# Pre-diabete e dislipidemia

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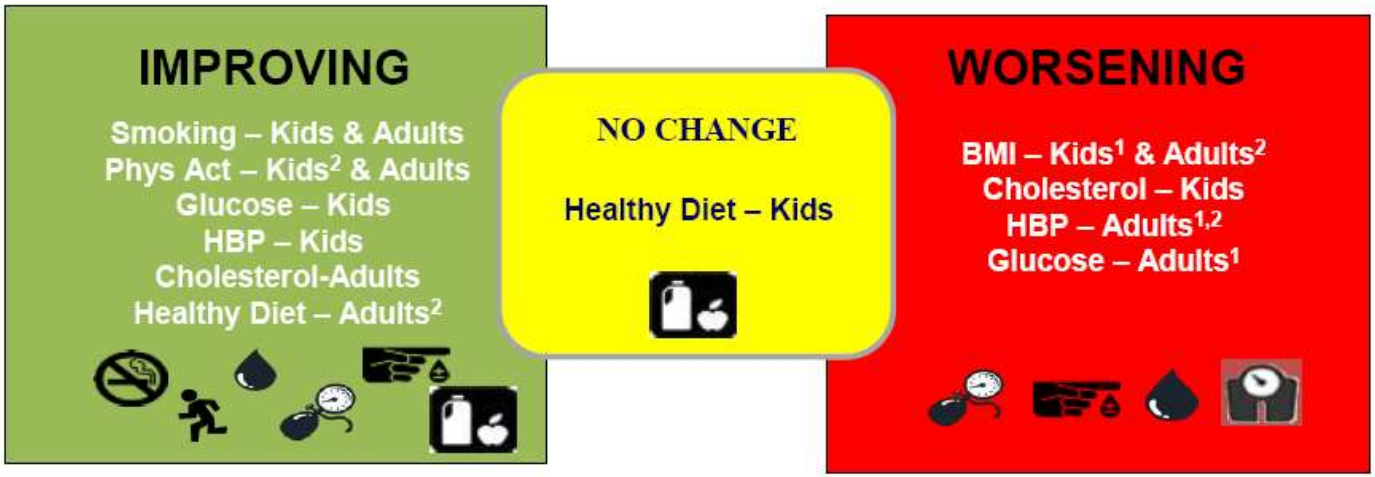
**Centro di Ricerca sulle Dislipidemie**
**Ospedale di Circolo - Università dell'Insubria**
**Varese**

# Reaching the 2020 Goal

## Progress to Date – Improving CV Health

**Overall Total Population Improvement 2007-8 to 2011-12: 3.5%**




NHANES 2011-2012 compared to 2007-2008

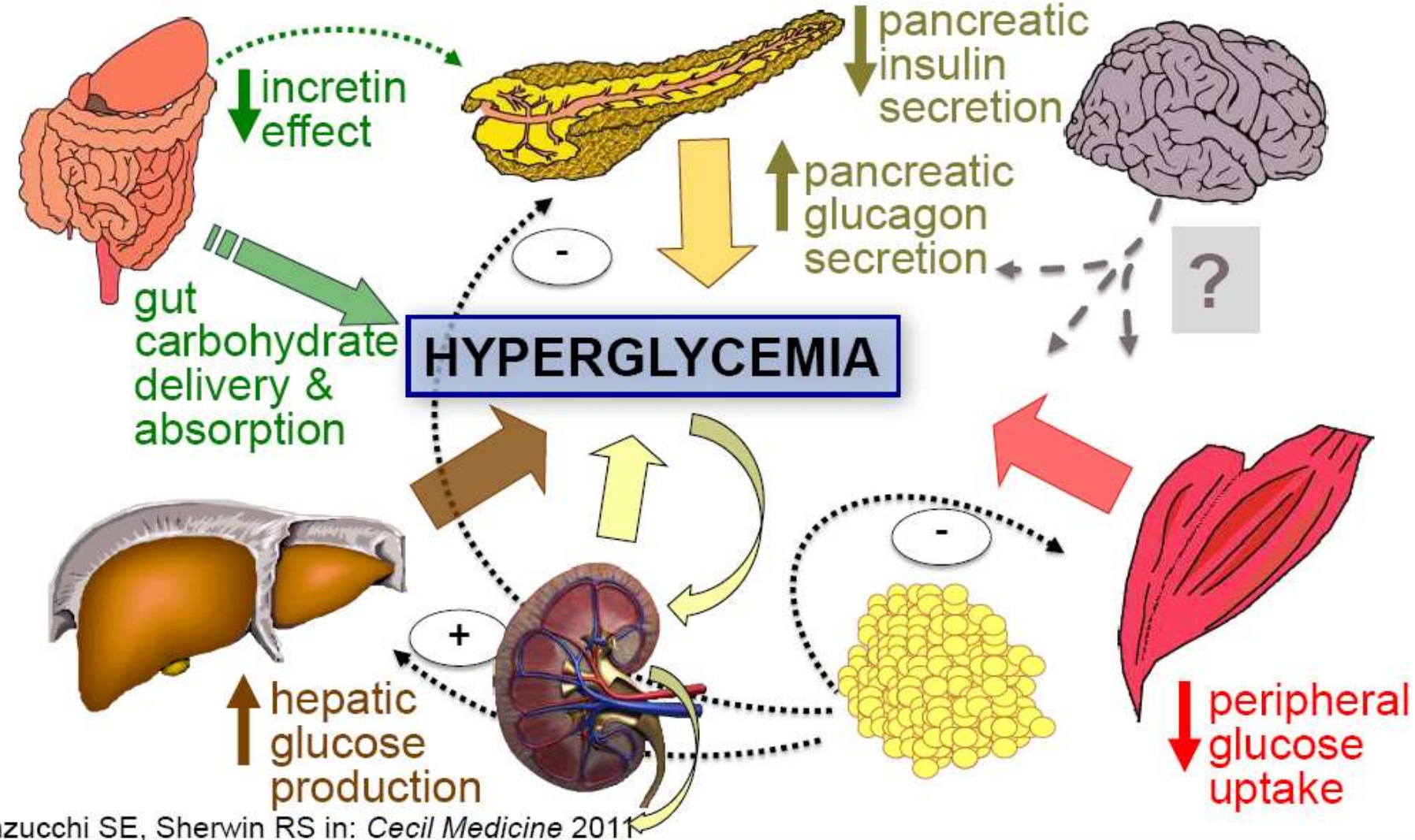
[1] Worsening in "poor" but improving in "ideal". Overall average decreased.
[2] Change is small: ~1-3%

BUILDING A CULTURE of HEALTH

American Heart Association | American Stroke Association

life is why

# Multiple, Complex Pathophysiological Defects in T2DM




Inzucchi SE, Sherwin RS in: *Cecil Medicine* 2011

POSITION STATEMENT

**Standards of Medical Care in Diabetes—2013**

American Diabetes Association

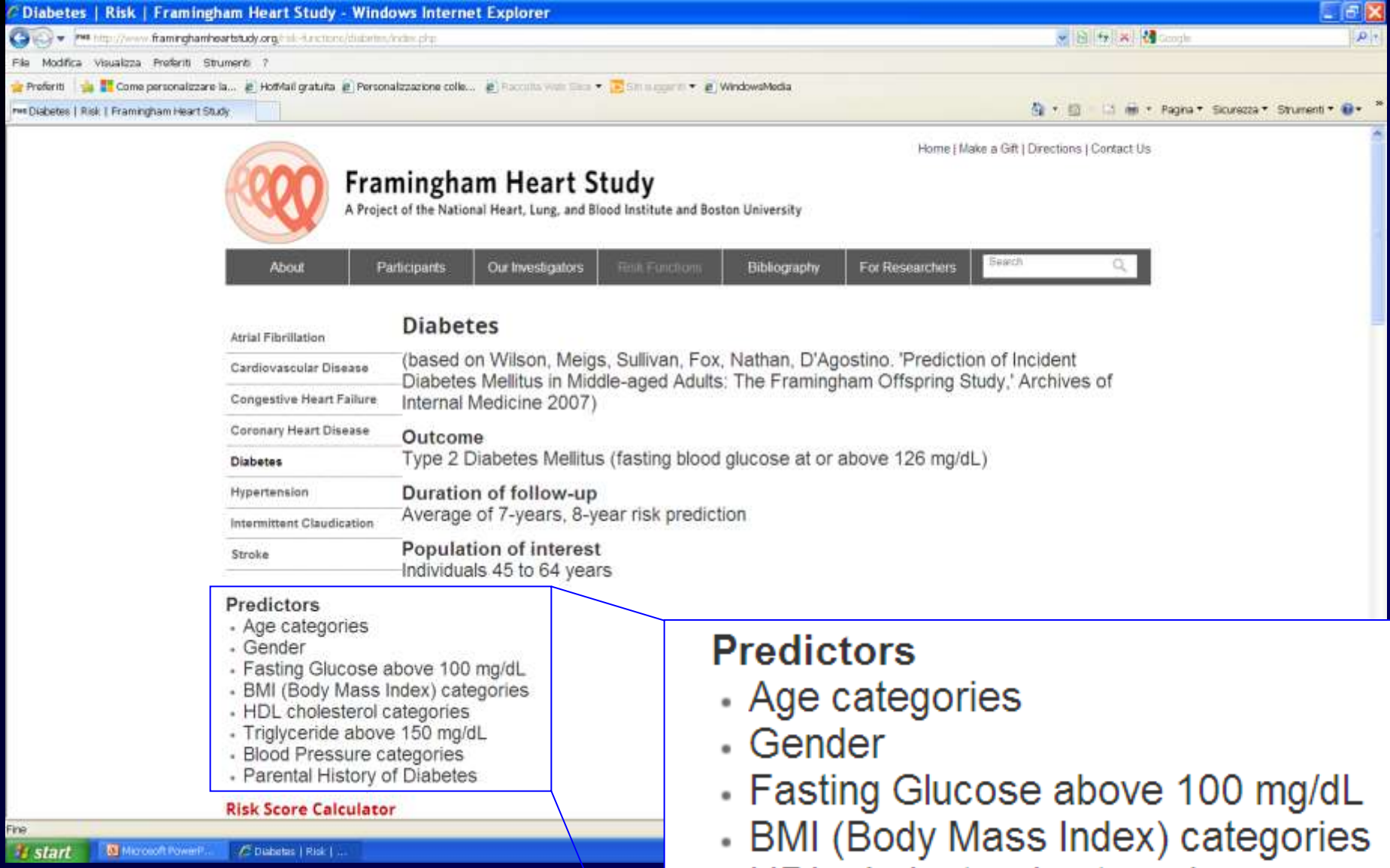
ADA

*Categories of increased risk for diabetes (prediabetes)**

| |
|---|
| FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG) |
| OR |
| 2-h plasma glucose in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT) |
| OR |
| A1C 5.7–6.4% |

*For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

- MetS
- Predictors? Framingham?
- markers? Liver markers? metabolomics?




## Predictors

- Age categories
- Gender
- Fasting Glucose above 100 mg/dL
- BMI (Body Mass Index) categories
- HDL cholesterol categories
- Triglyceride above 150 mg/dL
- Blood Pressure categories
- Parental History of Diabetes

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i24.7478

*World J Gastroenterol* 2015 June 28; 21(24): 7478-7487
ISSN 1007-9327 (print) ISSN 2219-2840 (online)


ORIGINAL ARTICLE

Retrospective Cohort Study

# Increased liver markers are associated with higher risk of type 2 diabetes

Sun-Hye Ko, Myong Ki Baeg, Kyung-Do Han, Seung-Hyun Ko, Yu-Bae Ahn

Metabolomics (2015) 11:1277–1286
DOI 10.1007/s11306-015-0784-9

ORIGINAL ARTICLE

# Identification of putative biomarkers for prediabetes by metabolome analysis of rat models of type 2 diabetes

Norihide Yokoi · Masayuki Beppu · Eri Yoshida · Ritsuko Hoshikawa · Shihomi Hidaka · Toshiya Matsubara · Masami Shinohara · Yasuhiro Irino · Naoya Hatano · Susumu Seino

# Effects of Prediabetes Mellitus Alone or Plus Hypertension on Subsequent Occurrence of Cardiovascular Disease and Diabetes Mellitus

## Longitudinal Study

Miaoyan Qiu,* Weili Shen,* Xiaomin Song,* Liping Ju, Wenxin Tong, Haiyan Wang, Sheng Zheng, Yan Jin, Yixin Wu, Weiqing Wang, Jingyan Tian

*Abstract*—Whether prediabetes mellitus alone or combined with other disorders means a higher risk for cardiovascular disease (CVD) is still controversial. This study aimed to investigate the association between prediabetes mellitus and CVD and diabetes mellitus and to explore whether prediabetes mellitus alone or combined with other syndromes, such as hypertension, could promote CVD risks significantly. This longitudinal population-based study of 1609 residents from Shanghai in Southern China was conducted between 2002 and 2014. Participants with a history of CVD at baseline were excluded from analysis. Multivariate log-binomial regression models were used to adjust possible coexisting factors. Incidence of CVD during follow-up was 10.1%. After adjusting for age, sex, and other factors, the association between prediabetes mellitus and CVD was not observed. When hypertension was incorporated in stratifying factors, adjusted CVD risk was elevated significantly (odds ratio, 2.41; 95% confidence interval, 1.25–4.64) in prediabetes mellitus and hypertension combined group, and coexistence of diabetes mellitus and hypertension made CVD risk highly significantly increased, reaching 3.43-fold higher than the reference group. Blood glucose level within prediabetic range is significantly associated with elevated risks for diabetes mellitus after multivariable adjustment, but only when it is concurrent with other disorders, such as hypertension, it will significantly increase CVD risk. (*Hypertension*. 2015;65:525-530. DOI: 10.1161/HYPERTENSIONAHA.114.04632.)



# Diabetes Mellitus, Prediabetes, and Incidence of Subclinical Myocardial Damage

Elizabeth Selvin, PhD, MPH; Mariana Lazo, MD, PhD, ScM; Yuan Chen, MS; Lu Shen, BS; Jonathan Rubin, MD, MHS; John W. McEvoy, MB, BCh, BAO, MRCPI; Ron C. Hoogeveen, PhD; A. Richey Sharrett, MD, DrPH; Christie M. Ballantyne, MD; Josef Coresh, MD, PhD, MHS

***Background***—Persons with prediabetes and diabetes mellitus are at high risk for cardiovascular events. However, the relationships of prediabetes and diabetes mellitus to the development of subclinical myocardial damage are unclear.

