have suffered a documented acute myocardial infarction at least 30 days before randomization
- Have completed any planned revascularization procedures associated with their initial infarction, and
- Have evidence of systemic inflammation on the basis of an hsCRP ≥2mg/L despite the stable use of standard secondary prevention therapies, including statins

*the**cantos**.org/*

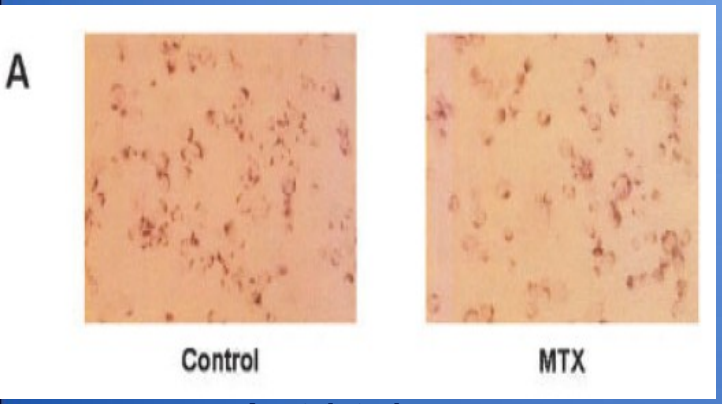
Dose-response effects of canakinumab at 4 months for C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen in placebo-subtracted analyses.



Ridker P M et al. Circulation. 2012;126:2739-2748

Atheroprotective Effects of Methotrexate on Reverse Cholesterol Transport Proteins and Foam Cell Transformation in Human THP-1 Monocyte/Macrophages

Allison B. Reiss,[1] Steven E. Carsons,[1] Kamran Anwar,[1] Soumya Rao,[1] Sari D. Edelman,[1] Hongwei Zhang,[1] Patricia Fernandez,[2] Bruce N. Cronstein,[2] and Edwin S. L. Chan[2]



Acetylated low-density lipoprotein–treated THP-1 macrophages show a significant decrease in foam cell transformation in the presence of MTX compared with control.

Conclusion. **This study provides evidence supporting the notion of an atheroprotective effect of MTX. Through adenosine A_{2A} receptor activation, MTX promotes reverse cholesterol transport and limits foam cell formation in THP-1 macrophages. This is the first reported evidence that any commonly used medication can increase expression of antiatherogenic reverse cholesterol transport proteins and can counteract the effects of COX-2 inhibition. Our results suggest that one mechanism by which MTX protects against cardiovascular disease in rheumatoid arthritis patients is through facilitation of cholesterol outflow from cells of the artery wall.**

CIRT | Cardiovascular Inflammation Reduction Trial

A Randomized, Double-blind, Placebo-controlled, Event-driven Trial of Weekly Low-dose Methotrexate (LDM) in the Prevention of Cardiovascular Events Among Stable Coronary Artery Disease Patients With Type 2 Diabetes or Metabolic Syndrome

The Cardiovascular Inflammation Reduction Trial (CIRT) is a randomized clinical trial investigating whether taking low-dose methotrexate reduces heart attacks, strokes, or death in people with type 2 diabetes or metabolic syndrome that have had a heart attack or multiple coronary blockages. This trial is funded by the National Heart, Lung, and Blood Institute (NHLBI)/National Institutes of Health (NIH).

Principal Investigator
Paul M Ridker, MD, MPH