This year in … lipidi

Anna Nelva e Francesco Tassone

This year in … lipidi

PARLEREMO DI:

- **PCSK9-I**: ultime notizie
- **Acidi grassi polinsaturi** nella prevenzione cardio-vascolare: nuove evidenze e controversie
- **PCR ad alta sensibilità**: nuovi risvolti terapeutici
- **HDL e CETP-inibitori**: nuove evidenze

Colesterolo LDL: “breaking news” su PCSK9i

Francesco Tassone, M.D.,PhD

S.C. di Endocrinologia, Diabetologia & Metabolismo

A.S.O. Santa Croce e Carle di Cuneo

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Novo Nordisk
- Astra Zeneca
- Mylan

Effect of PCSK9 Inhibitors on Clinical Outcomes in Patients With Hypercholesterolemia: A Meta-Analysis of 35 Randomized Controlled Trials

Aris Karatasakis, MD; Barbara A Danek, MD; Judit Karacsonyi, MD; Bavana V Rangan, BDS, MPH; Michele K Roesle, RN, BSN; Thomas Knickelbine, MD; Michael D Miedema, MD, MPH; Houman Khalili; MD; Zahid Ahmad, MD; Shuaib Abdullah, MD; Subhash Banerjee, MD; Emmanouil S. Brilakis, MD, PhD

Background—We sought to examine the efficacy and safety of 2 PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors: alirocumab and evolocumab.

Methods and Results—We performed a systematic review and meta-analysis of randomized controlled trials comparing treatment with and without PCSK9 inhibitors; 35 randomized controlled trials comprising 45 539 patients (mean follow-up: 85.5 weeks) were included. Mean age was 61.0±2.8 years, and mean baseline low-density lipoprotein cholesterol was 106±22 mg/dL. Compared with no PCSK9 inhibitor therapy, treatment with a PCSK9 inhibitor was associated with a lower rate of myocardial infarction (2.3% versus 3.6%; odds ratio [OR]: 0.72 [95% confidence interval (CI), 0.64–0.81]; $P<0.001$), stroke (1.0% versus 1.4%; OR: 0.80 [95% CI, 0.67–0.96]; $P=0.02$), and coronary revascularization (4.2% versus 5.8%; OR: 0.78 [95% CI, 0.71–0.86]; $P<0.001$). Overall, no significant change was observed in all-cause mortality (OR: 0.71 [95% CI, 0.47–1.09]; $P=0.12$) or cardiovascular mortality (OR: 1.01 [95% CI, 0.85–1.19]; $P=0.95$). A significant association was observed between higher baseline low-density lipoprotein cholesterol and benefit in all-cause mortality ($P=0.038$). No significant change was observed in neurocognitive adverse events (OR: 1.12 [95% CI, 0.88–1.42]; $P=0.37$), myalgia (OR: 0.95 [95% CI, 0.75–1.20]; $P=0.65$), new onset or worsening of preexisting diabetes mellitus (OR: 1.05 [95% CI, 0.95–1.17]; $P=0.32$), and increase in levels of creatine kinase (OR: 0.84 [95% CI, 0.70–1.01]; $P=0.06$) or alanine or aspartate aminotransferase (OR: 0.96 [95% CI, 0.82–1.12]; $P=0.61$).

Conclusions—Treatment with a PCSK9 inhibitor is well tolerated and improves cardiovascular outcomes. Although no overall benefit was noted in all-cause or cardiovascular mortality, such benefit may be achievable in patients with higher baseline low-density lipoprotein cholesterol. (***J Am Heart Assoc.* 2017;6:e006910. DOI: 10.1161/JAHA.117.006910.**)

Key Words: alirocumab • evolocumab • hyperlipidemia • outcome • PCSK9

J Am Heart Assoc. 2017;

Clinical Perspective

What Is New?

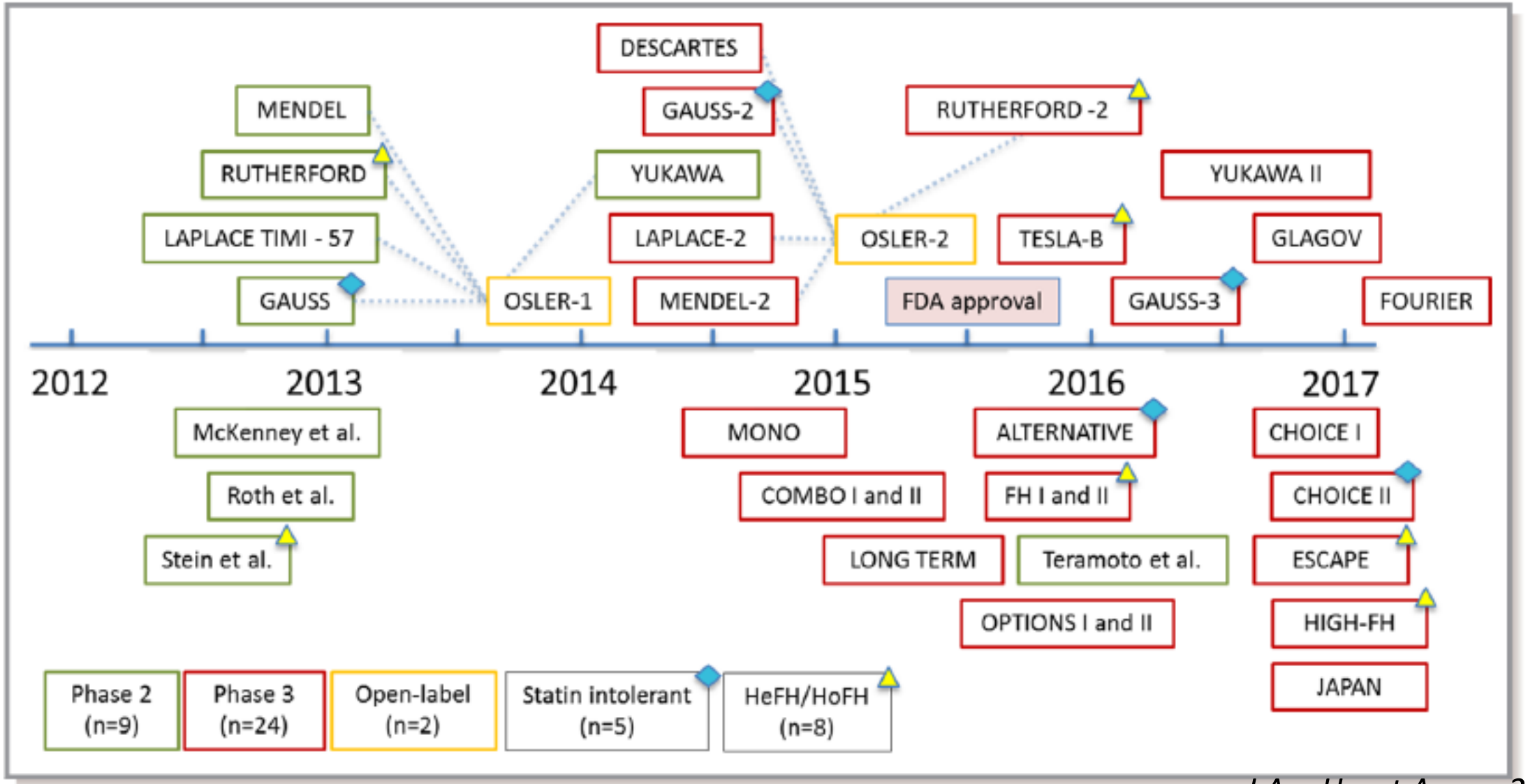
- PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors appear safe and are associated with dramatically reduced atherogenic lipid fraction levels and lower incidence of myocardial infarction, stroke, and coronary revascularization.
- Despite favorable early indications from lipid-lowering trials, the available clinical data do not demonstrate a mortality benefit with PCSK9 inhibitors.

What Are the Clinical Implications?

- Whether patient subgroups exist that can derive a significant mortality benefit from PCSK9 inhibitor treatment (eg, patients intolerant to statins or with familial hypercholesterolemia) needs to be further evaluated in randomized controlled trials.

J Am Heart Assoc. 2017;

Effect of PCSK9 Inhibitors on Clinical Outcomes in Patients With Hypercholesterolemia: A Meta-Analysis of 35 RCTs



J Am Heart Assoc. 2017;

Effect of PCSK9 Inhibitors on Clinical Outcomes in Patients With Hypercholesterolemia: A Meta-Analysis of 35 RCTs

Discussion

The main findings of this meta-analysis are that, compared with no PCSK9 inhibitor use, **treatment with PCSK9 inhibitors**:

1. is associated with a statistically significant **reduction in MI, stroke, and coronary revascularization;**

2. is **not significantly associated with all-cause or cardiovascular mortality**, **neurocognitive** adverse events, incident or worsening of preexisting **diabetes mellitus**, creatine kinase increase, myalgia, increase in alanine or aspartate aminotransferase, or treatment-emergent serious adverse events;

3. is associated with consistent and **favorable changes in lipid fractions.**

J Am Heart Assoc. 2017;

- ALIROCUMAB

The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,

Ph. Gabriel Steg

On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ODYSSEY OUTCOMES

ClinicalTrials.gov: NCT01663402

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

This article was published on November 7, 2018, at NEJM.org !!.

ODYSSEY OUTCOMES TRIAL

BACKGROUND

Patients who have had an acute coronary syndrome are at high risk for recurrent ischemic cardiovascular events. We sought to determine whether alirocumab, a human monoclonal antibody to proprotein convertase subtilisin–kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy.

METHODS

We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non–high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

This article was published on November 7, 2018, at NEJM.org !!

Main Inclusion Criteria

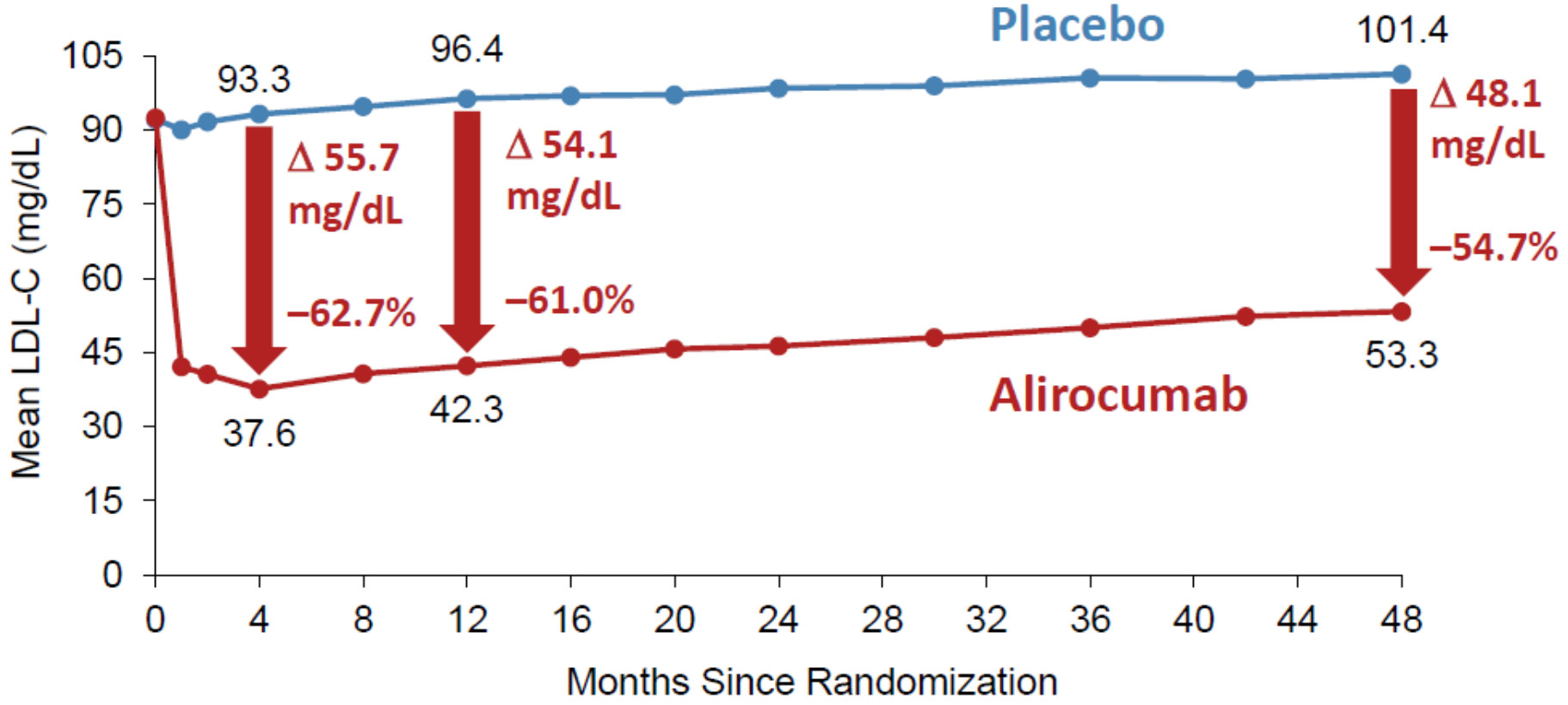
- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