***Methods and Results***—We measured cardiac troponin T with a highly sensitive assay (hs-cTnT) at 2 time points, 6 years apart, among 9051 participants of the community-based Atherosclerosis Risk in Communities Study with no diabetes mellitus, or prediabetes, and without cardiovascular disease including silent myocardial infarction by ECG. First, we examined the incidence of elevated hs-cTnT (≥14 ng/L) at 6 years of follow-up. Second, we examined clinical outcomes during the subsequent ≈14 years of follow-up among persons with and without incident elevations in hs-cTnT. Cumulative probabilities of elevated hs-cTnT at 6 years among persons with no diabetes mellitus, prediabetes, and diabetes mellitus were 3.7%, 6.4%, and 10.8%, respectively. Compared with normoglycemic persons, the adjusted relative risks for incident elevated hs-cTnT were 1.40 (95% CI, 1.08–1.80) for prediabetes and 2.47 (95% CI, 1.78–3.43) for diabetes mellitus. Persons with diabetes mellitus and incident elevations in hs-cTnT were at a substantially higher risk of heart failure (hazard ratio, 6.37 [95% CI, 4.27–9.51]), death (hazard ratio, 4.36 [95% CI, 3.14–6.07]), and coronary heart disease (hazard ratio, 3.84 [95% CI, 2.52–5.84]) compared with persons without diabetes mellitus and no incident elevation in hs-cTnT.

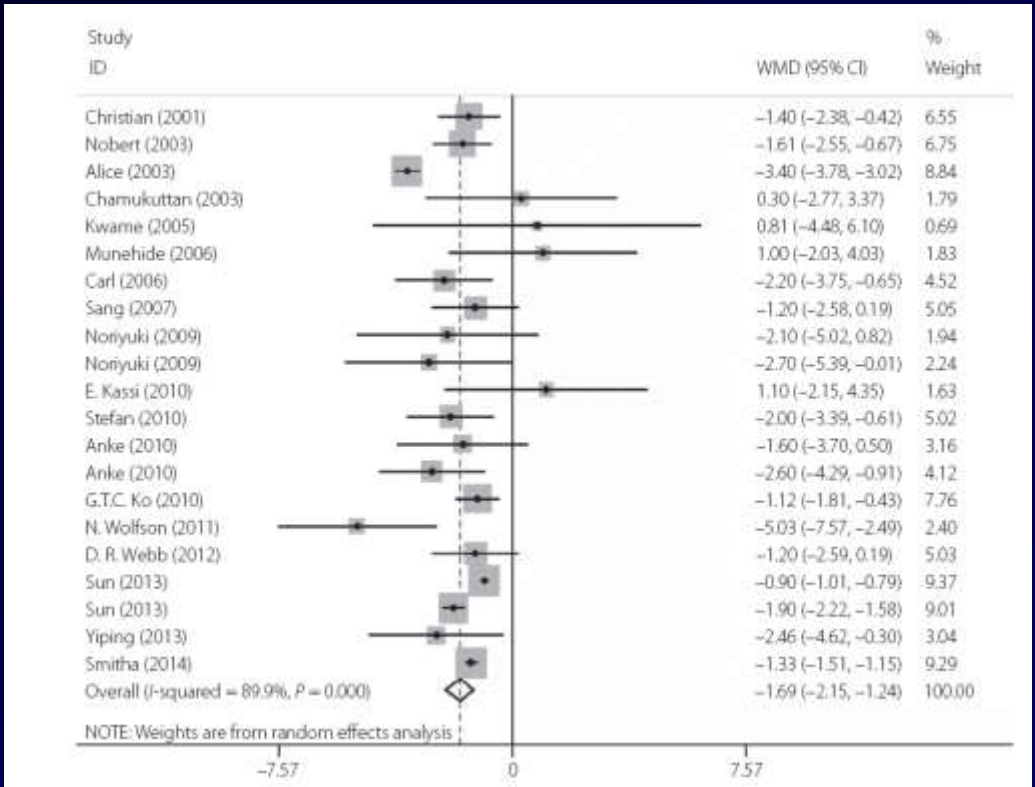
***Conclusions***—Prediabetes and diabetes mellitus were independently associated with the development of subclinical myocardial damage, as assessed by hs-cTnT, and those persons with evidence of subclinical damage were at highest risk for clinical events. These results support a possible deleterious effect of hyperglycemia on the myocardium, possibly reflecting a microvascular cause. (***Circulation***. **2014;130:1374-1382.**)

# Association between the level of circulating adiponectin and prediabetes: A meta-analysis

Huasheng Lai†, Nie Lin†, Zhenzhen Xing†, Huanhuan Weng†, Hua Zhang*

Department of Endocrinology, Zhujiang Hospital of Southern Medical University, Guangzhou, China

*J Diabetes Invest* 2015;

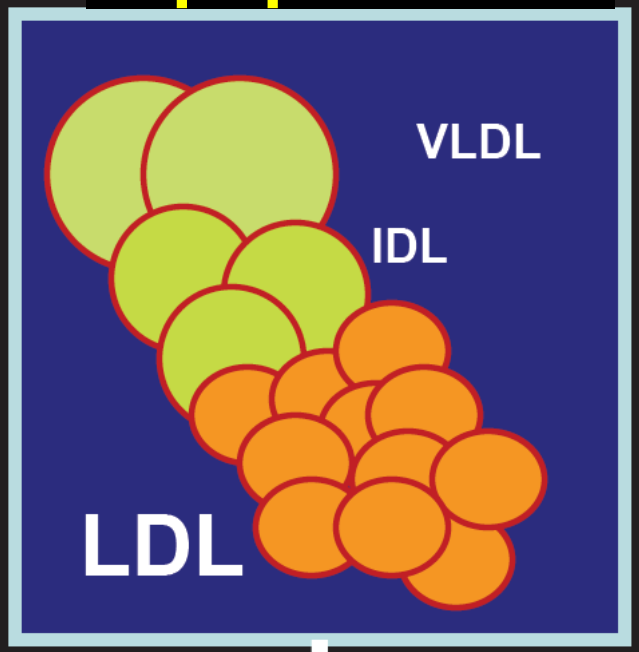



Forest plot for adiponectin levels in prediabetes patients and healthy controls in prediabetes patients were significantly lower than healthy controls (WMD –1.694 μg/mL; 95% CI –2.151, –1.237; P < 0.001).

Grundy S

**Elevated Atherogenic Lipoproteins**

**Metabolic Syndrome Type 2 Diabetes**




High TG
Low HDL
Elevated BP
Elevated glucose
Prothrombotic state
Proinflammatory state

**Cardiovascular Disease**

# Atherogenic Lipoprotein Profile

Lifestyle


Large VLDL1 ↑

Metabolic Syndrome
Type 2 Diabetes
FCH subjects
Low HDL subjects

genes

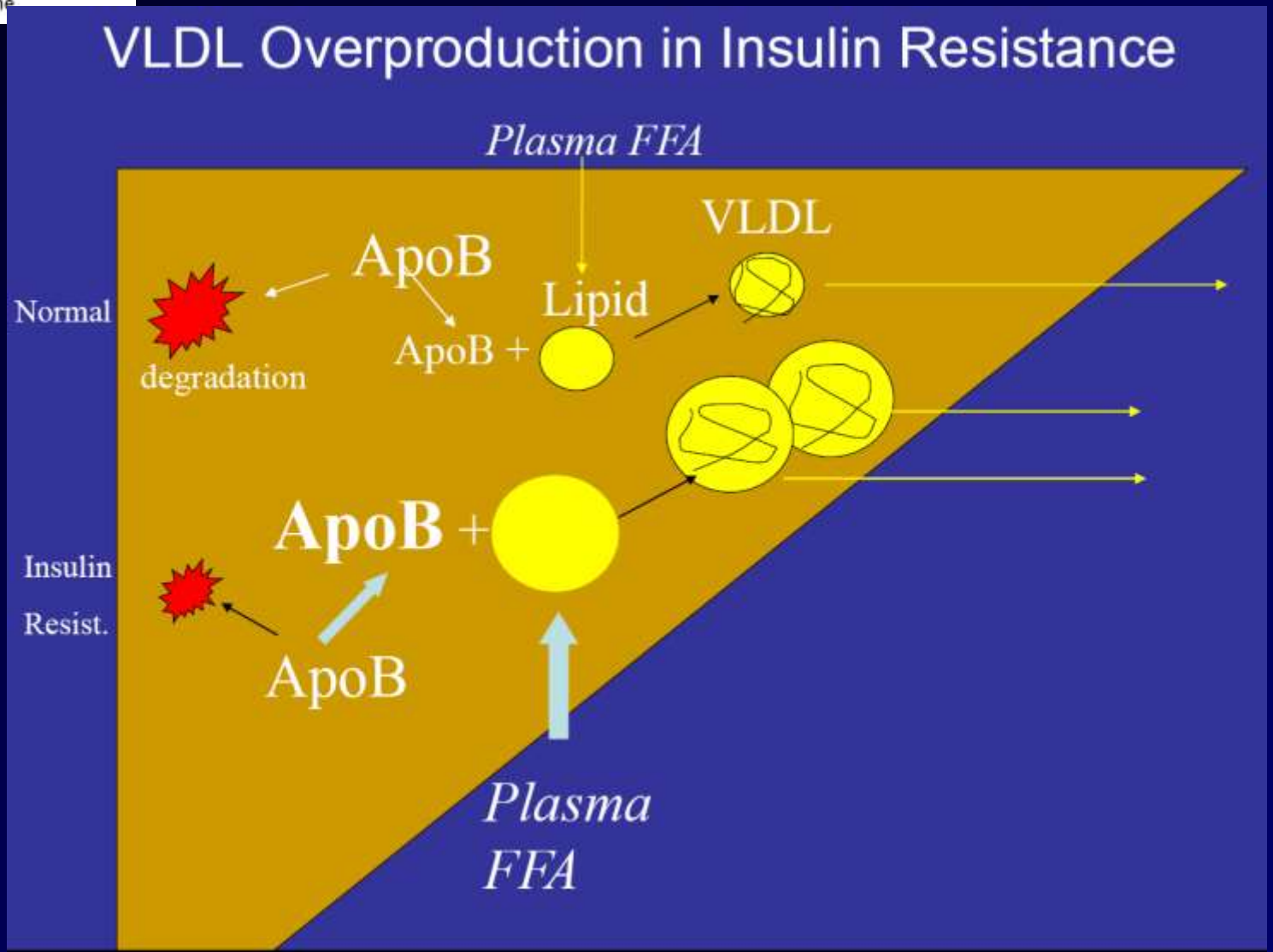
Increased CAD Risk

Small dense LDL

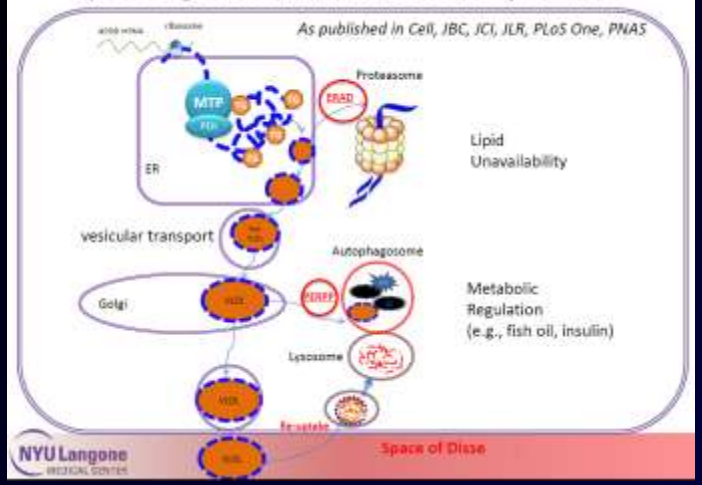
HDL ↓

How the Atherometabolic Syndrome Drives Hepatic Oversecretion of Apolipoprotein B, the major Protein of TGRLs and LDL

Edward A. Fisher, MD, PhD
Leon H. Charney Professor of Cardiovascular Medicine
NYU School of Medicine



## ApoB Degradation and the Pathway to VLDL




## GWAS Have Identified A Locus On Chromosome 1p13 As Having The Lowest P-Value For LDL-C In The Human Genome

| Chr | SNP (genes) | Combined *P* value |
|---|---|---|
| 1p13 | rs599839 (SORT1) | $7.70 \times 10^{-160}$ |
| 19p13 | rs4420638 (APOE) | $3.33 \times 10^{-140}$ |
| 19p13 | rs6511720 (LDLR) | $1.51 \times 10^{-110}$ |
| 2p24 | rs1367117 (APOB) | $5.62 \times 10^{-109}$ |
| 2p21 | rs6544713 (ABCG5/ABCG8) | $3.66 \times 10^{-47}$ |
| 5q13 | rs12916 (HMGCR) | $9.96 \times 10^{-46}$ |

(Global Lipids Genetics Consortium, N ~ 100,000)

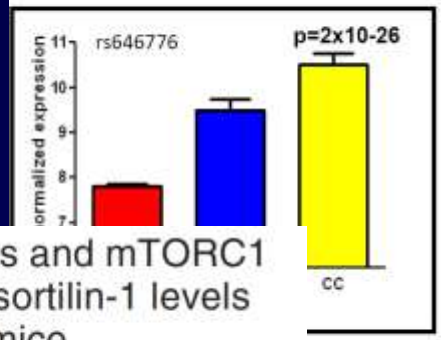
Teslovich, et al, Nature, 2010

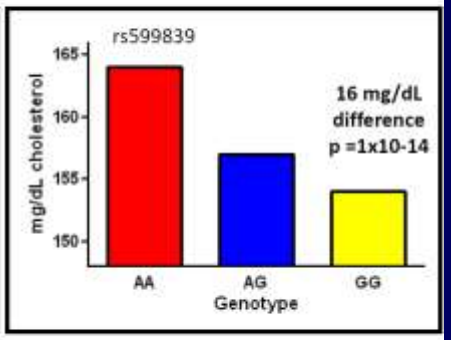
## Sortilin Overexpression Reduces The VLDL Triglyceride Secretion Rate

| Mouse Model | VLDL Secretion |
|---|---|
| ApoBEC KO, human apoB transgenic | ↓ 50% |
| ApoBEC KO, human apoB transgenic, LDLR KO | ↓ 25% |
| LDLR Knockout | ↓ 30 |
| Wild Type | ↓ 20 |

Musunuru, Strong e

## The Minor Allele Associated With Higher Sortilin mRNA Abundance In Human Liver and Lower LDL-C



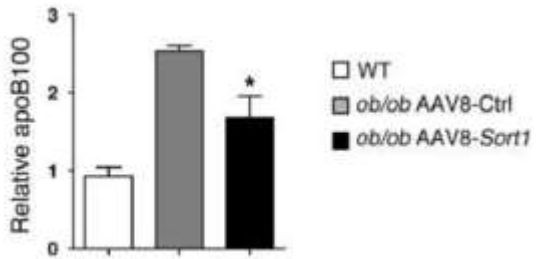




Kathiresan, *Nature Genetics* 2008

## Activation of ER stress and mTORC1 suppresses hepatic sortilin-1 levels in obese mice

Ding Ai,[1] Juan M. Baez,[1] Hongfeng Jiang,[1] Donna M. Conlon,[1] Antonio Hernandez-Ono,[1] Maria Frank-Kamenetsky,[2] Stuart Milstein,[2] Kevin Fitzgerald,[2] Andrew J. Murphy,[1] Connie W. Woo,[1] Alanna Strong,[3] Henry N. Ginsberg,[1] Ira Tabas,[1] Daniel J. Rader,[3] and Alan R. Tall[1]

JCI, 2012



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

ABSTRACT

**BACKGROUND**

Plasma triglyceride levels are heritable and are correlated with the risk of coronary heart disease. Sequencing of the protein-coding regions of the human genome (the exome) has the potential to identify rare mutations that have a large effect on phenotype.