ODYSSEY OUTCOMES TRIAL

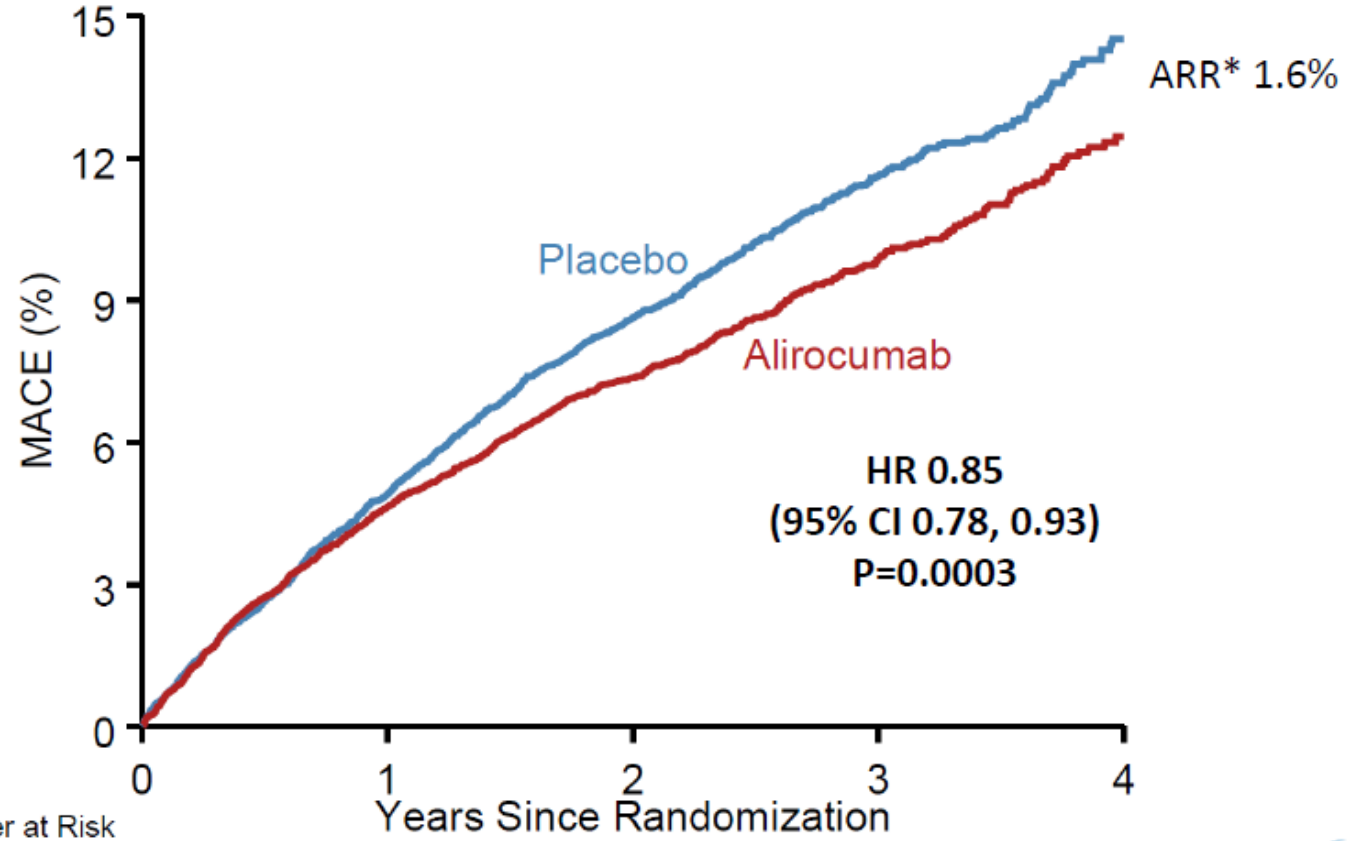
LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Number at Risk					
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

*Based on cumulative incidence

ODYSSEY OUTCOMES

Primary Efficacy and Components

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

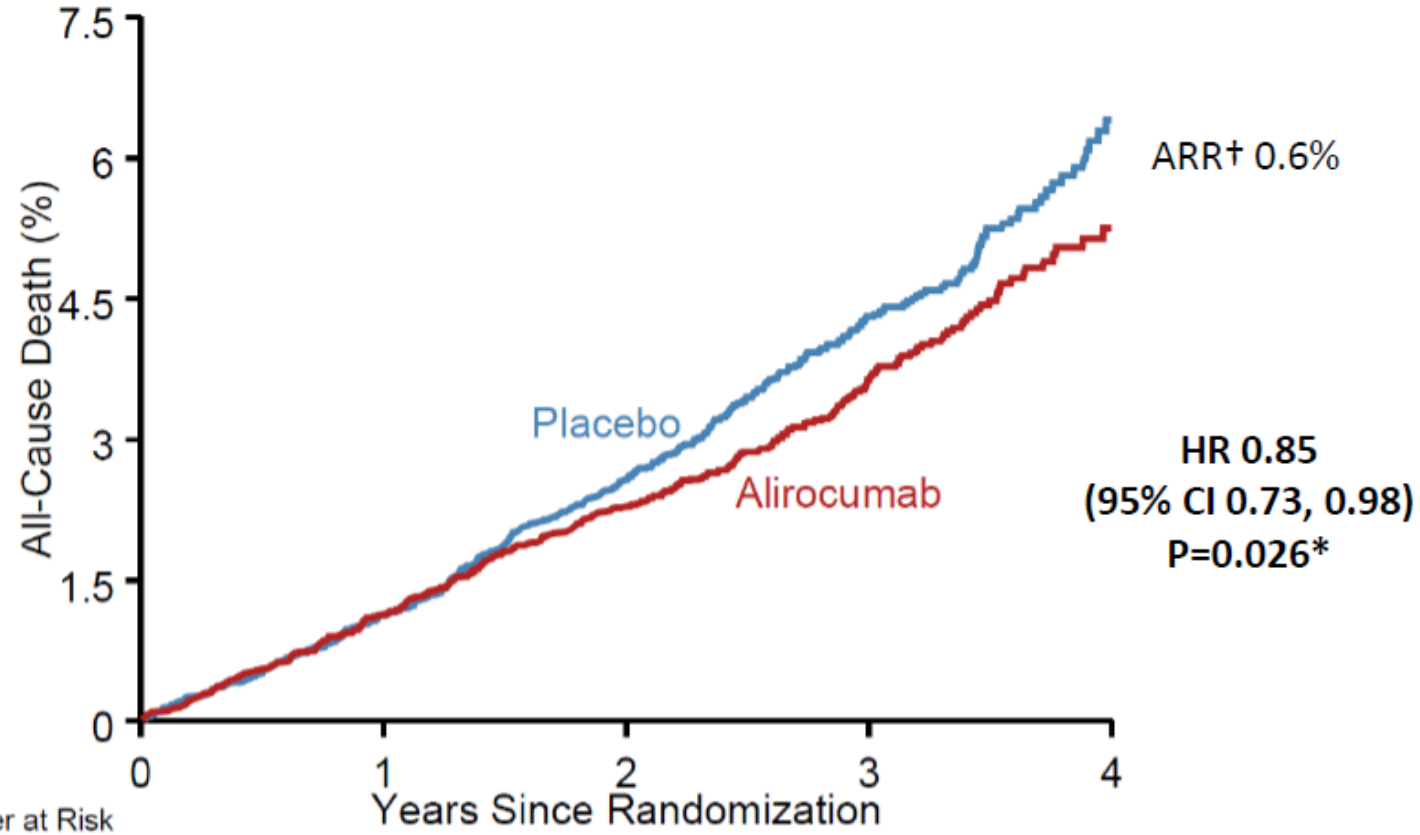
Main Secondary Efficacy Endpoints:
Hierarchical Testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	**1199 (12.7)**	**1349 (14.3)**	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	**793 (8.4)**	**899 (9.5)**	**0.88 (0.80, 0.96)**	**0.006**
CV event	**1301 (13.7)**	**1474 (15.6)**	**0.87 (0.81, 0.94)**	**0.0003**
Death, MI, ischemic stroke	**973 (10.3)**	**1126 (11.9)**	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
CV death	**240 (2.5)**	**271 (2.9)**	0.88 (0.74, 1.05)	0.15
All-cause death	**334 (3.5)**	**392 (4.1)**	**0.85 (0.73, 0.98)**	**0.026***

*Nominal P-value

ODYSSEY OUTCOMES

All-Cause Death

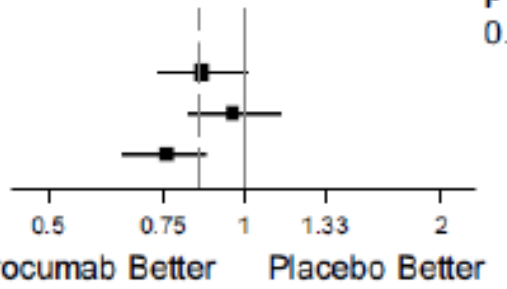


*Nominal P-value
†Based on cumulative incidence

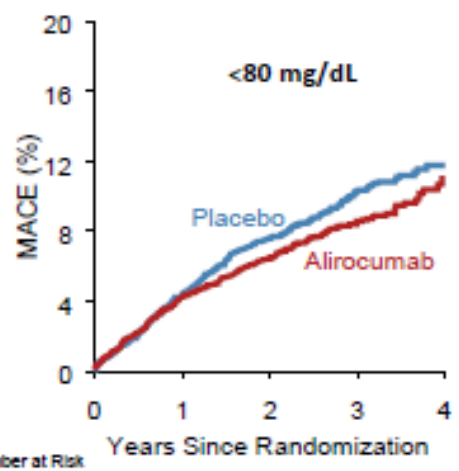
ODYSSEY OUTCOMES

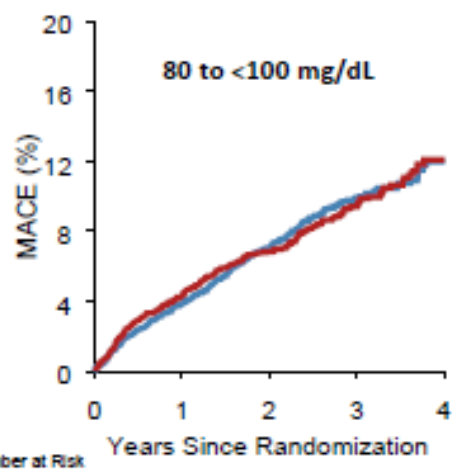
Primary Efficacy in Main Prespecified Subgroups

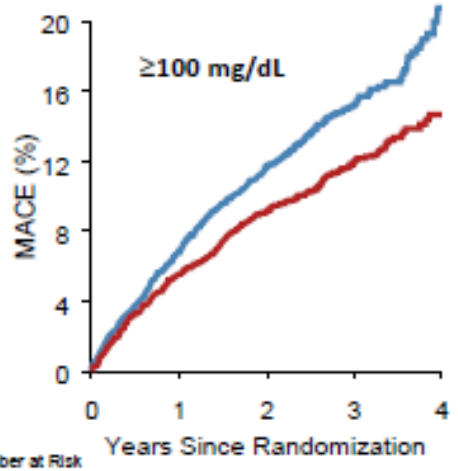
Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction







Number at Risk						
Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233

Number at Risk						
Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213

Number at Risk						
Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

ODYSSEY OUTCOMES

ODYSSEY OUTCOMES TRIAL

CONCLUSIONS

Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY OUTCOMES ClinicalTrials .gov number, NCT01663402.)