**METHODS**

We sequenced the protein-coding regions of 18,666 genes in each of 3734 participants of European or African ancestry in the Exome Sequencing Project. We conducted tests to determine whether rare mutations in coding sequence, individually or in aggregate within a gene, were associated with plasma triglyceride levels. For mutations associated with triglyceride levels, we subsequently evaluated their association with the risk of coronary heart disease in 110,970 persons.

**RESULTS**

An aggregate of rare mutations in the gene encoding apolipoprotein C3 (*APOC3*) was associated with lower plasma triglyceride levels. Among the four mutations that drove this result, three were loss-of-function mutations: a nonsense mutation (R19X) and two splice-site mutations (IVS2+1G→A and IVS3+1G→T). The fourth was a missense mutation (A43T). Approximately 1 in 150 persons in the study was a heterozygous carrier of at least one of these four mutations. Triglyceride levels in the carriers were 39% lower than levels in noncarriers ($P<1\times10^{-20}$), and circulating levels of APOC3 in carriers were 46% lower than levels in noncarriers ($P=8\times10^{-10}$). The risk of coronary heart disease among 498 carriers of any rare *APOC3* mutation was 40% lower than the risk among 110,472 noncarriers (odds ratio, 0.60; 95% confidence interval, 0.47 to 0.75; $P=4\times10^{-6}$).

**CONCLUSIONS**

Rare mutations that disrupt *APOC3* function were associated with lower levels of plasma triglycerides and APOC3. Carriers of these mutations were found to have a reduced risk of coronary heart disease. (Funded by the National Heart, Lung, and Blood Institute and others.)

Address reprint requests to Dr. Sekar Kathiresan at the Cardiovascular Research Center and Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge St., CPZN 5.252, Boston, MA 02114, or at skathiresan@partners.org.

*The authors and members of the Triglycerides and High-Density Lipoprotein (TG and HDL) Working Group and their affiliations are listed in the Appendix. Ms. Jacy Crosby and Drs. Gina Peloso, Paul L. Auer, Alex P. Reiner, Eric Boerwinkle, and Sekar Kathiresan contributed equally to this article and assume responsibility for its content and integrity.

This article was published on June 18, 2014, and updated on February 12, 2015, at NEJM.org.

N Engl J Med 2014;371:22-31.
DOI: 10.1056/NEJMoa1307095


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

ABSTRACT

**BACKGROUND**

High plasma levels of nonfasting triglycerides are associated with an increased risk of ischemic cardiovascular disease. Whether lifelong low levels of nonfasting triglycerides owing to mutations in the gene encoding apolipoprotein C3 (*APOC3*) are associated with a reduced risk of ischemic cardiovascular disease in the general population is unknown.

**METHODS**

Using data from 75,725 participants in two general-population studies, we first tested whether low levels of nonfasting triglycerides were associated with reduced risks of ischemic vascular disease and ischemic heart disease. Second, we tested whether loss-of-function mutations in *APOC3*, which were associated with reduced levels of nonfasting triglycerides, were also associated with reduced risks of ischemic vascular disease and ischemic heart disease. During follow-up, ischemic vascular disease developed in 10,797 participants, and ischemic heart disease developed in 7557 of these 10,797 participants.

**RESULTS**

Participants with nonfasting triglyceride levels of less than 1.00 mmol per liter (90 mg per deciliter) had a significantly lower incidence of cardiovascular disease than those with levels of 4.00 mmol per liter (350 mg per deciliter) or more (hazard ratio for ischemic vascular disease, 0.43; 95% confidence interval [CI], 0.35 to 0.54; hazard ratio for ischemic heart disease, 0.40; 95% CI, 0.31 to 0.52). Heterozygosity for loss-of-function mutations in *APOC3*, as compared with no *APOC3* mutations, was associated with a mean reduction in nonfasting triglyceride levels of 44% ($P<0.001$). The cumulative incidences of ischemic vascular disease and ischemic heart disease were reduced in heterozygotes as compared with noncarriers of *APOC3* mutations ($P=0.009$ and $P=0.05$, respectively), with corresponding risk reductions of 41% (hazard ratio, 0.59; 95% CI, 0.41 to 0.86; $P=0.007$) and 36% (hazard ratio, 0.64; 95% CI, 0.41 to 0.99; $P=0.04$).

**CONCLUSIONS**

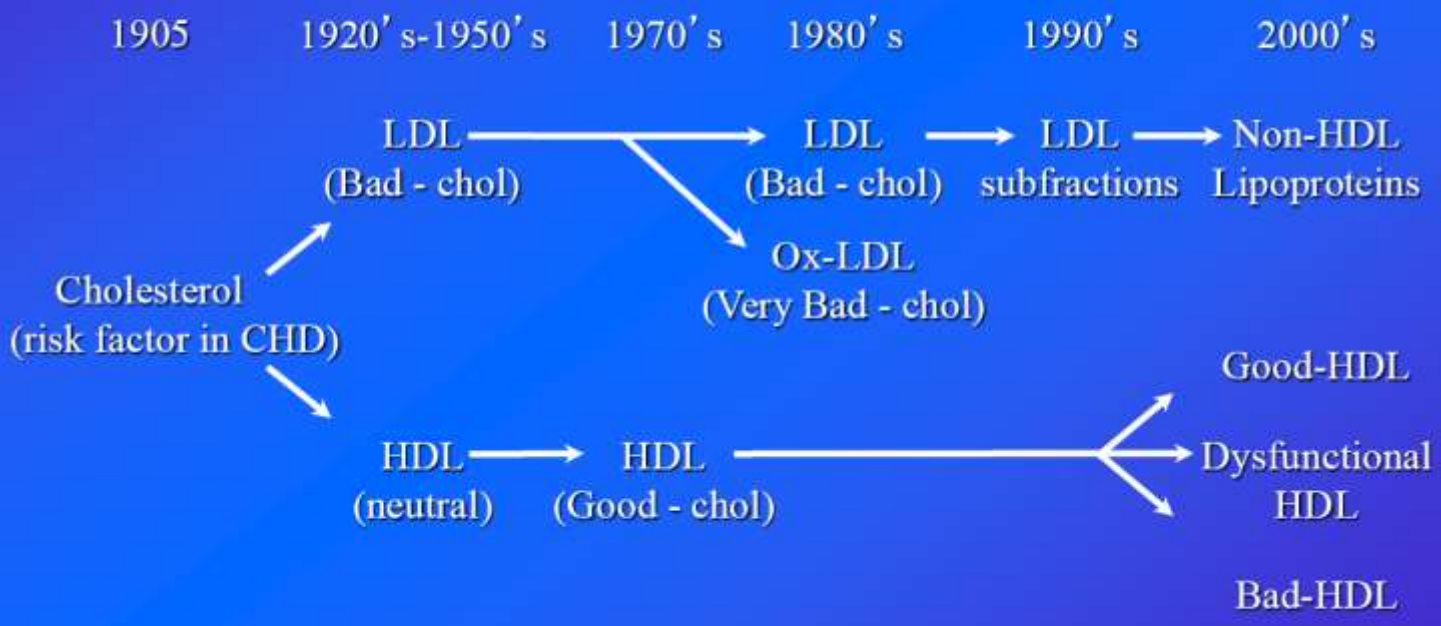
Loss-of-function mutations in *APOC3* were associated with low levels of triglycerides and a reduced risk of ischemic cardiovascular disease. (Funded by the European Union and others.)

From Copenhagen University Hospital and Faculty of Health and Medical Sciences, University of Copenhagen (A.B.J., R.F.-S., B.G.N., A.T.-H.), the Department of Clinical Biochemistry, Rigshospitalet (A.B.J., R.F.-S., A.T.-H.), the Department of Clinical Biochemistry (B.G.N.) and the Copenhagen General Population Study (R.F.-S., B.G.N., A.T.-H.), Herlev Hospital, and the Copenhagen City Heart Study, Frederiksberg Hospital (B.G.N., A.T.-H.) — all in Copenhagen. Address reprint requests to Dr. Tybjærg-Hansen at the Department of Clinical Biochemistry KB 3011, Section for Molecular Genetics, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark, or at anne.tybjaerg.hansen@regionh.dk.

This article was published on June 18, 2014, at NEJM.org.

N Engl J Med 2014;371:32-41.
DOI: 10.1056/NEJMoa1308027

# Evolution of Cholesterol as a CHD Risk Marker



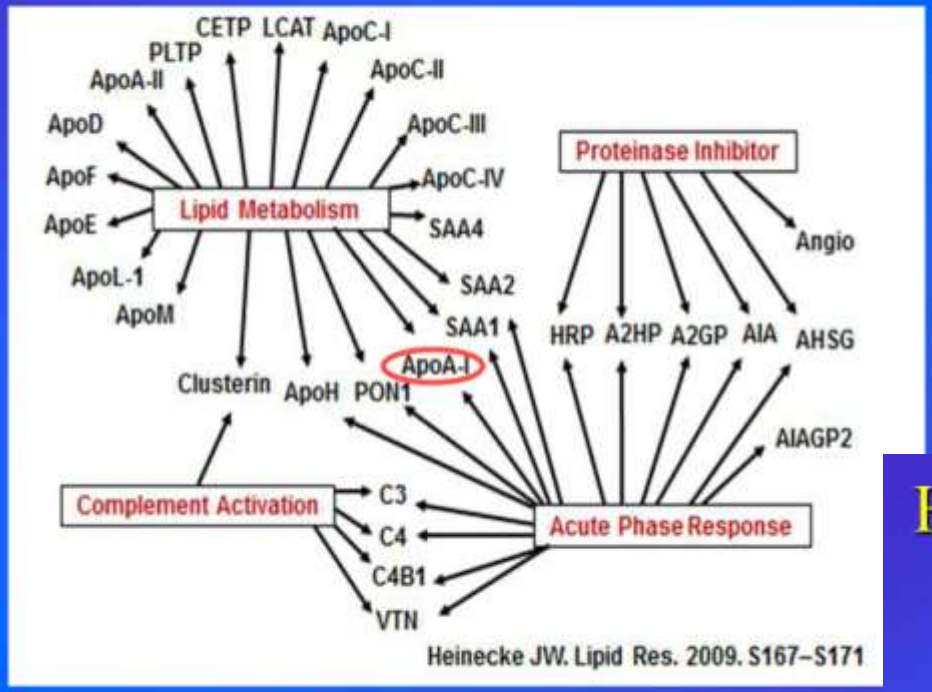

+ qualità (proteomica lipidomica)
+ fz

Novel Approaches for Studying HDL Function

(How do you best measure HDL?)