FINE PRIMA (MIA) PARTE

Acidi grassi polinsaturi nella prevenzione cardiovascolare: nuove evidenze e controversie

Anna Nelva

SSD Diabetologia e Endocrinologia

Ospedale degli Infermi di Biella

aslBI

Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento **(finanziamento convegni AME regionali e partecipazioni a congressi)** con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

NOVARTIS

VIGLIA s.r.l.

SHIRE

SAVIO PHARMA

LILLY

OTSUKA

NOVO NORDISK

IBSA

ABBOT

ASTRA ZENECA

SANOFI

This year in … lipidi

Cochrane Library

Cochrane Database of Systematic Reviews

Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Abdelhamid AS, Martin N, Bridges C, Brainard JS, Wang X, Brown TJ, Hanson S, Jimoh OF, Ajabnoor SM, Deane KHO, Song F, Hooper L

Objectives

To assess effects of increasing total PUFA intake on cardiovascular disease and all-cause mortality, lipids and adiposity in adults.

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD012345.
DOI: 10.1002/14651858.CD012345.pub2.

"The World Health Organization (WHO) is currently updating its guidance on polyunsaturated fatty acid intake in adults and children. This new review was commissioned by WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health **in order to inform and contribute to the development of updated WHO recommendations**.»

Polyunsaturated fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

"49 RCTs randomising 24,272 participants, with duration of one to eight year"
"Increasing PUFA **does reduce total cholesterol, probably reduces triglyceride, probably has little or no effect on high-density lipoprotein (HDL) or low-density lipoprotein (LDL)** and probably **increases body weight**."

Authors' conclusions

This is the most extensive systematic review of RCTs conducted to date to assess effects of increasing PUFA on cardiovascular disease, mortality, lipids or adiposity. Increasing PUFA intake probably **slightly reduces risk of coronary heart disease and cardiovascular disease events, may slightly reduce risk of coronary heart disease mortality and stroke** (though not ruling out harms), **but has little or no effect on all-cause or cardiovascular disease mortality.** The mechanism may be **via lipid reduction**, but increasing PUFA probably slightly increases weight.

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD012345. DOI: 10.1002/14651858.CD012345.pub2.

This year in … lipidi

Cochrane Library

Cochrane Database of Systematic Reviews

Omega-6 fats for the primary and secondary prevention of cardiovascular disease (Review)

Hooper L, Al-Khudairy L, Abdelhamid AS, Rees K, Brainard JS, Brown TJ, Ajabnoor SM, O'Brien AT, Winstanley LE, Donaldson DH, Song F, Deane KHO

"The World Health Organization (WHO) is currently updating its guidance on polyunsaturated fatty acid intake in adults and children. The update and extension of scope of this review was commissioned by WHO **in order to inform and contribute to the development of updated WHO recommendations**."

Objectives

To assess effects of increasing omega-6 fats (linoleic acid (LA), gamma-linolenic acid (GLA), dihomo-gamma-linolenic acid (DGLA) and arachidonic acid (AA)) on CVD and all-cause mortality.

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD011094.
DOI: 10.1002/14651858.CD011094.pub3.

Omega-6 fats for the primary and secondary prevention of cardiovascular disease (Review)

We included 19 RCTs in 6461 participants who were followed for one to eight years.

We found that increasing omega-6 fats may make **little or no difference to deaths or cardiovascular events** but **may reduce risk of heart attacks (low-quality evidence**).

Evidence suggests that increasing omega-6 fats **reduces blood cholesterol (high-quality evidence),** probably has little or no effect on body weight adjusted for height (all moderate-quality evidence), and may **make little or no difference to triglycerides, high-density lipoprotein (HDL, the 'good' cholesterol) or low-density lipoprotein (LDL, the 'bad' cholesterol, low-quality evidence).**

We found that increasing omega-6 fats **may reduce risk of myocardial infarction (low-quality evidence), but 53 people would need to increase the amount of omega-6 fat in their diet to prevent one person having a myocardial infarction (NNTB 53, 95% CI −334 to 28).**

In spite of its limitations, the **weak evidence** we collected in this review appears to suggest that omega-6 fats **are not harmful.**

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD011094. DOI: 10.1002/14651858.CD011094.pub3.

This year in … lipidi

Cochrane Library

Cochrane Database of Systematic Reviews

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KHO, AlAbdulghafoor FK, Summerbell CD, Worthington HV, Song F, Hooper L

"The World Health Organization (WHO) is currently updating its
guidance on polyunsaturated fatty acid intake in adults and children. The update and expansion of this review was commissioned by **WHO in order to inform and contribute to the development of updated WHO recommendations**.»

Objectives

To assess effects of increased intake of fish- and plant-based omega-3 for all-cause mortality, cardiovascular (CVD) events, adiposity and lipids.

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177.
DOI: 10.1002/14651858.CD003177.pub3.

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

We included **79 RCTs (112,059 participants)** in this review update and found that 25 were at low summary risk of bias.

Trials were of 12 to 72 months' duration and included adults at varying cardiovascular risk, mainly in high-income countries.

Most studies assessed **LCn3 supplementation with capsules, but some used LCn3- or ALA-rich or enriched foods or dietary advice** compared to placebo or usual diet.

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub3.

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with lower LCn3	Risk with higher LCn3				
All-cause mortality - deaths Assessed with: number of participants dying of any cause, whether reported as an outcome or a reason for dropout Duration: range 12 to 72 months	90 per 1,000	88 per 1,000 (83 to 92)	RR 0.98 (0.93 to 1.03)	92,653 (39 RCTs)	⊕⊕⊕⊕ High[a]	Meta-analysis and indications of bias suggest risk reduction of less than 2%. Long-chain omega-3 fat intake makes little or no difference to all-cause mortality
Cardiovascular mortality - cardiovascular deaths Assessed with: deaths from any cardiovascular cause. Where this was not available, cardiac death was used instead where known	69 per 1,000	66 per 1,000 (60 to 71)	RR [illegible]	67,772 (25 RCTs)	⊕⊕⊕◯ Moderate[b]	Meta-analysis and indications of bias suggest risk reduction of less than 5%. Long-chain omega-3 fat intake probably makes little or no difference to cardiovascular deaths
Duration: range 12 to [illegible] months						

LITTLE OR NO DIFFERENCE

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub3.

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Cardiovascular events - cardiovascular events Assessed with: number of participants experiencing any cardiovascular event Duration: range 12 to 72 months	165 per 1,000	164 per 1,000 (155 to 172)	RR 0.99 (0.94 to 1.04)	90,378 (38 RCTs)	⊕⊕⊕⊕ High[c]	Meta-analysis and indications of bias suggest risk reduction of less than 7%. Long-chain omega-3 fat intake makes little or no difference to risk of cardiovascular events
Coronary heart disease mortality - CHD deaths Assessed with: coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (in that order) Duration: range 12 to 72 months	22 per 1,000	21 per 1,000 (18 to 24)	RR 0.93 (0.79 to 1.09)	73,491 (21 RCT	⊕⊕⊕ rate[d]	Meta-analysis and indications of bias suggest risk reduction of less than 7%. Long-chain omega-3 fat intake probably makes little or no difference to coronary heart mortality
Coronary heart disease events - CHD events Assessed with: number of participants experiencing the first outcome in this list reported for each trial: CHD or co ary events; tota MI; a te coron y sy ome r angina stable nd u stable) Duration ge 12 to 72 months	68 per 1,000	63 per 1 0 5)	RR 0.93 (0.88 to 0.97)	84,301 (28 RCTs)	⊕⊕⊕◯ Moderate[e]	Meta-analysis and indications of bias suggest risk reduction of less than 7%. Long-chain omega-3 fat intake probably makes little or no difference to risk of coronary heart events

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177. DOI:

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Stroke Assessed with: number of participants experiencing at least one fatal or non-fatal, ischaemic or haemorrhagic stroke Duration: range 12 to 72 months	20 per 1,000	21 per 1,000 (19 to 23)	RR 1.06 (0.96 to 1.16)	89,358 (28 RCTs)	⊕⊕⊕◯ Modera	Meta-analysis and indications of bias suggest increased risk of less than 6%. Long-chain omega-3 fat intake probably makes little or no difference to risk of experiencing a stroke
Arrhythmias Assessed with: number of participants experiencing fatal or non-fatal, new or recurrent arrhythmia, including atrial fibrillation, ventricular tachycardia and ventricular fibrillation Duration: range 12 72 months	68 per 1,000	66 per 1,000 (62 to 72)	RR 0.9 (0. 1.05	53,796 (28 RCTs)	⊕⊕⊕◯ Moderate[g]	Meta-analysis and indications of bias suggest risk reduction of less than 3%. Long-chain omega-3 fat intake probably makes little or no difference to risk of arrhythmia

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub3.

Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease (Review)

Harms: bleeding Assessed with: number of participants experiencing bleeding events Duration: range 12 to 72 months	8 per 1,000	**8 per** 1,000 (5 to 11)	**RR 1.06** (0.73 to 1.52)	45,562 (8 RCT[illegible])	⊕◯◯◯ Very low[h]	The effect of long-chain omega-3 fat intake on bleeding is unclear as the evidence is of very low quality
Harms: pulmonary embolus or DVT Assessed with: number of participants experiencing pulmonary embolus or deep vein thrombosis Duration: range 18 to 36	5 per 1,000	**6 per** 1,000 (2 to 18)	**RR 1[illegible]5** (0.[illegible])	3,011 (4 RCTs)	⊕◯◯◯ Very low[i]	The effect of long-chain omega-3 fat intake on pulmonary embolus or DVT is unclear as the evidence is of very low quality

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub3.

Dietary fish is likely to have different health effects, as it may take the place of less healthy foods in the diet (leading to reduced saturated fat intake, for example) and provides many nutrients in addition to omega-3 fats (such as protein, selenium, iodine, calcium, magnesium, etc.)…

There was no evidence that increasing LCn3 or ALA altered serious adverse events, **adiposity** or lipids, although **LCn3 slightly reduced triglycerides and increased HDL.**
ALA probably reduces HDL (high- or moderate-quality evidence).

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub3.

Authors' conclusions

This is **the most extensive systematic assessment** of effects of omega-3 fats on cardiovascular health to date.

Moderate- and high-quality evidence suggests that increasing EPA and DHA has **little or no effect on mortality or cardiovascular health** (evidence mainly from supplement trials).

Previous suggestions of benefits from EPA and DHA supplements appear to spring **from trials with higher risk of bias.**

Low-quality evidence suggests ALA may slightly reduce CVD event risk, CHD mortality and arrhythmia.

Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD003177. DOI: 10.1002/14651858.CD003177.pub3.

This year in...lipidi

JAMA Cardiology | Original Investigation

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

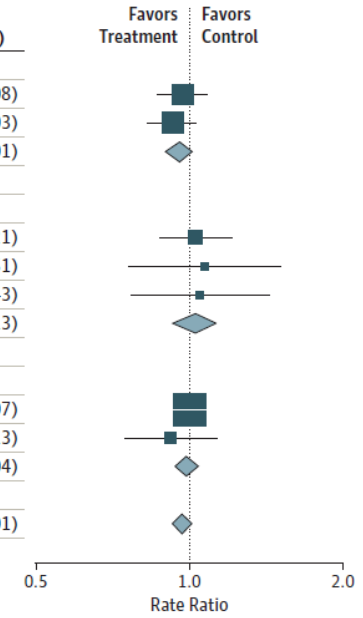
Meta-analysis of 10 Trials Involving 77 917 Individuals

Theingi Aung, MBBS, FRCP; Jim Halsey, BSc; Daan Kromhout, PhD; Hertzel C. Gerstein, MD; Roberto Marchioli, MD; Luigi Tavazzi, MD; Johanna M. Geleijnse, PhD; Bernhard Rauch, MD; Andrew Ness, PhD, FFPH; Pilar Galan, MD, PhD; Emily Y. Chew, MD; Jackie Bosch, PhD; Rory Collins, FMedSci, FRCP; Sarah Lewington, DPhil; Jane Armitage, FRCP, FFPH; Robert Clarke, MD, FRCP, FFPH; for the Omega-3 Treatment Trialists' Collaboration

JAMA Cardiol. 2018;3(3):225-233. doi:10.1001/jamacardio.2017.5205 Published online January 31, 2018. Last corrected on September 19, 2018.

Figure 1. Associations of Omega-3 Fatty Acids With Major Vascular Events

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87-1.08)
Coronary heart disease death	1301 (3.3)	1394 (3.6)	0.93 (0.83-1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88-1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76-1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77-1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93-1.13)
			P = .60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93-1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75-1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94-1.04)
			P = .60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P = .10



CONCLUSIONS AND RELEVANCE This meta-analysis demonstrated that omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events. It provides no support for current recommendations for the use of such supplements in people with a history of coronary heart disease.

This year in...lipidi

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

This article was published on August 26,
2018, at NEJM.org.
N Engl J Med 2018;379:1540-50.

METHODS

We randomly assigned **15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules containing either n−3 fatty acids (fatty acid group) or matching placebo (olive oil) daily.** The primary outcome was a first serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

CONCLUSIONS

Among patients with diabetes without evidence of cardiovascular disease, **there was no significant difference in the risk of serious vascular events** between those who were assigned to receive n−3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others; Current Controlled Trials number, ISRCTN60635500; ClinicalTrials.gov number, NCT00135226.)

This year in...lipidi

THE END?

JAMA Cardiology | Original Investigation

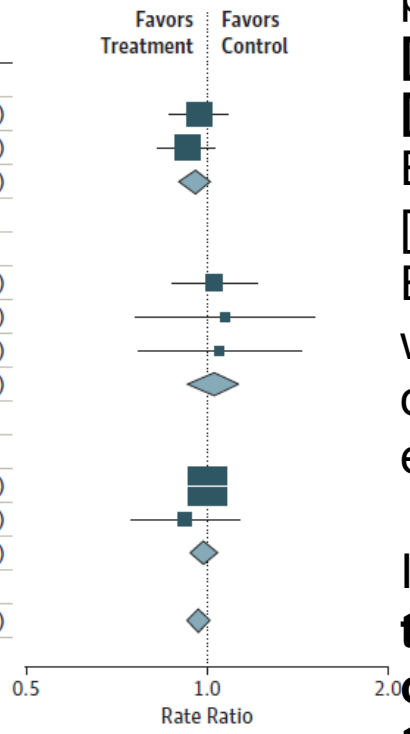
Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks

Meta-analysis of 10 Trials Involving 77 917 Individuals

Theingi Aung, MBBS, FRCP; Jim Halsey, BSc; Daan Kromhout, PhD; Hertzel C. Gerstein, MD; Roberto Marchioli, MD; Luigi Tavazzi, MD; Johanna M. Geleijnse, PhD; Bernhard Rauch, MD; Andrew Ness, PhD, FFPH; Pilar Galan, MD, PhD; Emily Y. Chew, MD; Jackie Bosch, PhD; Rory Collins, FMedSci, FRCP; Sarah Lewington, DPhil; Jane Armitage, FRCP, FFPH; Robert Clarke, MD, FRCP, FFPH; for the Omega-3 Treatment Trialists' Collaboration

Figure 1. Associations of Omega-3 Fatty Acids With Major Vascular Events

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87-1.08)
Coronary heart disease death	1301 (3.3)	1394 (3.6)	0.93 (0.83-1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88-1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76-1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77-1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93-1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93-1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75-1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94-1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P=.10



"The 95% CI in the present meta-analysis of 10 trials, involving 77 917 high-risk individuals, 12 001 major vascular events, and 6273 CHD events, cannot exclude **a 7% lower risk of major vascular events and a 10% lower risk of CHD associated with omega-3 FA supplements.** Several ongoing large randomized trials involving a total of 54 354 additional participants (A Study of Cardiovascular Events in Diabetes **[ASCEND**], 25 n = 15480; VITaminDandOmegA-3 TriaL **[VITAL],**26n = 25874; StatinResidual risk reduction with EpaNova in hiGh CV risk patienTs with Hypertriglyceridemia [**STRENGTH**], 27 n = 13000 and Reduction of Cardiovascular Events With EPA–Intervention Trial [**REDUCE-IT],** n = 8000) will provide additional evidence about the associations of omega-3 FA supplementation with the risk of major vascular events, any CHD, and subtypes of fatal and nonfatal CHD.

Importantly**, the STRENGTH and REDUCE-IT trials will test the effects on major vascular events of much higher doses of omega-3FAs (3-4 g/d), which will lower plasma levels of triglycerides.»**

This year in...lipidi

News > Medscape Medical News REDUCE-IT: 25% Reduction in MACE With High-Dose EPA
Sue Hughes September 25, 2018

High doses (4-g daily) of the omega-3 oil eicosapentaenoic acid (EPA) have shown a large benefit on cardiovascular events in the randomized, double-blind REDUCE-IT trial.
Top-line results of the trial were announced yesterday in a press release by the sponsor, …, which manufactures the high-dose EPA product …
The study involved 8179 patients from 11 countries who were at elevated cardiovascular risk (had a previous cardiovascular event or diabetes with one additional risk factor) and had raised triglyceride levels. All participants, who **were already taking a statin**, were randomized to **4 g** of the pure EPA product daily or placebo.

After a median follow-up of 4.9 years, there was an approximately 25% relative risk reduction in the primary endpoint of first occurrence of a major adverse cardiovascular event — any one of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization — in the EPA group, which was **highly significant (*P* < .001), the company reported.**
There were also "robust demonstrations of efficacy across multiple secondary endpoints," the company's statement said

This year in...lipidi

INVESTOR RELATIONS / REDUCE-IT™ TRIAL PRIMARY RESULTS ACCEPTED FOR PRESENTATION AT 2018 SCIENTIFIC SESSIONS OF AMERICAN HEART ASSOCIATION

Sep 12, 2018

… The presentation, classified as late-breaking clinical trial results, is scheduled **to commence on November 10, 2018 in Chicago, Illinois. at 2:16 pm Central Time and listed as Main Event 1 for that timeframe**.

A link to this notice is provided at:
http://www.abstractsonline.com/pp8/#!/4682/presentation/59402.

IL SEGUITO ALLA PROSSIMA PUNTATA!

GRAZIE

2) PCR ad alta sensibilità: "un nuovo protagonista sulla scena": analisi secondaria Fourier, studio Cantos

Francesco Tassone, M.D.,PhD

S.C. di Endocrinologia, Diabetologia & Metabolismo

A.S.O. Santa Croce e Carle di Cuneo

- EVOLOCUMAB

Circulation

Circulation 2018;138:131-140

ORIGINAL RESEARCH ARTICLE

Inflammatory and Cholesterol Risk in the FOURIER Trial

BACKGROUND: In the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk), the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor evolocumab reduced low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk. It is not known whether the efficacy of evolocumab is modified by baseline inflammatory risk. We explored the efficacy of evolocumab stratified by baseline high-sensitivity C-reactive protein (hsCRP). We also assessed the importance of inflammatory and residual cholesterol risk across the range of on-treatment LDL-C concentrations.

METHODS: Patients (n=27 564) with stable atherosclerotic cardiovascular disease and LDL-C ≥70 mg/dL on a statin were randomly assigned to evolocumab versus placebo and followed for a median of 2.2 years (1.8–2.5). The effects of evolocumab on the primary end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization, and the key secondary end point of

Erin A. Bohula, MD, DPhil
Robert P. Giugliano, MD, SM
Lawrence A. Leiter, MD
Subodh Verma, MD
Jeong-Gun Park, PhD
Peter S. Sever, MD
Armando Lira Pineda, MD
Narimon Honarpour, MD
Huei Wang, PhD
Sabina A. Murphy, MPH
Anthony Keech, MD
Terje R. Pedersen, MD
Marc S. Sabatine, MD, MPH

Inflammatory and Cholesterol Risk in the FOURIER Trial

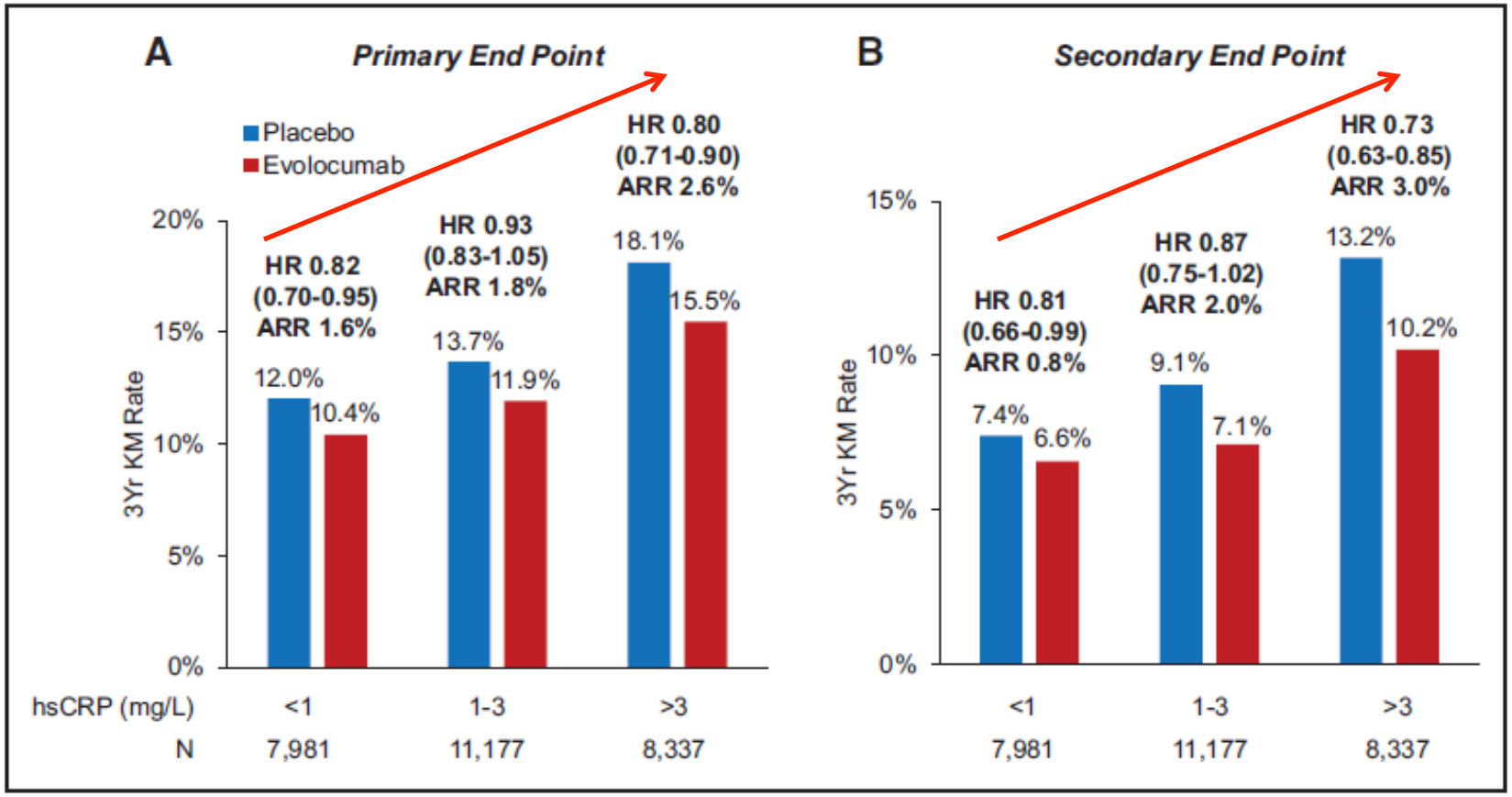


Figure 2. Rate of cardiovascular events by hsCRP and randomized treatment.
Three-year Kaplan-Meier event rates stratified by baseline hsCRP subgroup and randomization to evolocumab versus placebo for the primary composite end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (**A**) and the key secondary composite end point of cardiovascular death, MI, or stroke (MACE) (**B**). Hazard ratio (HR) and 95% confidence interval and the absolute risk reduction (ARR) shown for evolocumab versus placebo for each subgroup. Interaction *P* value for randomized treatment by hsCRP subgroup is 0.17 for the primary end point and 0.26 for the secondary end point. hsCRP indicates high-sensitivity C-reactive protein; KM, Kaplan-Meier; MACE, major adverse cardiovascular events; and MI, myocardial infarction.