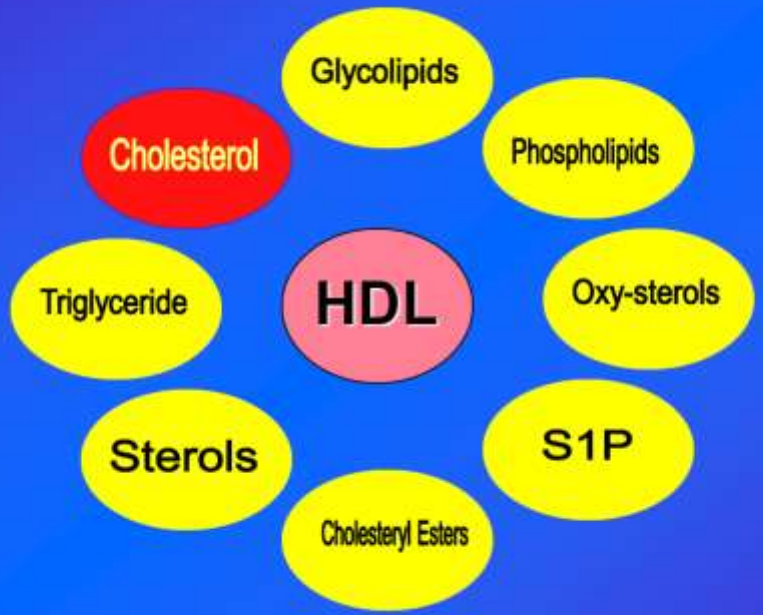
*Alan T. Remaley, MD, PhD*

# HDL-Proteome



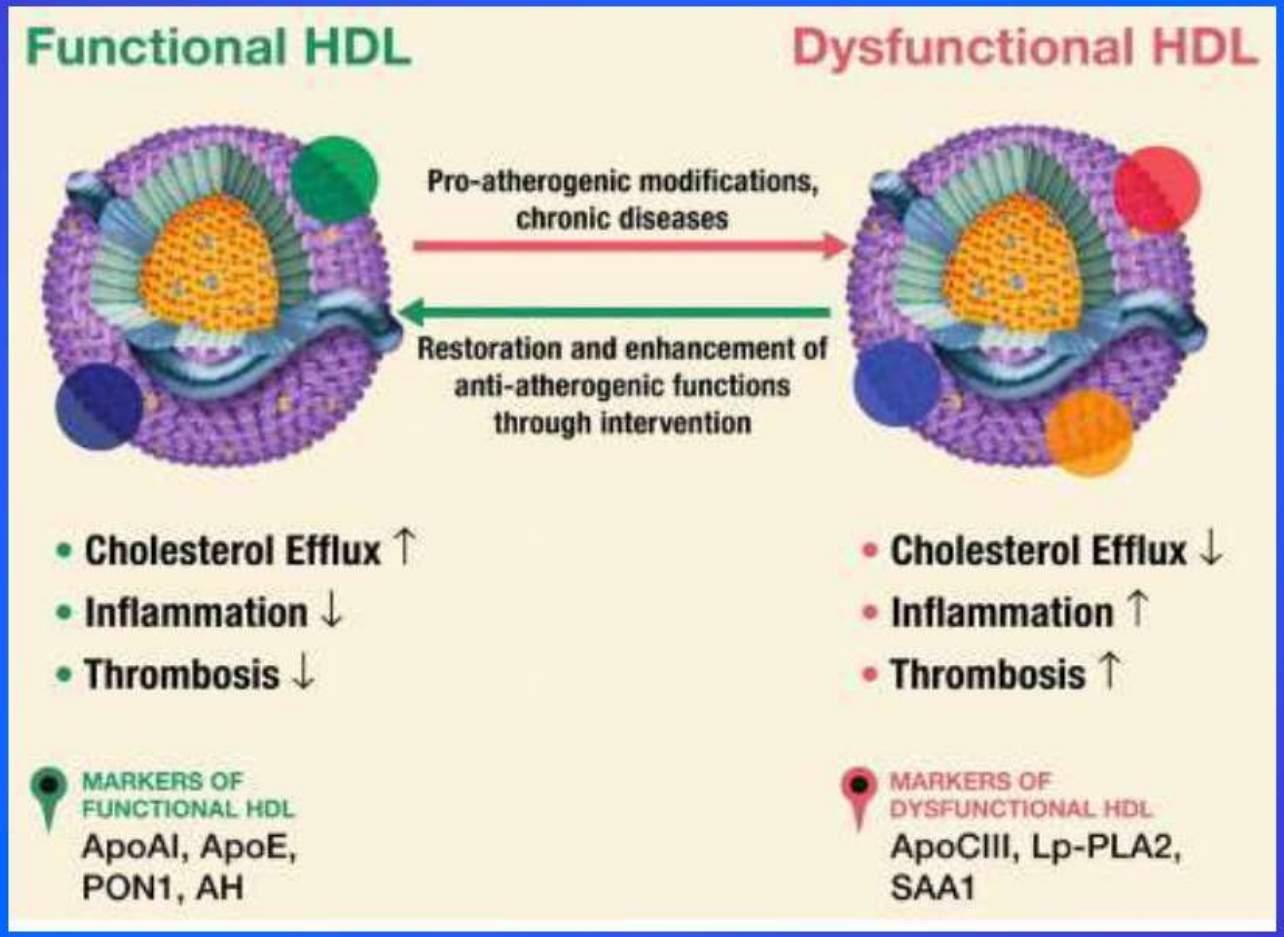

*J Clin Invest* 2007; 117: 746

# HDL-Lipidome: Major Lipid Classes




>200 species of specific lipids

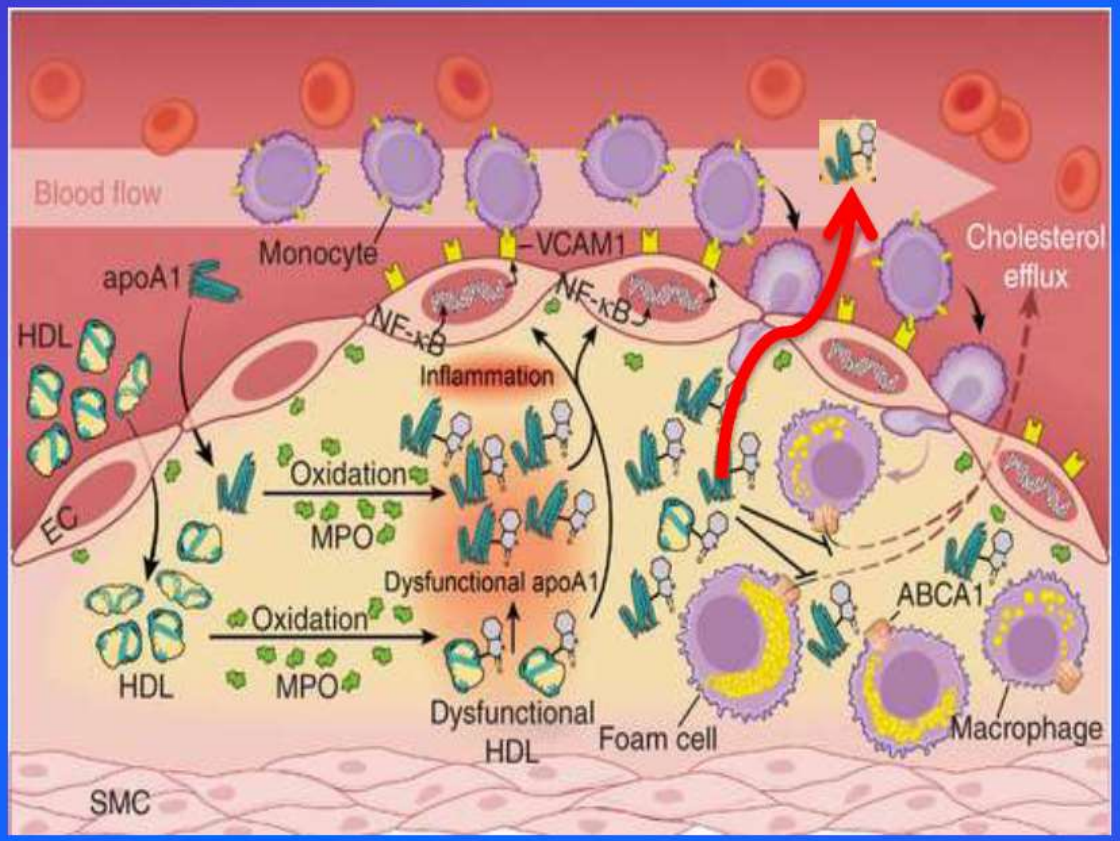
# Dysfunctional HDL



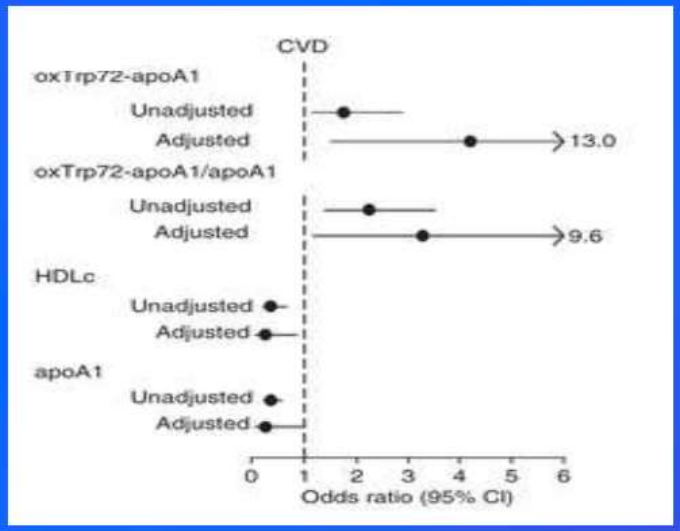

*J Am Coll Cardiol*. 2012; 60: 2380

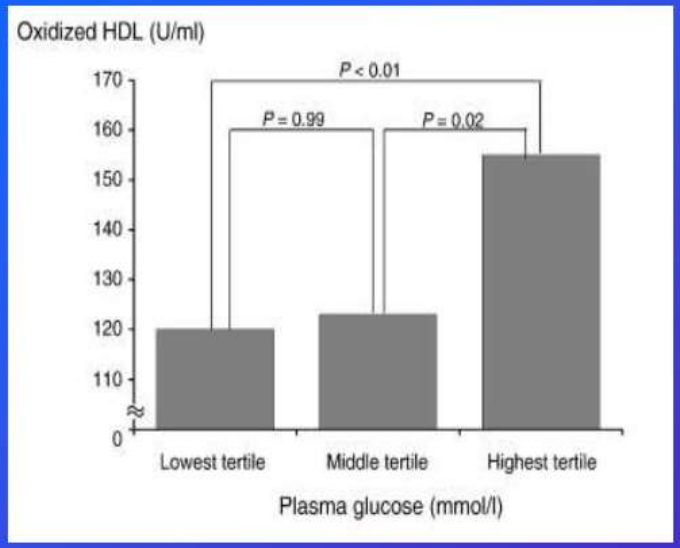
# Oxidized ApoA-I

## HDL Retention Model



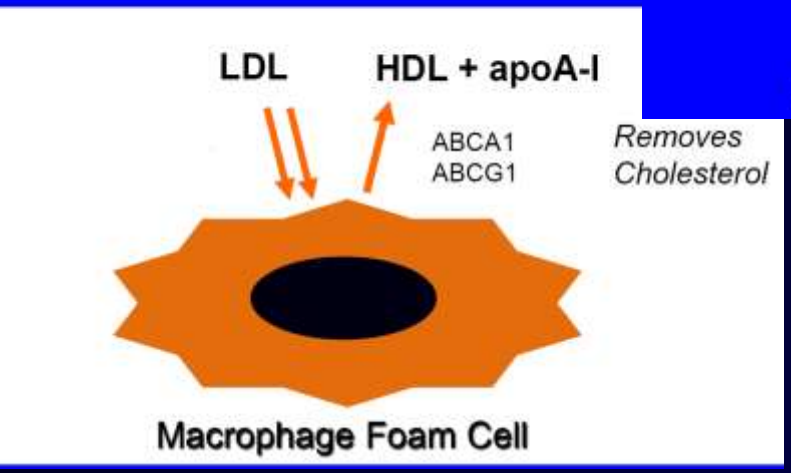

*Nature Medicine* 2014; 20: 193




*Clin Chim* 2012; 414: 125

## Macrophage Sterol Efflux: Proposed Cardioprotective Function of HDL




## Regulation of HDL Function by the HDL Proteome

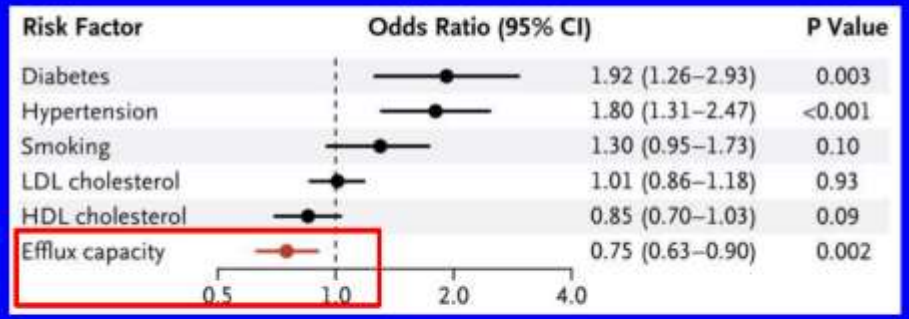
Jay Heinecke

University of Washington

# funzione

## Sterol Efflux Capacity of Serum HDL Strongly Associates with Cardiovascular Disease (CAD) Status

Khera et al. *N Engl J Med.* 2011;364:127.



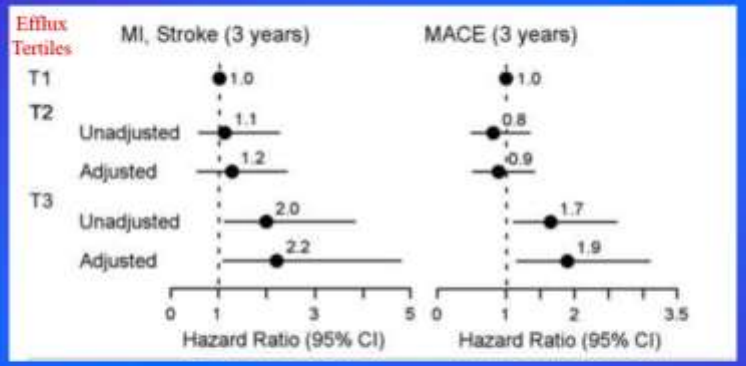

Impaired sterol efflux in CAD subjects (~20%)
Independent of HDL-C and ApoA-I

## Novel Approaches for Studying HDL Function

(How do you best measure HDL?)