ORIGINAL RESEARCH ARTICLE

Inflammatory and Cholesterol Risk in the FOURIER Trial

Circulation 2018;138:131-140

CONCLUSIONS: LDL-C reduction with evolocumab reduces cardiovascular events across hsCRP strata with greater absolute risk reductions in patients with higher-baseline hsCRP. Event rates were lowest in patients with the lowest hsCRP and LDL-C.

ORIGINAL RESEARCH ARTICLE

Residual Inflammatory Risk on Treatment With PCSK9 Inhibition and Statin Therapy

Aruna D. Pradhan, MD, MPH
Aaron W. Aday, MD
Lynda M. Rose, MS
Paul M Ridker, MD, MPH

BACKGROUND: The combination of statin therapy and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition markedly lowers low-density lipoprotein cholesterol (LDL-C) and reduces cardiovascular event rates. Whether residual inflammatory risk as measured by on-treatment high sensitivity C-reactive protein (hsCRP) remains an important clinical issue in such patients is uncertain.

METHODS: We evaluated residual inflammatory risk among 9738 patients participating in the SPIRE-1 and SPIRE-2 cardiovascular outcomes trials (Studies of PCSK9 Inhibition and the Reduction in Vascular Events), who were receiving both statin therapy and bococizumab, according to on-treatment levels of hsCRP ($hsCRP_{OT}$) and LDL-C_{OT} measured 14 weeks after drug initiation. The primary end point was nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death.

Circulation. 2018;138:141–149

Residual Inflammatory Risk on Treatment With PCSK9 Inhibition and Statin Therapy

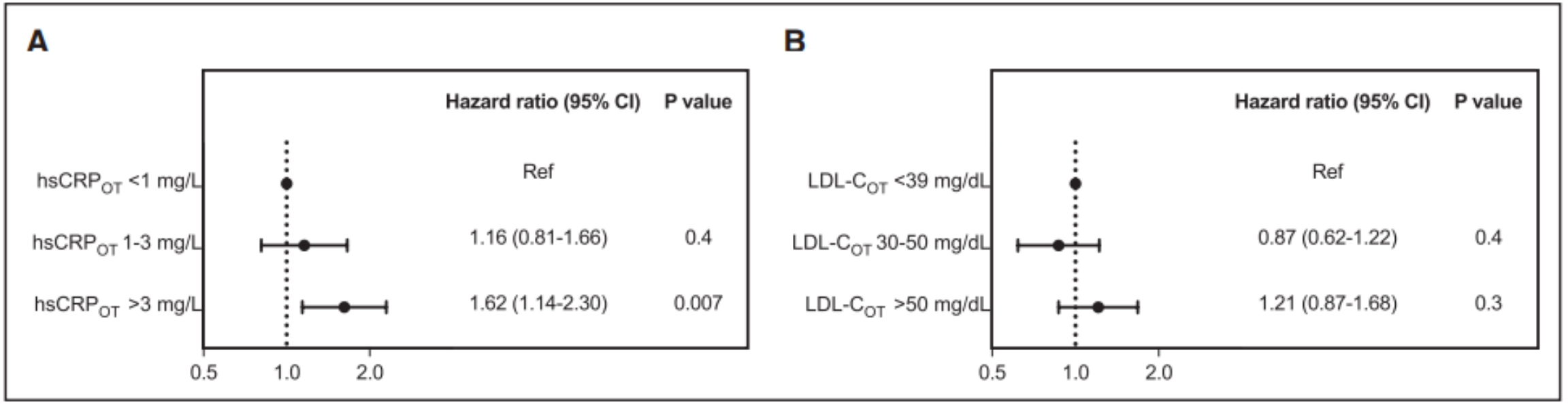


Figure 3. Risk association of hsCRP$_{OT}$ and LDL-C$_{OT}$ with incident cardiovascular events according to categories of each biomarker.
Adjusted for age, sex, current smoking, diabetes mellitus, hypertension, body mass index, statin intensity at enrollment (moderate or high), and hsCRP$_{OT}$ and LDL-C$_{OT}$ as appropriate. **A**, Models for hsCRP$_{OT}$. **B**, Models for LDL-C$_{OT}$. CI indicates confidence interval; hsCRP$_{OT}$, on-treatment levels of high-sensitivity C-reactive protein; LDL-C$_{OT}$, on-treatment levels of low-density lipoprotein cholesterol; and Ref, reference.

PCR ad alta sensibilità (infiammazione)

ATHEROSCLEROSIS : AN INFLAMMATORY DISEASE

RUSSELL ROSS, PH.D. – NEJM 1999

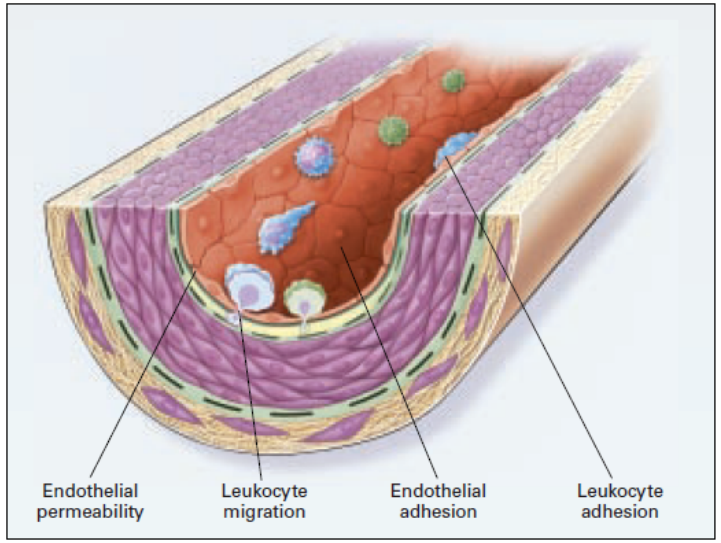


Figure 1. Endothelial Dysfunction in Atherosclerosis.

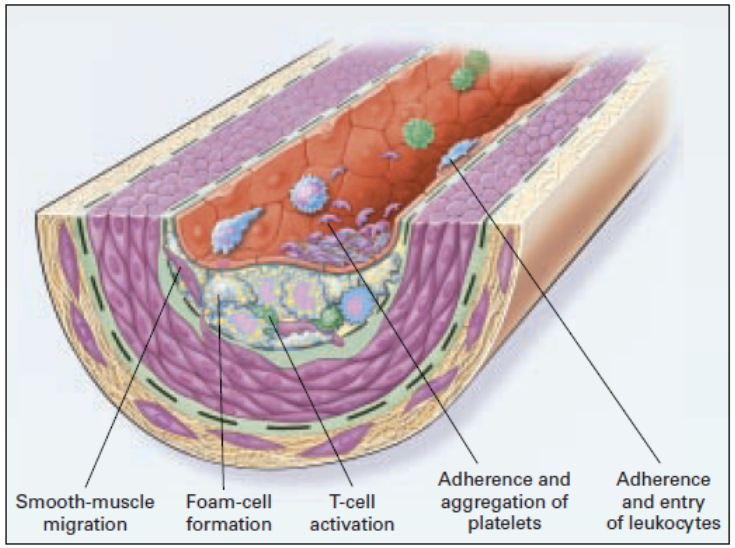


Figure 2. Fatty-Streak Formation in Atherosclerosis.

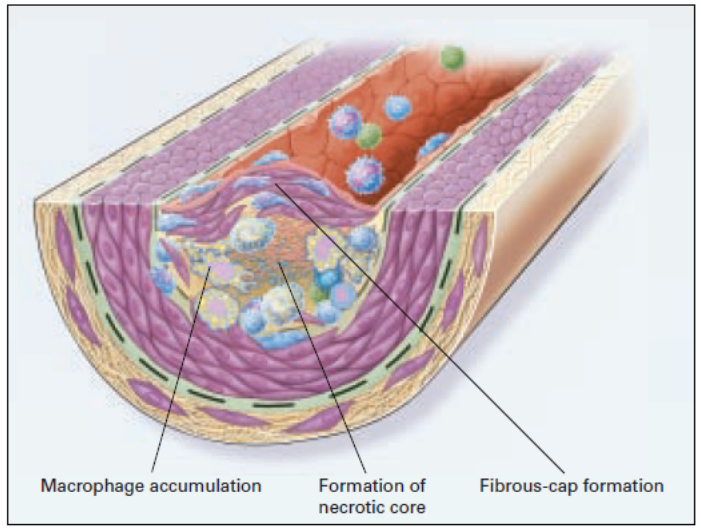


Figure 3. Formation of an Advanced, Complicated Lesion of Atherosclerosis.

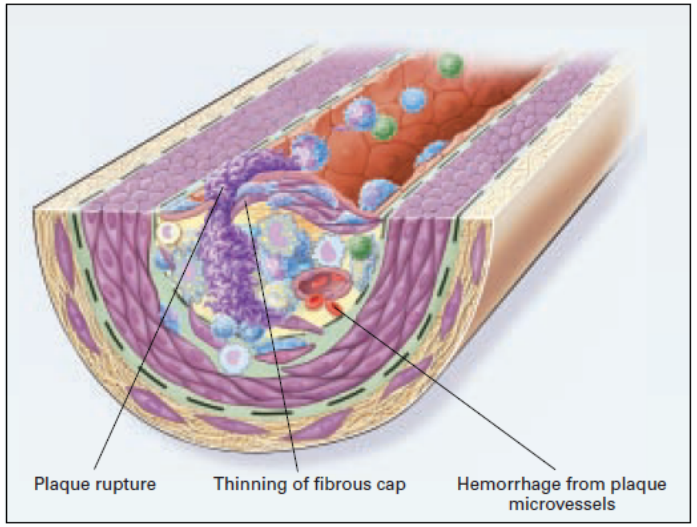


Figure 4. Unstable Fibrous Plaques in Atherosclerosis.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 21, 2017 VOL. 377 NO. 12