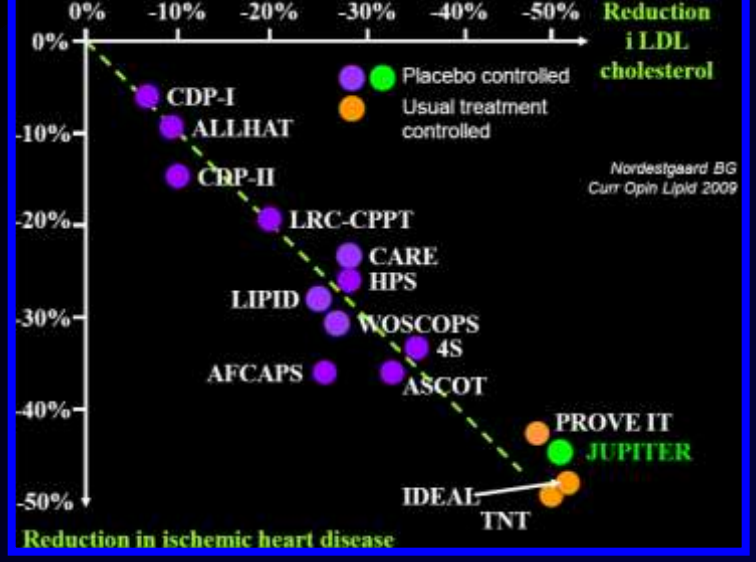
*Alan T. Remaley, MD, PhD*

## HDL Functional Tests: Cholesterol Efflux

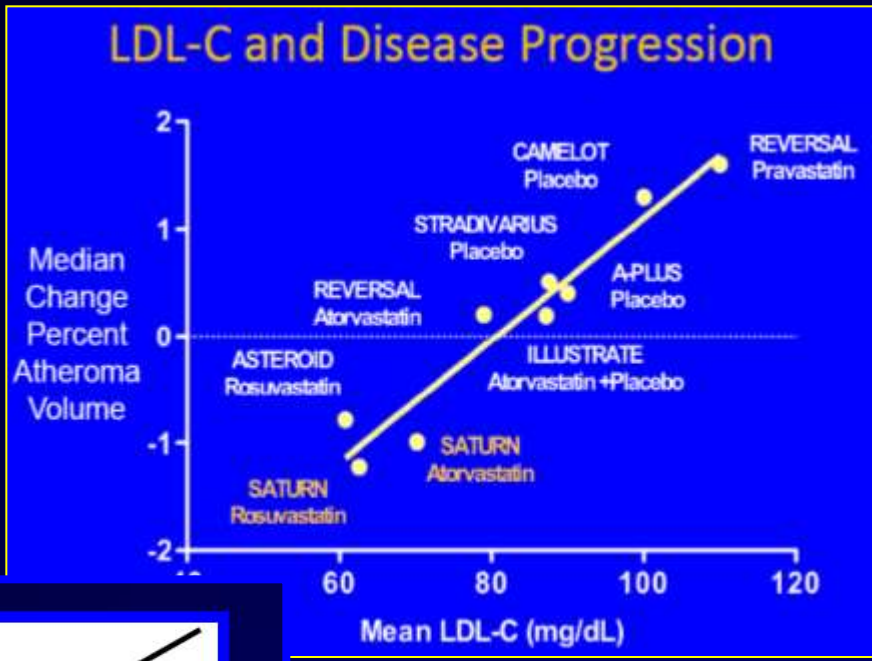


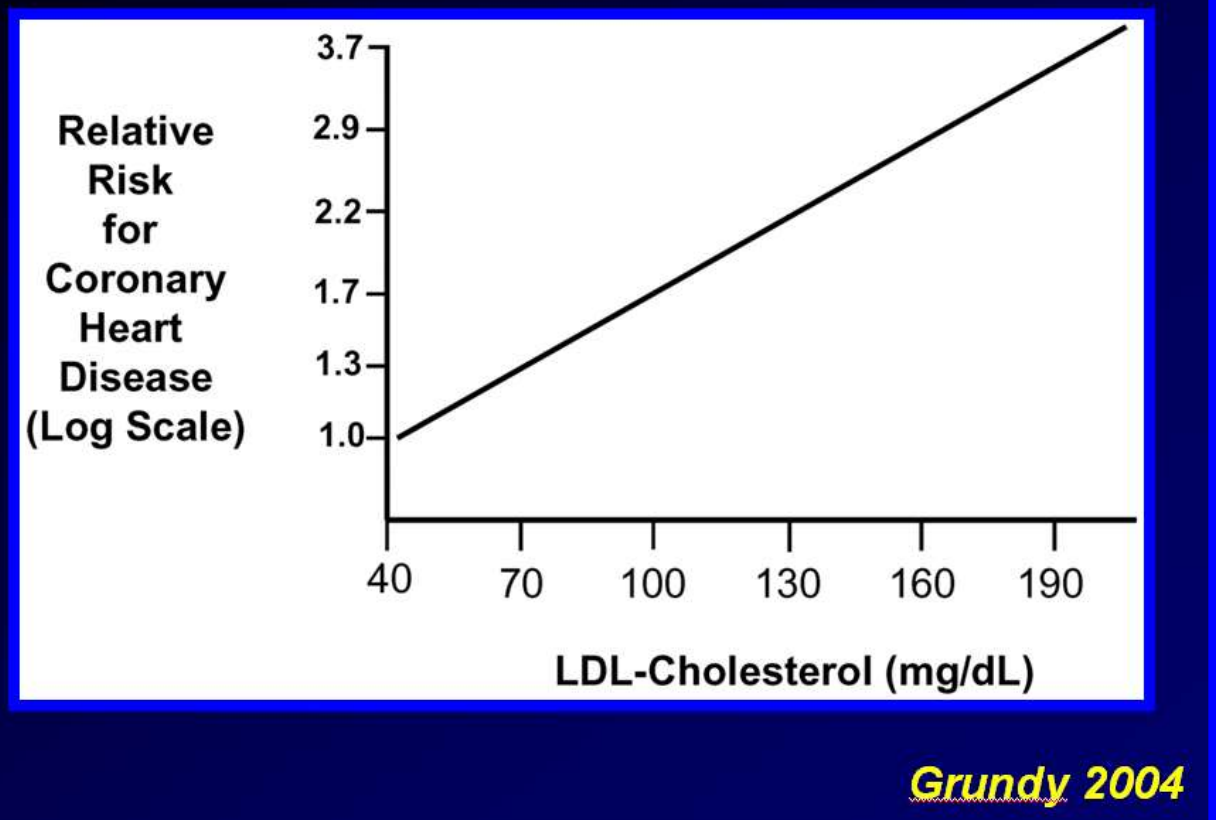

Efflux capacity of HDL is a positively related to future CHD events.

*ATVB* 2014; 33 :1696




# LDL




Grundy 2004

# ACC/AHA Blood Cholesterol Guideline

## Statin Benefit Groups

**Secondary Prevention**

**Diabetes – 40 to 75 yrs**
**LDL-C 70-189 mg/dl**

**LDL-C ≥ 190 mg/dL**

Rx: Optimal benefit with high intensity statins → lower LDL-C ≥ 50%
Use moderate intensity if age >75 or can't tolerate high intensity

---

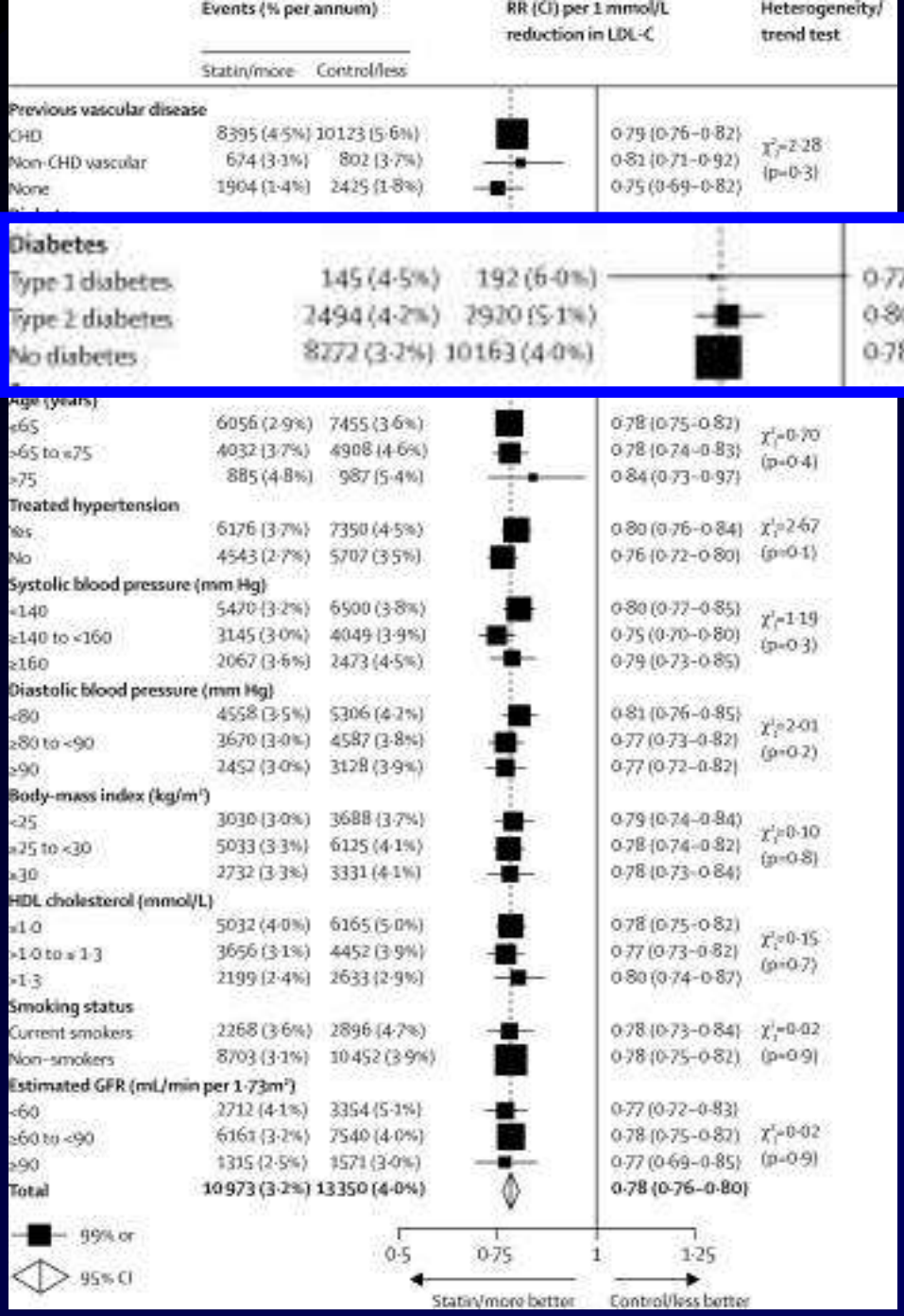
**Primary Prevention –**
**40 to 75 yrs**
**LDL-C 70-189 mg/dl**
**ASCVD Risk ≥ 7.5 %**
Rx: Moderate intensity
or high intensity statin

**Statin Rx not automatic, requires clinician-patient discussion**

Neil J. Stone

# Lancet. 2010

**Efficacy and safety of more intensive lowering of rol: a meta-analysis of data from cipants in 26 randomised trials.**




## Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline prognostic factors

Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups, and are weighted per 1·0 mmol/L LDL cholesterol (LDL-C) difference at 1 year. Missing data are not plotted. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds showing 95% CIs. CHD=coronary heart disease. GFR=glomerular filtration rate.

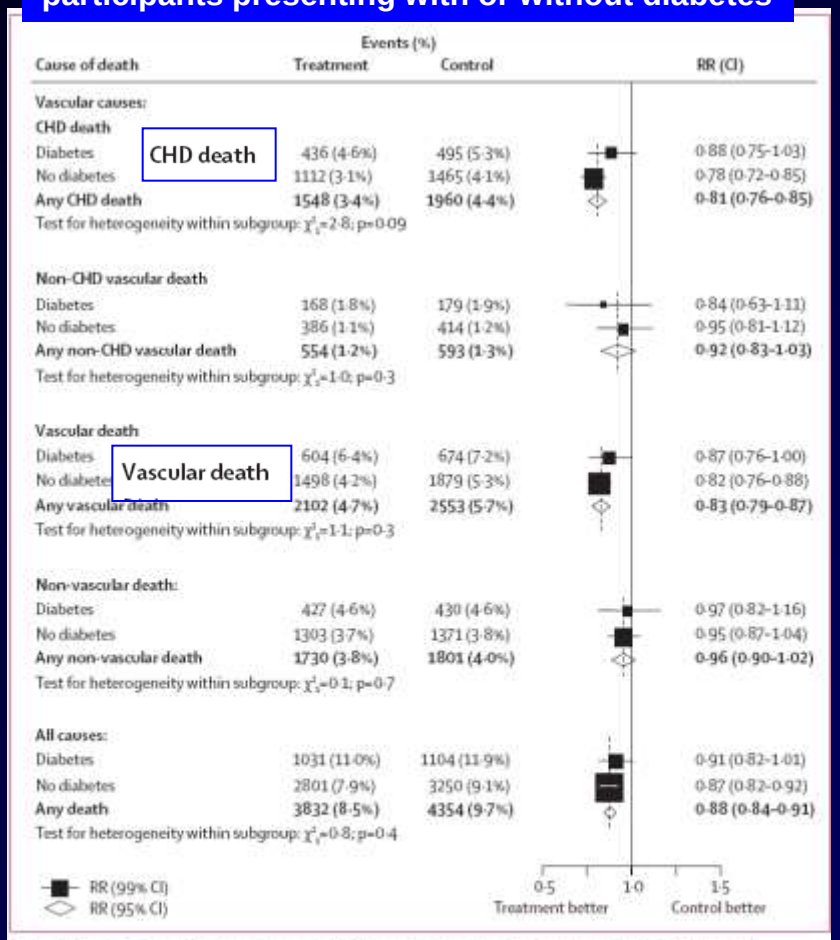
Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

# Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

*Lancet* 2008;