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) Trial

ABSTRACT

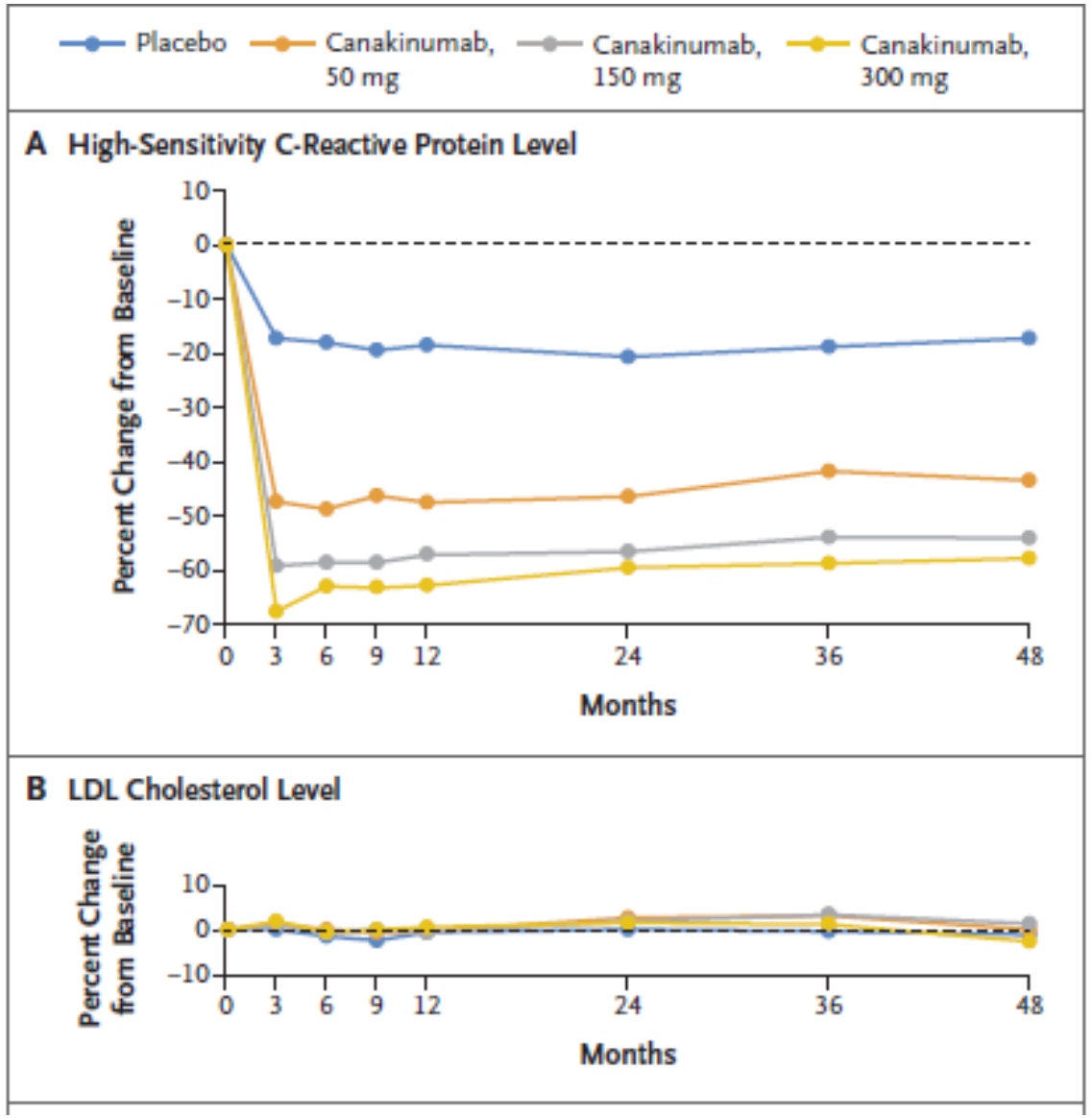
BACKGROUND

Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.

METHODS

We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) Trial



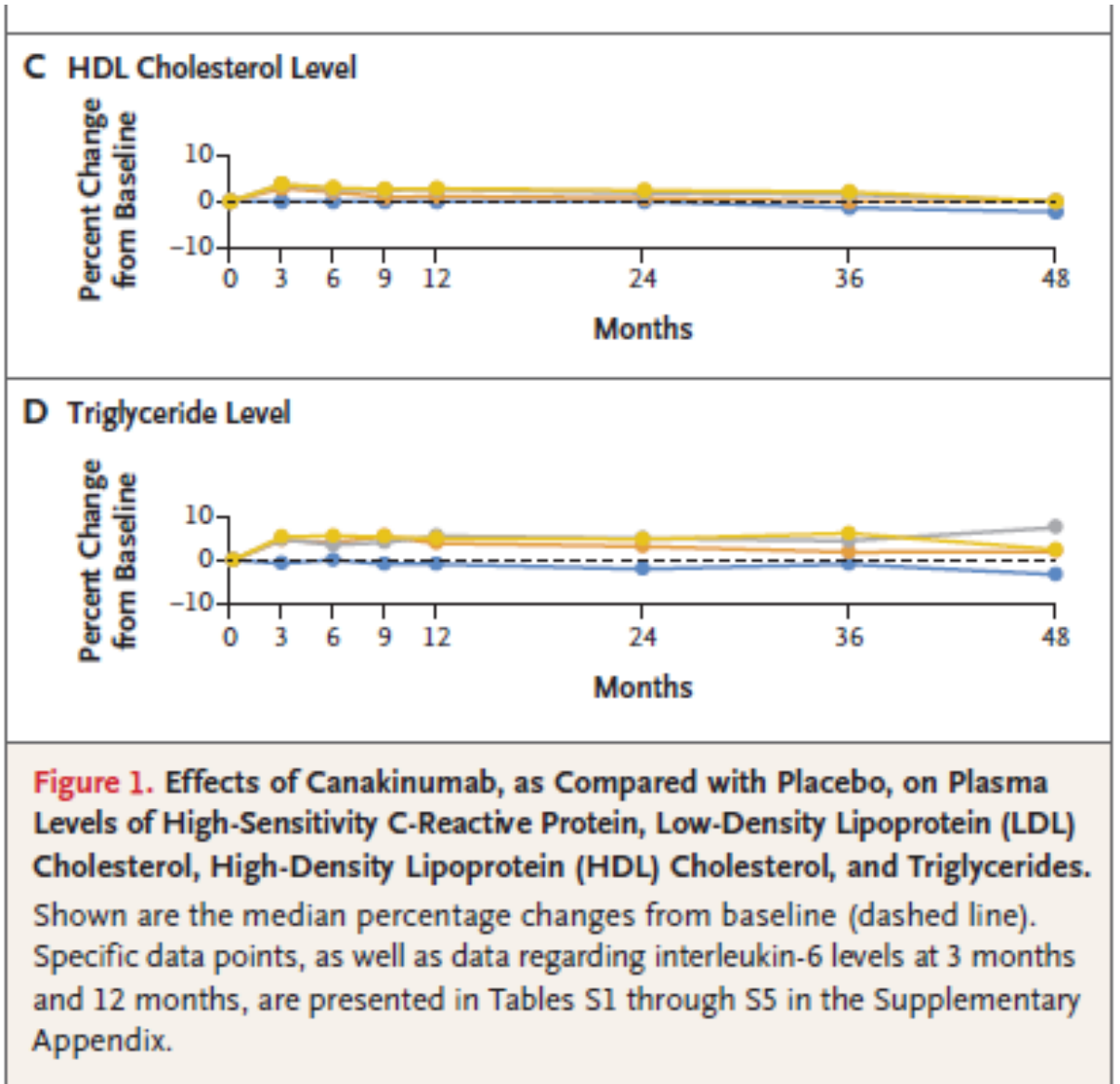
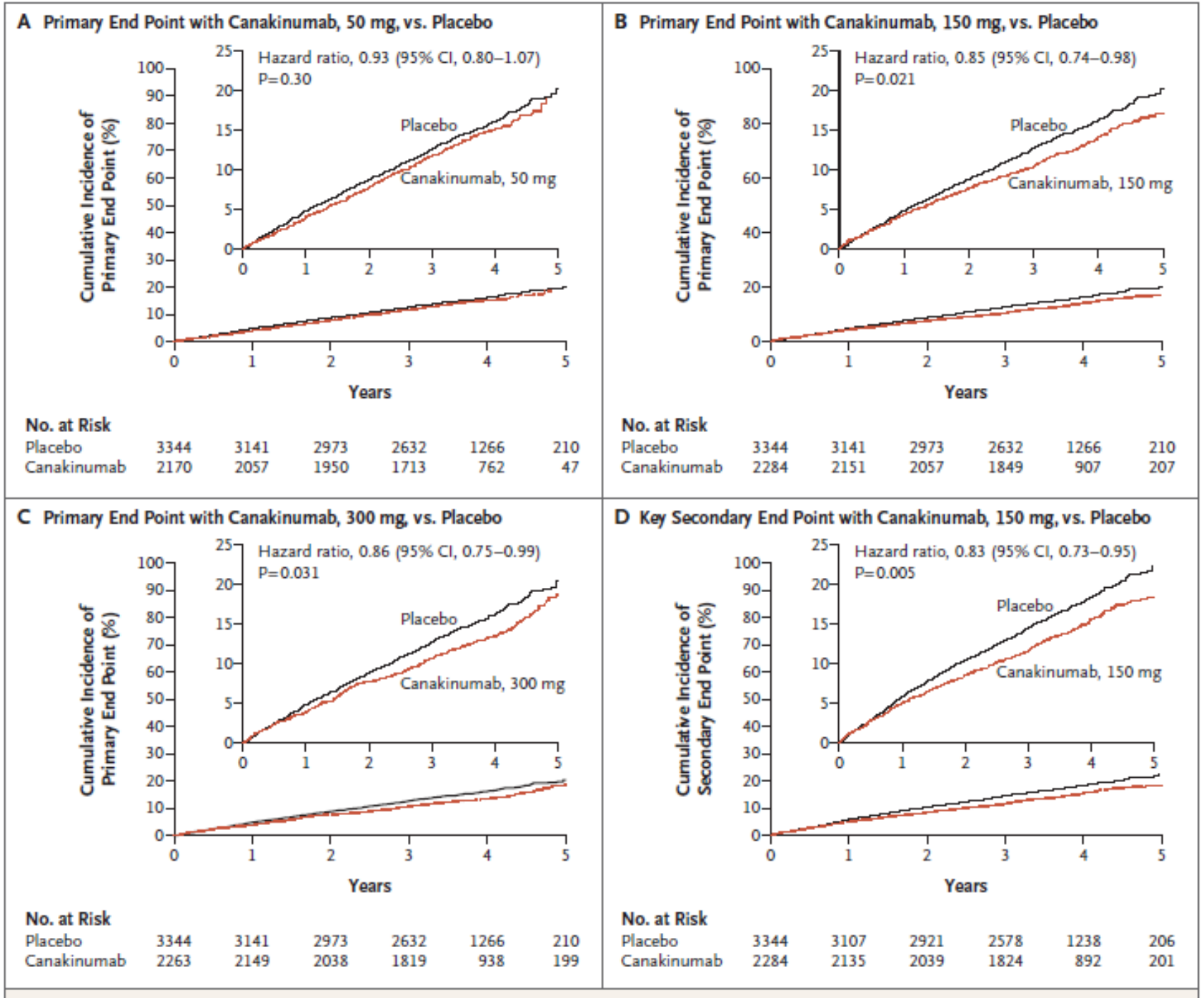


Figure 1. Effects of Canakinumab, as Compared with Placebo, on Plasma Levels of High-Sensitivity C-Reactive Protein, Low-Density Lipoprotein (LDL) Cholesterol, High-Density Lipoprotein (HDL) Cholesterol, and Triglycerides.

Shown are the median percentage changes from baseline (dashed line). Specific data points, as well as data regarding interleukin-6 levels at 3 months and 12 months, are presented in Tables S1 through S5 in the Supplementary Appendix.

primary end point:
nonfatal myocardial infarction, nonfatal stroke, or CV death



key secondary CV end point:

additionally included hospitalization for unstable angina that led to urgent revascularization

Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) Trial

CONCLUSIONS

Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)

Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) Trial

Adverse Events and Other Clinical Outcomes

Neutropenia was more common among patients who were assigned to receive canakinumab than among those in the placebo group, and **significantly more deaths were attributed to infection or sepsis in the pooled canakinumab groups than in the placebo** group (incidence rate, 0.31 vs. 0.18 events per 100 person-years; P = 0.02)

...