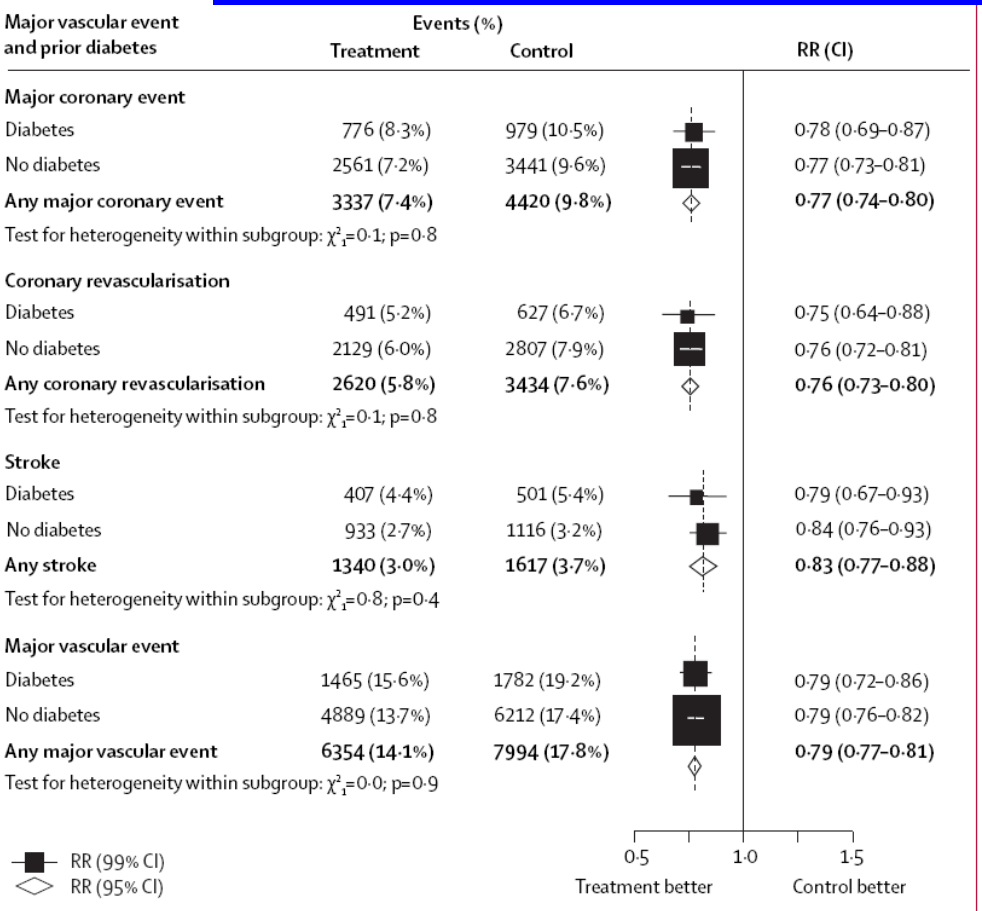
**Proportional effects on cause-specific mortality per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes**



| Cause of death | Events (%) Treatment | Control | RR (CI) |
|---|---|---|---|
| **Vascular causes:** | | | |
| **CHD death** | | | |
| Diabetes | 436 (4·6%) | 495 (5·3%) | 0·88 (0·75–1·03) |
| No diabetes | 1112 (3·1%) | 1465 (4·1%) | 0·78 (0·72–0·85) |
| **Any CHD death** | **1548 (3·4%)** | **1960 (4·4%)** | **0·81 (0·76–0·85)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=2·8; p=0·09 | | | |
| **Non-CHD vascular death** | | | |
| Diabetes | 168 (1·8%) | 179 (1·9%) | 0·84 (0·63–1·11) |
| No diabetes | 386 (1·1%) | 414 (1·2%) | 0·95 (0·81–1·12) |
| **Any non-CHD vascular death** | **554 (1·2%)** | **593 (1·3%)** | **0·92 (0·83–1·03)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=1·0; p=0·3 | | | |
| **Vascular death** | | | |
| Diabetes | 604 (6·4%) | 674 (7·2%) | 0·87 (0·76–1·00) |
| No diabetes | 1498 (4·2%) | 1879 (5·3%) | 0·82 (0·76–0·88) |
| **Any vascular death** | **2102 (4·7%)** | **2553 (5·7%)** | **0·83 (0·79–0·87)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=1·1; p=0·3 | | | |
| **Non-vascular death:** | | | |
| Diabetes | 427 (4·6%) | 430 (4·6%) | 0·97 (0·82–1·16) |
| No diabetes | 1303 (3·7%) | 1371 (3·8%) | 0·95 (0·87–1·04) |
| **Any non-vascular death** | **1730 (3·8%)** | **1801 (4·0%)** | **0·96 (0·90–1·02)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=0·1; p=0·7 | | | |
| **All causes:** | | | |
| Diabetes | 1031 (11·0%) | 1104 (11·9%) | 0·91 (0·82–1·01) |
| No diabetes | 2801 (7·9%) | 3250 (9·1%) | 0·87 (0·82–0·92) |
| **Any death** | **3832 (8·5%)** | **4354 (9·7%)** | **0·88 (0·84–0·91)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=0·8; p=0·4 | | | |



**Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants presenting with or without diabetes**



| Major vascular event and prior diabetes | Events (%) Treatment | Control | RR (CI) |
|---|---|---|---|
| **Major coronary event** | | | |
| Diabetes | 776 (8·3%) | 979 (10·5%) | 0·78 (0·69–0·87) |
| No diabetes | 2561 (7·2%) | 3441 (9·6%) | 0·77 (0·73–0·81) |
| **Any major coronary event** | **3337 (7·4%)** | **4420 (9·8%)** | **0·77 (0·74–0·80)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=0·1; p=0·8 | | | |
| **Coronary revascularisation** | | | |
| Diabetes | 491 (5·2%) | 627 (6·7%) | 0·75 (0·64–0·88) |
| No diabetes | 2129 (6·0%) | 2807 (7·9%) | 0·76 (0·72–0·81) |
| **Any coronary revascularisation** | **2620 (5·8%)** | **3434 (7·6%)** | **0·76 (0·73–0·80)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=0·1; p=0·8 | | | |
| **Stroke** | | | |
| Diabetes | 407 (4·4%) | 501 (5·4%) | 0·79 (0·67–0·93) |
| No diabetes | 933 (2·7%) | 1116 (3·2%) | 0·84 (0·76–0·93) |
| **Any stroke** | **1340 (3·0%)** | **1617 (3·7%)** | **0·83 (0·77–0·88)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=0·8; p=0·4 | | | |
| **Major vascular event** | | | |
| Diabetes | 1465 (15·6%) | 1782 (19·2%) | 0·79 (0·72–0·86) |
| No diabetes | 4889 (13·7%) | 6212 (17·4%) | 0·79 (0·76–0·82) |
| **Any major vascular event** | **6354 (14·1%)** | **7994 (17·8%)** | **0·79 (0·77–0·81)** |
| Test for heterogeneity within subgroup: $\chi^2_1$=0·0; p=0·9 | | | |

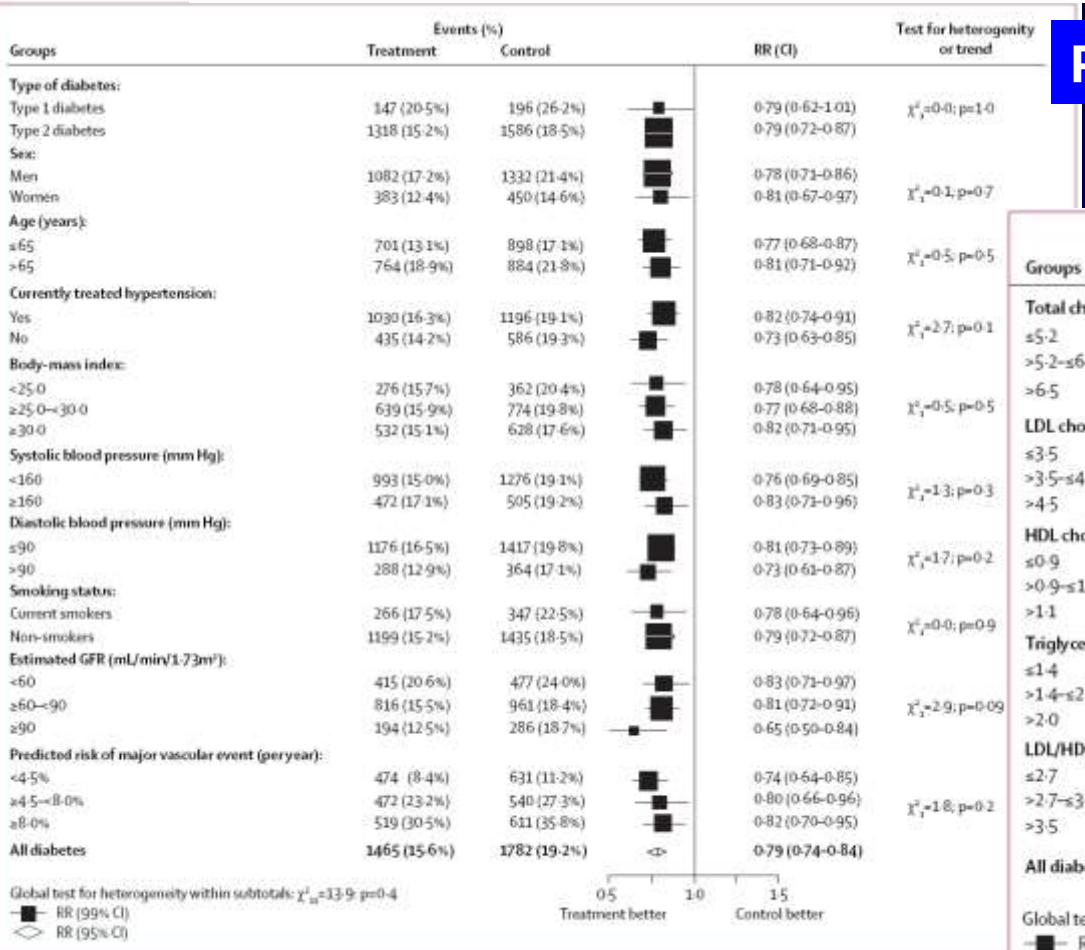
# Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

*Cholesterol Treatment Trialists' (CTT) Collaborators**

*Lancet* 2008;

**Pts with diabetes**

**by baseline lipid profile**



| Groups | Events (%) Treatment | Control | RR (CI) | Test for heterogeneity or trend |
|---|---|---|---|---|
| **Type of diabetes:** | | | | |
| Type 1 diabetes | 147 (20·5%) | 196 (26·2%) | 0·79 (0·62–1·01) | $\chi^2_1$=0·0; p=1·0 |
| Type 2 diabetes | 1318 (15·2%) | 1586 (18·5%) | 0·79 (0·72–0·87) | |
| **Sex:** | | | | |
| Men | 1082 (17·2%) | 1332 (21·4%) | 0·78 (0·71–0·86) | |
| Women | 383 (12·4%) | 450 (14·6%) | 0·81 (0·67–0·97) | $\chi^2_1$=0·1; p=0·7 |
| **Age (years):** | | | | |
| ≤65 | 701 (13·1%) | 898 (17·1%) | 0·77 (0·68–0·87) | |
| >65 | 764 (18·9%) | 884 (21·8%) | 0·81 (0·71–0·92) | $\chi^2_1$=0·5; p=0·5 |
| **Currently treated hypertension:** | | | | |
| Yes | 1030 (16·3%) | 1196 (19·1%) | 0·82 (0·74–0·91) | |
| No | 435 (14·2%) | 586 (19·3%) | 0·73 (0·63–0·85) | $\chi^2_1$=2·7; p=0·1 |
| **Body-mass index:** | | | | |
| <25·0 | 276 (15·7%) | 362 (20·4%) | 0·78 (0·64–0·95) | |
| ≥25·0–<30·0 | 639 (15·9%) | 774 (19·8%) | 0·77 (0·68–0·88) | $\chi^2_1$=0·5; p=0·5 |
| ≥30·0 | 532 (15·1%) | 628 (17·6%) | 0·82 (0·71–0·95) | |
| **Systolic blood pressure (mm Hg):** | | | | |
| <160 | 993 (15·0%) | 1276 (19·1%) | 0·76 (0·69–0·85) | |
| ≥160 | 472 (17·1%) | 505 (19·2%) | 0·83 (0·71–0·96) | $\chi^2_1$=1·3; p=0·3 |
| **Diastolic blood pressure (mm Hg):** | | | | |
| ≤90 | 1176 (16·5%) | 1417 (19·8%) | 0·81 (0·73–0·89) | |
| >90 | 288 (12·9%) | 364 (17·1%) | 0·73 (0·61–0·87) | $\chi^2_1$=1·7; p=0·2 |
| **Smoking status:** | | | | |
| Current smokers | 266 (17·5%) | 347 (22·5%) | 0·78 (0·64–0·96) | |
| Non-smokers | 1199 (15·2%) | 1435 (18·5%) | 0·79 (0·72–0·87) | $\chi^2_1$=0·0; p=0·9 |
| **Estimated GFR (mL/min/1·73m²):** | | | | |
| <60 | 415 (20·6%) | 477 (24·0%) | 0·83 (0·71–0·97) | |
| ≥60–<90 | 816 (15·5%) | 961 (18·4%) | 0·81 (0·72–0·91) | |
| ≥90 | 194 (12·5%) | 286 (18·7%) | 0·65 (0·50–0·84) | $\chi^2_2$=2·9; p=0·09 |
| **Predicted risk of major vascular event (per year):** | | | | |
| <4·5% | 474 (8·4%) | 631 (11·2%) | 0·74 (0·64–0·85) | |
| ≥4·5–<8·0% | 472 (23·2%) | 540 (27·3%) | 0·80 (0·66–0·96) | |
| ≥8·0% | 519 (30·5%) | 611 (35·8%) | 0·82 (0·70–0·95) | $\chi^2_1$=1·8; p=0·2 |
| **All diabetes** | **1465 (15·6%)** | **1782 (19·2%)** | **0·79 (0·74–0·84)** | |