Thrombocytopenia was more common among patients who were assigned to receive canakinumab than among those in the placebo group, but no significant difference in the incidence of hemorrhage was observed. The incidence rate of injection-site reaction did not differ significantly between any canakinumab group and the placebo group.

In a finding that was consistent with known effects of **interleukin-1β inhibition, canakinumab resulted in significantly fewer reports of arthritis, gout, and osteoarthritis** than did placebo.

Cancer mortality was significantly lower with canakinumab than with placebo.

Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) Trial

J Am Coll Cardiol. 2018 May 29;71(21):2392-2401. doi: 10.1016/j.jacc.2018.03.002. Epub 2018 Mar 12.

Anti-Inflammatory Therapy With Canakinumab for the Prevention and Management of Diabetes.

Everett BM[1], Donath MY[2], Pradhan AD[3], Thuren T[4], Pais P[5], Nicolau JC[6], Glynn RJ[7], Libby P[8], Ridker PM[9].

Author information

Abstract

BACKGROUND: Subclinical inflammation mediated in part by interleukin (IL)-1β participates in peripheral insulin resistance and impaired pancreatic insulin secretion.

OBJECTIVES: The authors tested the hypothesis that the IL-1β inhibitor canakinumab reduces incident diabetes.

METHODS: The authors randomized 10,061 patients with prior myocardial infarction and high-sensitivity C-reactive protein (hsCRP) ≥2 mg/l to placebo or canakinumab at doses of 50 mg, 150 mg, or 300 mg subcutaneously once every 3 months. The authors tested the effects of canakinumab on major cardiovascular events in patients with and without diabetes at baseline, and evaluated as a pre-specified analysis whether canakinumab would reduce the risk of adjudicated cases of new-onset type 2 diabetes among those with protocol-defined pre-diabetes at trial entry. The authors also evaluated the effect of canakinumab on fasting plasma glucose and glycosylated hemoglobin (HbA_{1c}) in patients with and without established diabetes.

RESULTS: Of the participants, 4,057 (40.3%) had baseline diabetes, 4,960 (49.3%) had pre-diabetes, and 1,044 (10.4%) had normal glucose levels. Among those without diabetes, increasing tertiles of hsCRP at baseline associated with an increased risk of developing diabetes during the median follow-up period of 3.7 years (incidence rates 3.2, 4.1, and 4.4 per 100 person-years; p = 0.003). Canakinumab 150 mg as compared with placebo had similar magnitude effects on major cardiovascular event rates among those with diabetes (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.70 to 1.03), pre-diabetes (HR: 0.86; 95% CI: 0.70 to 1.06), and normoglycemia (HR: 0.81; 95% CI: 0.49 to 1.35). Despite large reductions in hsCRP and IL-6, canakinumab did not reduce the incidence of new-onset diabetes, with rates per 100 person-years in the placebo, 50 mg, 150 mg, and 300 mg canakinumab groups of 4.2, 4.2, 4.4, and 4.1, respectively (log-rank p = 0.84). The HR comparing all canakinumab doses to placebo was 1.02 (95% CI: 0.87 to 1.19; p = 0.82). Canakinumab reduced HbA_{1c} during the first 6 to 9 months of treatment, but no consistent long-term benefits on HbA_{1c} or fasting plasma glucose were observed.

CONCLUSIONS: Although IL-1β inhibition with canakinumab had similar effects on major cardiovascular events among those with and without diabetes, treatment over a median period of 3.7 years did not reduce incident diabetes. (Canakinumab Anti-inflammatory Thrombosis Outcomes Study [CANTOS]; NCT01327846).

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Targeting Inflammation in Coronary Artery Disease

Robert A. Harrington, M.D.

"... Given monthly for approved indications, canakinumab is ***priced at approximately $200,000 per year in the United States****. Such pricing may be suitable for rare diseases, but not for a common indication such as coronary artery disease, even if given every 3 months. ... Now that an agent targeting inflammation and autoimmunity has been shown to provide clinical benefit, the* ***field is opened to further investigation*** *to find agents that exert more substantial benefit than was seen in CANTOS and perhaps to find agents that do not increase the risk of death from infection as was seen with canakinumab. For example, an* ***ongoing trial sponsored by the National Heart, Lung, and Blood Institute is testing whether low-dose methotrexate*** *can effectively and safely reduce the risk of cardiac events among patients with a previous myocardial infarction who have diabetes or the metabolic syndrome.*

November 7, 2018 — Here is a list of some of the key clinical trial presentations at the 2018 **American Heart Association (AHA) annual meeting**. More details on the AHA **Scientific Sessions**.

Answers to Critical Questions in Cardiovascular Prevention

Saturday, Nov. 10, 2018, 2-3:15 p.m. — Where: Main Event I

• **VITAL — The VITamin D and OmegA-3 TriaL**: Principal Results for Vitamin D and Omega-3 Fatty Acid Supplementation in the Primary Prevention of Cardiovascular Disease and Cancer

• **REDUCE-IT** — The Primary Results of the REDUCE-IT Trial

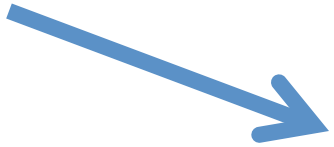
• **EWTOPIA75 — Ezetimibe in Prevention of Cerebro- and Cardiovascular Events** in Middle- to High-risk, Elderly (75 Years Old or Over) Patients With Elevated LDL-cholesterol: A Multicenter, Randomized, Controlled, Open-label Trial

• **Cost-Effectiveness of Alirocumab** Based on Evidence from a Large Multinational Outcome Trial: the ODYSSEY OUTCOMES Economics Study

Novel Approaches to Cardiovascular Prevention

Saturday, Nov. 10, 2018, 3:45-5 p.m. — Main Event I

• **DECLARE–TIMI 58** — The Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial



• **CIRT** — The Cardiovascular Inflammation Reduction Trial (CIRT): Low Dose Methotrexate for the Prevention of Atherosclerotic Event

GRAZIE PER L'ATTENZIONE !!!!

HDL-C E CETP INIBITORI

Ci sono novità?

Anna Nelva

SSD Diabetologia e Endocrinologia

Ospedale degli Infermi di Biella

aslBI

European Heart Journal (2016) **37**, 2999–3058
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

"Overall, HDL-C **has a modest but useful** effect in refining risk estimation, but **this may not be universal**, as **its effect may not be seen in some low-risk populations**, particularly with a relatively high mean HDL-C level."
Pag. 3010

HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.

AACE 2017 Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE

- **R7.** When the HDL-C concentration is >60 mg/dL, 1 risk factor should be subtracted from an individual's overall risk profile (**Grade B; BEL 2**).

- **R42.** HDL-C should be >40 mg/dL, but also as high as possible, primarily through the use of lifestyle interventions (e.g., weight loss, physical activity, and tobacco cessation), and if risk factors are present (e.g., borderline elevated LDL-C levels, a family history of premature ASCVD, or a personal history of ASCVD), also through the use of pharmacotherapy primarily focused on reducing LDL-C (**Grade A; BEL 1**).

Research shows a strong predictive link between HDL-C levels and longevity; healthy older individuals tend to have higher HDL-C levels than younger individuals, regardless of the younger individuals' ASCVD status (86 [EL 2; PCS]; 87 [EL 3; CSS]; 88 [EL 3; CSS]; 89 [EL 4; NE]). These results apply to the general population, though a high HDL-C concentration may not confer cardioprotection for every individual (90 [EL 4; NE]).

Pag .20 CPG for Managing Dyslidemia and Prevention of CVD, Endocr Pract. 2017;23(Suppl 2) Copyright © 2017 AACE

This year in … lipidi

Table 1
Overview of major trials evaluating the effects of raising HDL-cholesterol

Trial	Major Finding	Ref
The Arterial Disease Multiple Intervention Trial (ADMIT)	Niacin therapy achieved 29% increase in HDL-C.	Elam et al,[28] 2000
The HDL-Atherosclerosis Treatment Study (HATS)	Reduction of 60%–90% in the rate of major coronary events with combination of simvastatin and niacin therapy.	Brown et al,[29] 2001
The AIM-HIGH study (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health)	In 3414 patients with established CV disease and low HDL-C levels extended-release niacin therapy did not improve CV outcome during a 3-y follow-up	AIM-HIGH Investigators,[30] 2011
The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events study (HPS2-THRIVE)	Trial involving more than 25,000 patients showed that extended-release niacin therapy with laropiprant in addition to statin therapy did not significantly reduce the risk of major vascular events but increased the risk of serious adverse events during a median follow-up period of 3.9 y.	Parish et al,[31] 2014
ILLUMINATE trial (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events)	Trial involving more than 15,000 patients at high CV risk who received either the CETP inhibitor torcetrapib plus atorvastatin or atorvastatin alone. Torcetrapib therapy increased HDL-C by 72% and reduced LDL-C by 25%. However, it resulted in an increased risk of mortality and morbidity.	Barter et al,[32] 2007
Dal-Outcomes trial	A phase III trial to evaluate the effects of dalcetrapib on CV risk among patients with a recent acute coronary syndrome. Addition of dalcetrapib to standard therapy after an acute coronary syndrome raised the levels of HDL cholesterol and apolipoprotein A1, but the risk of major CV outcomes was not significantly altered.	Schwartz et al,[33] 2012
ACCELERATE trial (Assessment of the clinical effects of cholesteryl ester transfer protein inhibition with evacetrapib)	Phase III trial to evaluate the effect of the CETP inhibitor evacetrapib on major adverse CV outcomes in patients with high-risk vascular disease. Although evacetrapib lead to an increase of more than 130% in the mean HDL-C level, it did not result in a lower rate of CV events than placebo among patients with high-risk vascular disease.	Lincoff et al,[34] 2017
The HPS3/TIMI55–REVEAL trial	Trial tested the effects of anacetrapib in patients with atherosclerotic vascular disease. The so far largest outcome trial with a CETP inhibitor involved 30,449 adults with atherosclerotic vascular disease who were receiving intensive atorvastatin therapy. Anacetrapib lowered incidence of major coronary events as compared with placebo during a median follow-up period of 4.1 y. This effect may, however, also be attributable to the LDL-C lowering with the compound.	HPS3/TIMI55-REVEAL Collaborative Group,[35] 2017

(continued on next page)

(continued)

Abbreviations: CETP, cholesterol ester transfer protein; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

High-Density Lipoproteins. Effects on Vascular Function and Role in the Immune Response Arash Haghikia,, Ulf Landmesser, Cardiol Clin 36 (2018) 317–327 https://doi.org/10.1016/j.ccl.2017.12.013 0733-8651/18/ 2017

This year in … lipidi

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 28, 2017 VOL. 377 NO. 13

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

The HPS3/TIMI55–REVEAL Collaborative Group*

CONCLUSIONS

Among patients with atherosclerotic vascular disease who were receiving intensive statin therapy, the use of anacetrapib resulted in **a lower incidence of major coronary events than the use of placebo**.

ClinicalTrials.gov number, NCT01252953; and EudraCT number, 2010-023467-18.

This year in … lipidi

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 28, 2017 VOL. 377 NO. 13

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

The HPS3/TIMI55–REVEAL Collaborative Group*

DISCUSSION … On the basis of evidence from trials of statin therapy, **the lower level of non-HDL cholesterol** (by 17 mg per deciliter) in the anacetrapib group than in the placebo group as seen in our trial would be anticipated to result in a 10% relative reduction in the risk of coronary death or myocardial infarction (Fig. S5 in Supplementary Appendix 1), a finding that is entirely consistent with the 11% reduction that we observed.