Global test for heterogeneity within subtotals: $\chi^2_{10}$=13·9; p=0·4

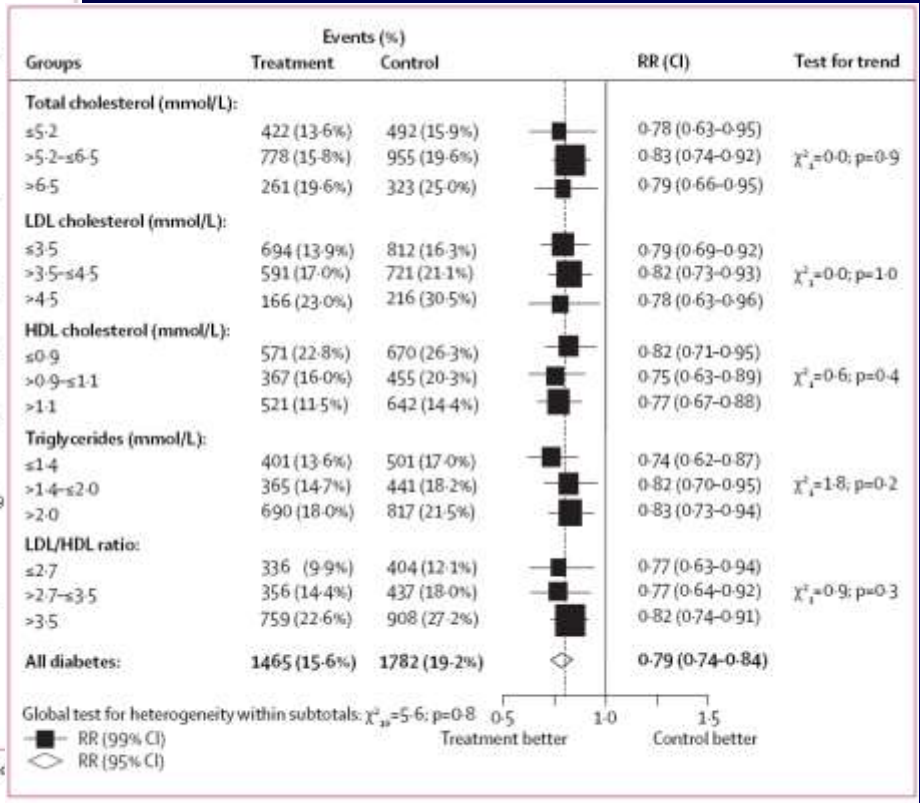
RR (99% CI)

RR (95% CI)

0·5 Treatment better 1·0 1·5 Control better

ure 4: Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol by baseline prognostic factors in participants with
mbols and conventions as in figure 1. Tests for trend are shown for subgroups involving three categories, heterogeneity tests for those involving two.
Performance filtration rate

**by baseline prognostic factors**



| Groups | Events (%) Treatment | Control | RR (CI) | Test for trend |
|---|---|---|---|---|
| **Total cholesterol (mmol/L):** | | | | |
| ≤5·2 | 422 (13·6%) | 492 (15·9%) | 0·78 (0·63–0·95) | |
| >5·2–≤6·5 | 778 (15·8%) | 955 (19·6%) | 0·83 (0·74–0·92) | $\chi^2_1$=0·0; p=0·9 |
| >6·5 | 261 (19·6%) | 323 (25·0%) | 0·79 (0·66–0·95) | |
| **LDL cholesterol (mmol/L):** | | | | |
| ≤3·5 | 694 (13·9%) | 812 (16·3%) | 0·79 (0·69–0·92) | |
| >3·5–≤4·5 | 591 (17·0%) | 721 (21·1%) | 0·82 (0·73–0·93) | $\chi^2_1$=0·0; p=1·0 |
| >4·5 | 166 (23·0%) | 216 (30·5%) | 0·78 (0·63–0·96) | |
| **HDL cholesterol (mmol/L):** | | | | |
| ≤0·9 | 571 (22·8%) | 670 (26·3%) | 0·82 (0·71–0·95) | |
| >0·9–≤1·1 | 367 (16·0%) | 455 (20·3%) | 0·75 (0·63–0·89) | $\chi^2_1$=0·6; p=0·4 |
| >1·1 | 521 (11·5%) | 642 (14·4%) | 0·77 (0·67–0·88) | |
| **Triglycerides (mmol/L):** | | | | |
| ≤1·4 | 401 (13·6%) | 501 (17·0%) | 0·74 (0·62–0·87) | |
| >1·4–≤2·0 | 365 (14·7%) | 441 (18·2%) | 0·82 (0·70–0·95) | $\chi^2_1$=1·8; p=0·2 |
| >2·0 | 690 (18·0%) | 817 (21·5%) | 0·83 (0·73–0·94) | |
| **LDL/HDL ratio:** | | | | |
| ≤2·7 | 336 (9·9%) | 404 (12·1%) | 0·77 (0·63–0·94) | |
| >2·7–≤3·5 | 356 (14·4%) | 437 (18·0%) | 0·77 (0·64–0·92) | $\chi^2_1$=0·9; p=0·3 |
| >3·5 | 759 (22·6%) | 908 (27·2%) | 0·82 (0·74–0·91) | |
| **All diabetes:** | **1465 (15·6%)** | **1782 (19·2%)** | **0·79 (0·74–0·84)** | |

Global test for heterogeneity within subtotals: $\chi^2_{10}$=5·6; p=0·8

RR (99% CI)

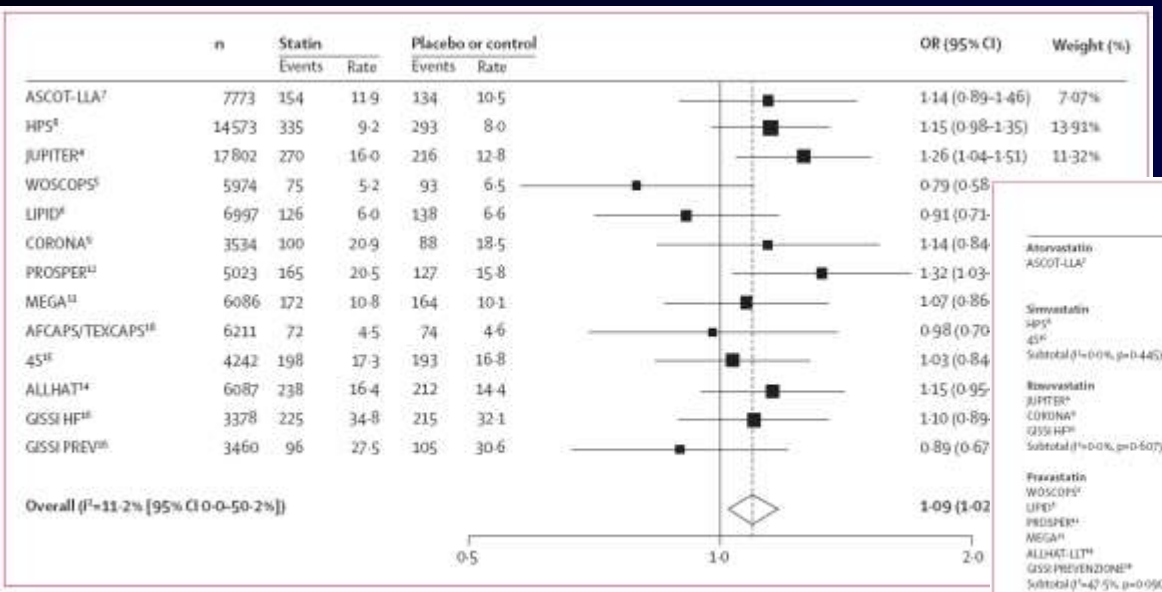
RR (95% CI)

0·5 Treatment better 1·0 1·5 Control better

*Figure 5*: Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol by baseline lipid profile in participants with diabetes

# Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

*Lancet* 2010;



| | n | Statin Events | Statin Rate | Placebo or control Events | Placebo or control Rate | OR (95% CI) | Weight (%) |
|---|---|---|---|---|---|---|---|
| ASCOT-LLA[7] | 7773 | 154 | 11·9 | 134 | 10·5 | 1·14 (0·89–1·46) | 7·07% |
| HPS[8] | 14573 | 335 | 9·2 | 293 | 8·0 | 1·15 (0·98–1·35) | 13·91% |
| JUPITER[9] | 17802 | 270 | 16·0 | 216 | 12·8 | 1·26 (1·04–1·51) | 11·32% |
| WOSCOPS[5] | 5974 | 75 | 5·2 | 93 | 6·5 | 0·79 (0·58 | |
| LIPID[6] | 6997 | 126 | 6·0 | 138 | 6·6 | 0·91 (0·71 | |
| CORONA[9] | 3534 | 100 | 20·9 | 88 | 18·5 | 1·14 (0·84 | |
| PROSPER[10] | 5023 | 165 | 20·5 | 127 | 15·8 | 1·32 (1·03 | |
| MEGA[11] | 6086 | 172 | 10·8 | 164 | 10·1 | 1·07 (0·86 | |
| AFCAPS/TEXCAPS[18] | 6211 | 72 | 4·5 | 74 | 4·6 | 0·98 (0·70 | |
| 4S[16] | 4242 | 198 | 17·3 | 193 | 16·8 | 1·03 (0·84 | |
| ALLHAT[14] | 6087 | 238 | 16·4 | 212 | 14·4 | 1·15 (0·95 | |
| GISSI HF[19] | 3378 | 225 | 34·8 | 215 | 32·1 | 1·10 (0·89 | |
| GISSI PREV[20] | 3460 | 96 | 27·5 | 105 | 30·6 | 0·89 (0·67 | |
| Overall ($I^2$=11·2% [95% CI 0·0–50·2%]) | | | | | | 1·09 (1·02 | |



*Figure 2:* Association between statin therapy and incident diabetes in 13 major cardiovascular trials†
†Events per 1000 patient-years. ‡Weights are from random-effects analysis.

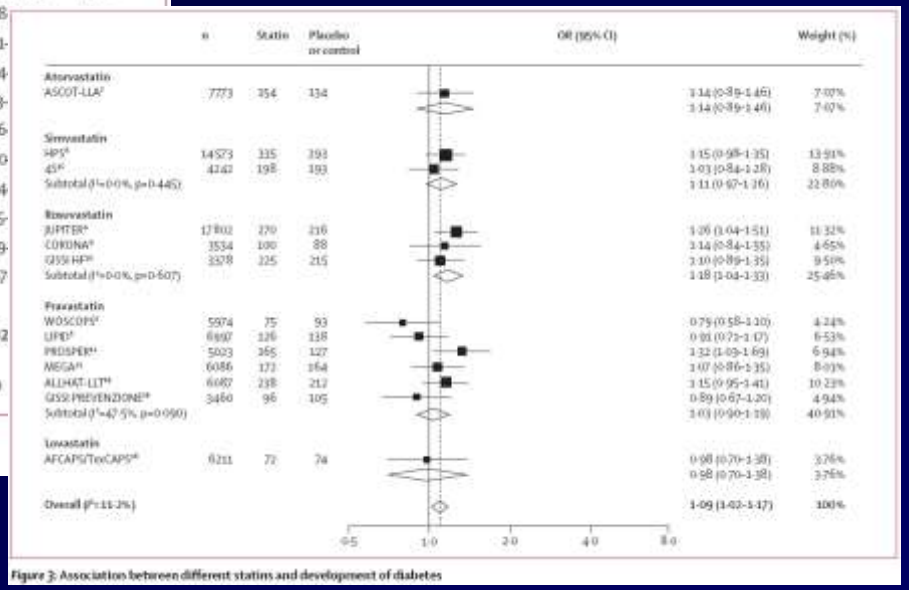




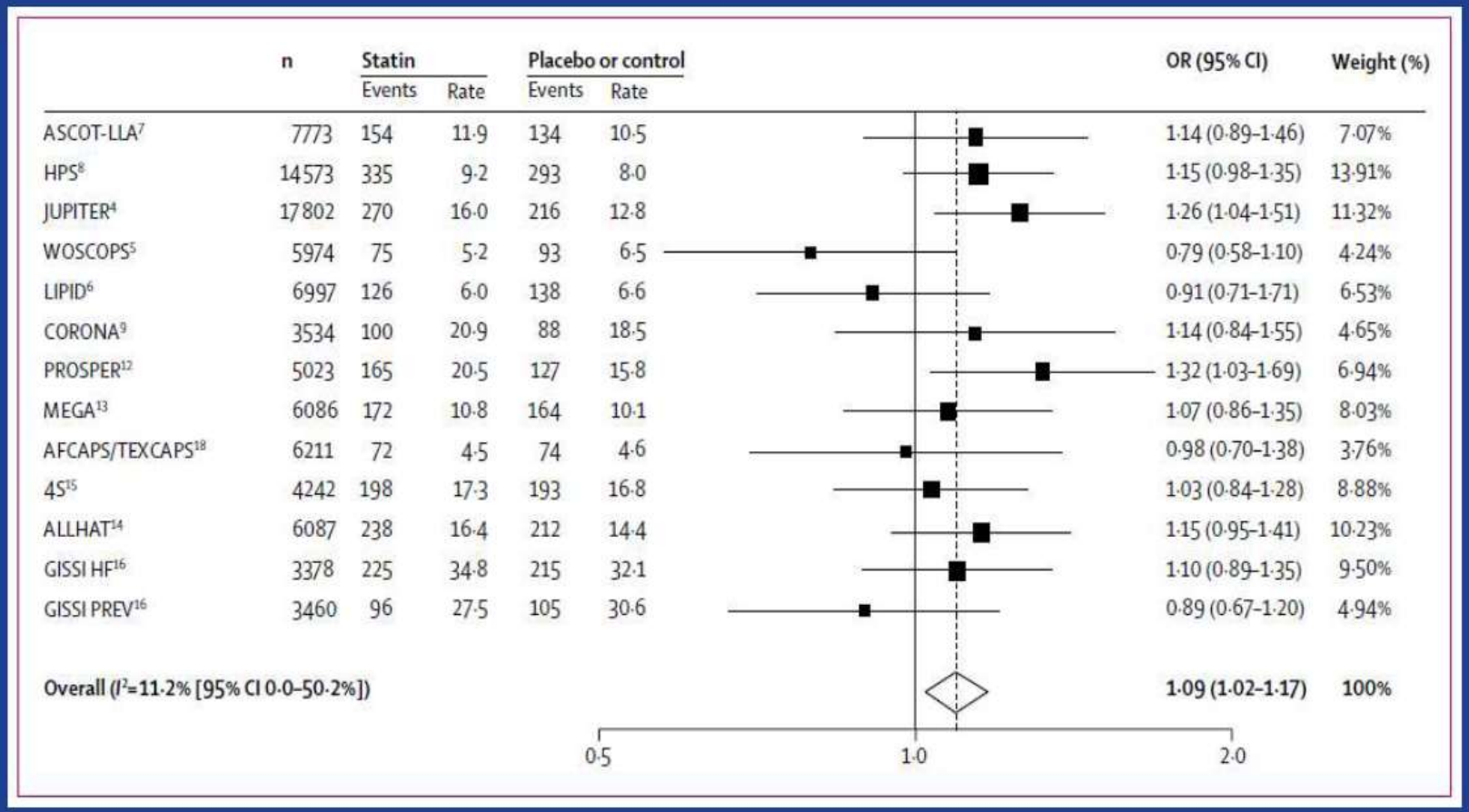
Figure 3: Associations between different statins and development of diabetes

**In view of the overwhelming benefit of statins for reduction of cardiovascular events, the small absolute risk for development of diabetes is outweighed by cardiovascular benefi t in the short and medium term in individuals for whom statin therapy is recommended.**

# Statin Induced Dysglycaemia: How big a deal is it ?

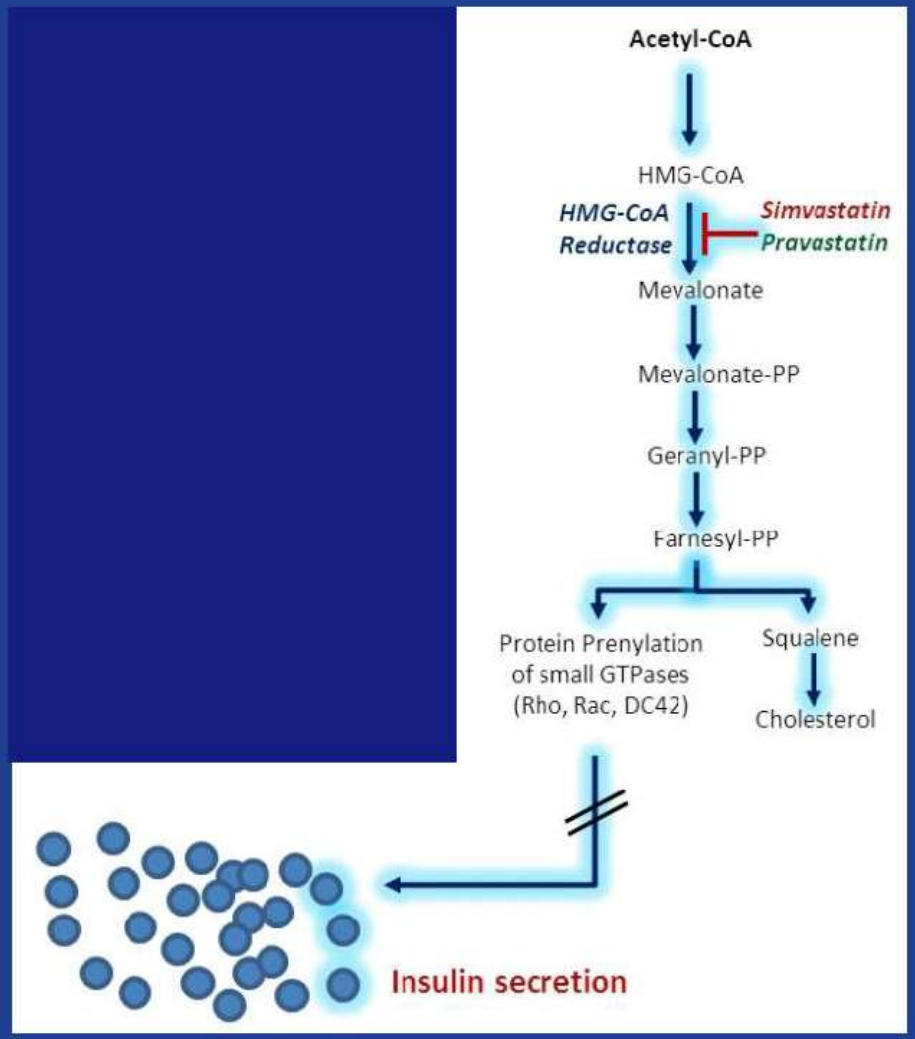
Prof Kausik Ray,
BSc (hons), MBChB, MD, MPhil (Cantab), FRCP, FACC, FESC, FAHA

# Statins increase risk of Dysglycaemia



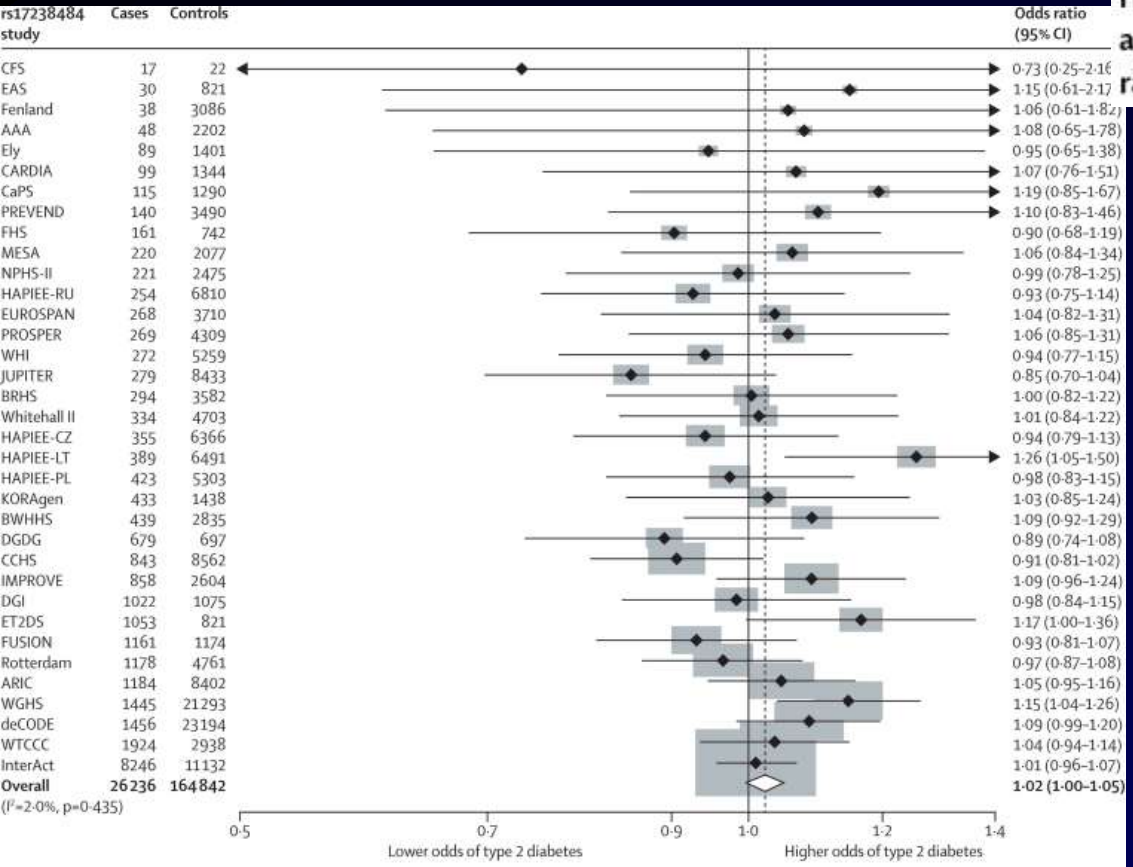

*Sattar N, et al Ray KK. Lancet 2010; 375: 735-42*

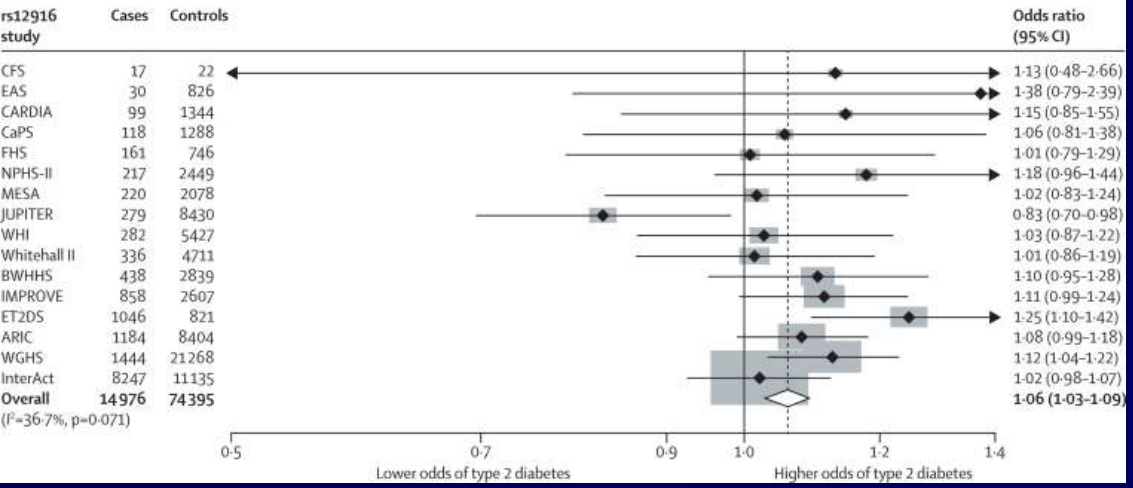
# Inhibiting HMG-CoA may mediate glucose levels via prenylation pathways



HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials

*Lancet* 2015;




Meta-analyses of the associations of 3-hydroxy-3-methylglutaryl-CoA reductase variants rs17238484 and rs12916 with risk of type 2 diabetes

**Interpretation**
**The increased risk of type 2 diabetes noted with statins is at least partially explained by HMGCR inhibition.**

# Statin Induced Dysglycaemia: How big a deal is it ?

AHA2014

Prof Kausik Ray,
BSc (hons), MBChB, MD, MPhil (Cantab), FRCP, FACC, FESC, FAHA
London, UK

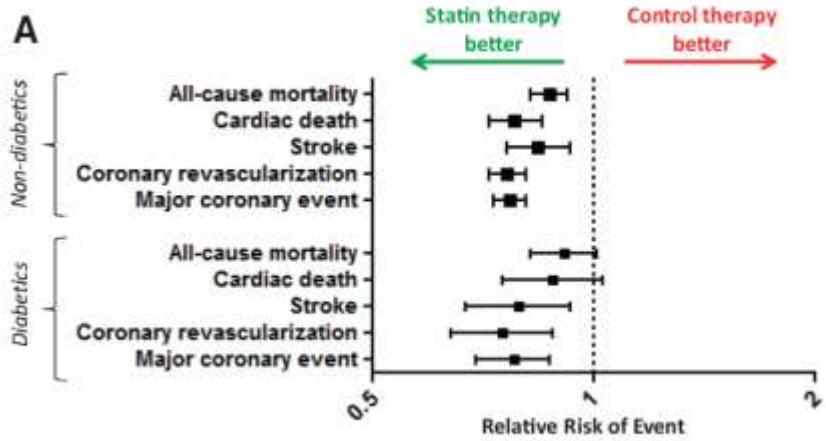
## Associazione statina-disglicemia

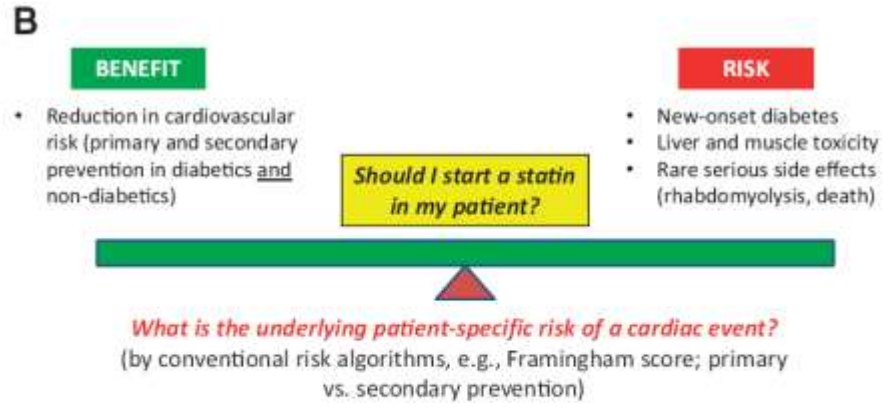
Età
Dose dipendente
Più alta in pz con fattori di rischio
No effetti su micorvascular diseases
benefici ++di rischi

## Statins and Risk of New-Onset Diabetes Mellitus

Ravi V. Shah, MD; Allison B. Goldfine, MD

*Circulation.* 2012



# Screening for Heart Disease in Diabetes

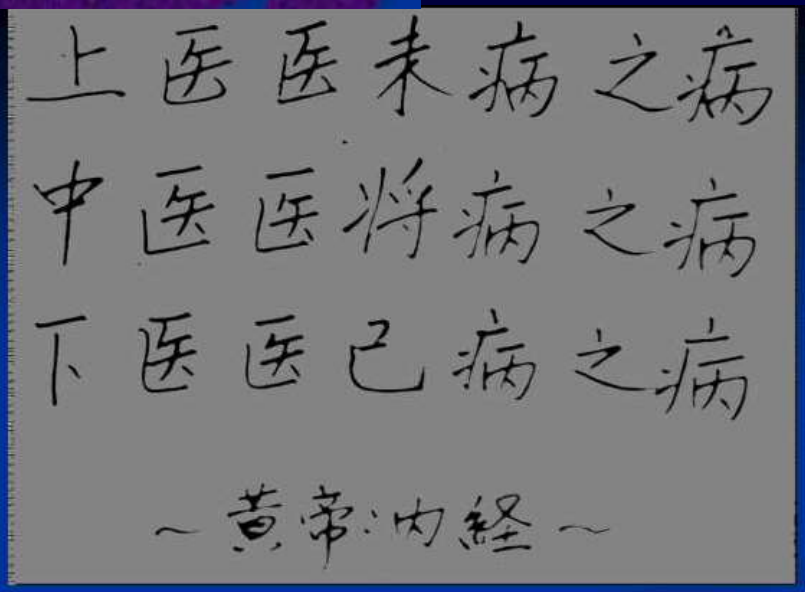
*Matthew Budoff, MD, FACC, FAHA*

*Professor of Medicine*

*Program Director*

*Director, Cardiac CT*

*Harbor-UCLA Medical Center, Torrance, CA*




Superior doctors prevent the disease.
Mediocre doctors treat the disease
before evident. **Subclinical Atherosclerosis**
Inferior doctors treat the full-blown disease.
--Huang Dee: Nai-Ching
(2600 BC First Chinese Medical Text)

grazie per l’attenzione