This result reduces the likelihood that other actions of anacetrapib played a major role in modifying the risk of coronary events …

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

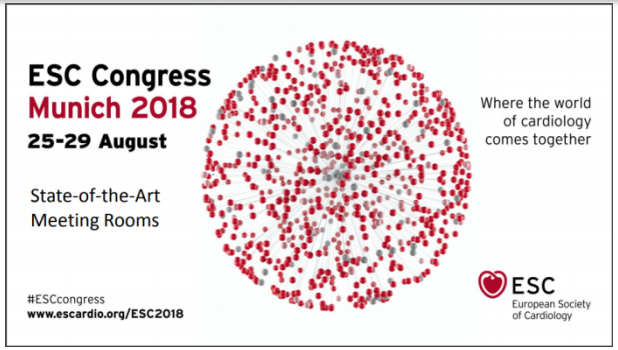
Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, et al

N Engl J Med 2012;367:2089-99. DOI: 10.1056/NEJMoa1206797

There are several possible explanations for the lack of benefit of dalcetrapib treatment. First, and in contrast to findings in epidemiologic analyses and post hoc analyses of data from some placebo-controlled trials of statins,[2-7] no association was shown between HDL cholesterol levels and cardiovascular risk among the patients evaluated in this trial, even those in the placebo group. The absence of such an association may indicate that HDL cholesterol levels are no longer a determinant of risk when patients are treated with the type of evidence-based therapies that were used in the trial, including statins, dual antiplatelet therapy, beta-blockers, ACE inhibitors or ARBs, and coronary revascularization procedures. Another possibility is that HDLs are protective in healthy persons who do not have established cardiovascular disease but that their composition is altered in the presence of cardiovascular disease, rendering them nonprotective even at high levels or after therapeutic intervention. Specifically, the composition and function of HDLs might have been altered in an adverse fashion after the qualifying acute coro-

This year in … lipidi



Elevated HDLC is associated with adverse cardiovascular outcomes

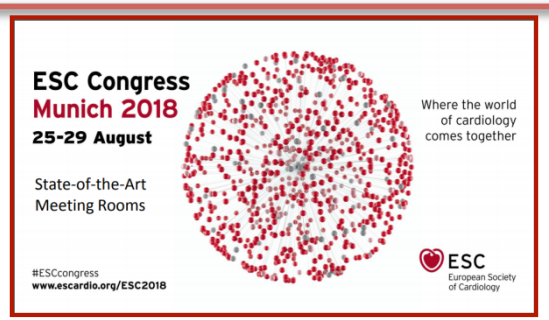
Authors: M. AllardRatick,J. Khambhati, M. Topel, P. Sandesara, L. Sperling, A. Quyyumi

Citation:
European Heart Journal (2018) 39 (Supplement), 3

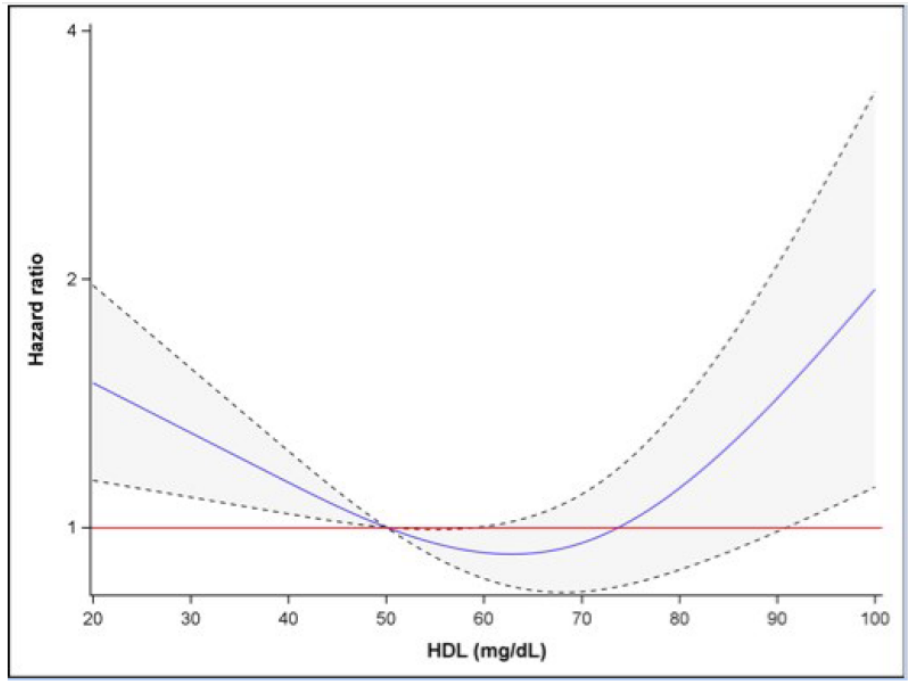
Purpose: To study the relationship between elevated HDLC levels (>60 mg/dl) and adverse CV outcomes in an at risk population.

Methods: Participants included 5,965 individuals (mean age 63.3±12.4 years, 35% female, 23% African American) enrolled in the cardiovascular biobank …

This year in … lipidi



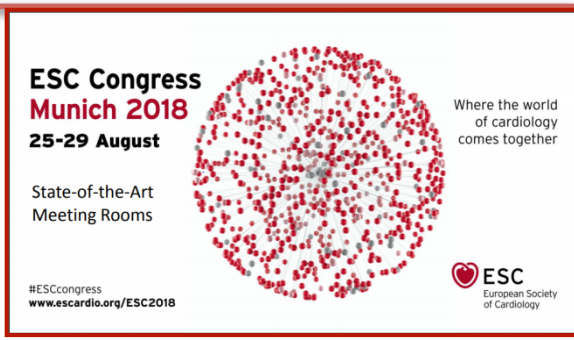
Results: Over a median follow-up of 3.9 years (interquartile range 1.6 to 6.6 years), there were 769 CV death/nonfatal MI events. Restricted cubic spline regression models demonstrated **a "U shaped" association between HDLC and CV death/nonfatal MI and all cause mortality.** Individuals with HDLC <30 mg/dL (n=825) and ≥60 mg/dL (n=570) had an increased risk of all cause mortality and CV death/nonfatal MI (HR 1.62; 95% CI=1.16–2.26, p=0.005 and HR 1.44; 95% CI = 1.01–2.06, p=0.04 respectively) after adjusting for aforementioned variables.



Association of HDL-C and CV death/MI

European Heart Journal (2018) 39 (Supplement), 3

This year in … lipidi



Conclusion: Elevated HDLC levels **are paradoxically associated with an increased risk of adverse CV events in an at risk population**, suggesting dysfunctional HDL and impaired atheroprotection.

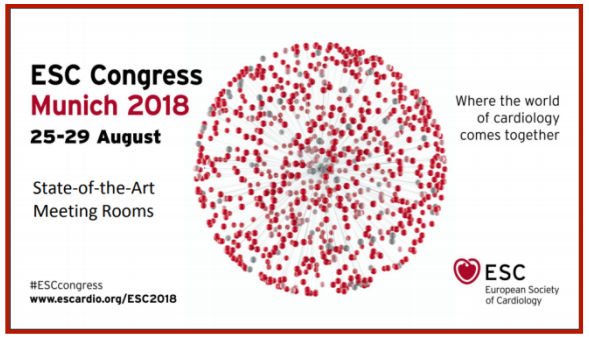
European Heart Journal (2018) 39 (Supplement), 3

This year in … lipidi

Serum modified high density lipoprotein levels assessed by a novel assay was associated with coronary artery calcification in an apparently healthy population

Authors: T. Okamura, A. Kakino, K. Miura, A. Fujiyoshi, A. Kadota, Y. Fujita, M. Zaid, Y. Usami, T. Hisamastu, S. Horiuchi, A. Kunimura, D. Sugiyama, K. Kondo, T. Sawamura, H. Ueshima

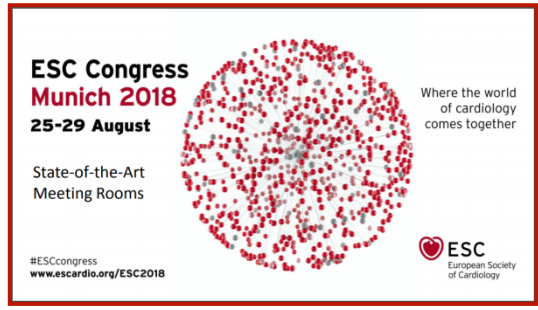
European Heart Journal (2018) 39 (Supplement), 4



Introduction: … we have developed a **brand-new assay to detect serum modified HDL**, which is thought to be a nonfunctional or atherogenic form of HDL.

Purpose: **The relationship between modified HDL and coronary artery calcification (CAC)** was examined in apparently healthy Japanese individuals who participated in a cohort study for examination of subclinical atherosclerosis of community dwellers. Participants were randomly selected from one city in the west part of Japan.

This year in … lipidi

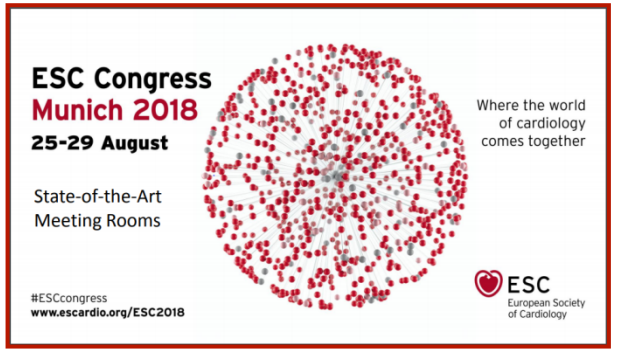


Method: Study population consists of 1,009 Japanese men aged 40–79 years without clinical cardiovascular diseases, of which mean age was 64 (Standard Deviation, SD: 10.1)…

In the present study, serum LOX1 ligand containing Apo A1 was defined as modified HDL. Modified HDL levels were measured by enzyme linked immunosorbent assays (ELISAs) with recombinant LOX1 and antiApo A1 antibody…

European Heart Journal (2018) 39 (Supplement), 4

This year in … lipidi



Results: Mean HDL cholesterol level was 58.5 mg/dl (SD: 16.8) and mean modified HDL cholesterol level was 204 ng/ml (SD: 89.7). **Serum modified HDL levels were significantly associated with CAC**; age adjusted OR (odd ratio) for the presence of CAC was 1.29 (95% confidence interval: 95% CI: 1.12–1.48). After further adjustment for hypertension, diabetes, smoking, body mass index, HDL cholesterol, non HDL cholesterol and lipid lowering medication, the significant association was still observed, of which OR was 1.22 (95% CI: 1.05–1.42). Additional adjustment for high sensitivity C reactive protein (CRP) also did not alter the results.

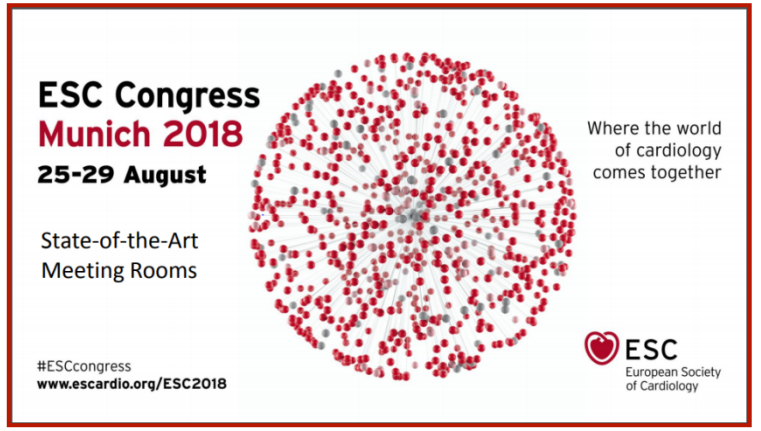
Conclusions: Serum modified HDL, i.e., LOX1 ligand containing Apo A1, might be a novel biomarker for subclinical atherosclerosis in apparently healthy individuals.

European Heart Journal (2018) 39 (Supplement), 4

This year in … lipidi

Therapy with cholesteryl ester transfer protein (CETP) inhibitors and diabetes risk. A Meta-analysis

Authors: L.M. Lobo1, W. Masson, G. Molinero, D. Siniawski, M. Huerin, J.P. Nogueira, R. Valero,
European Heart Journal (2018) 39 (Supplement), 4

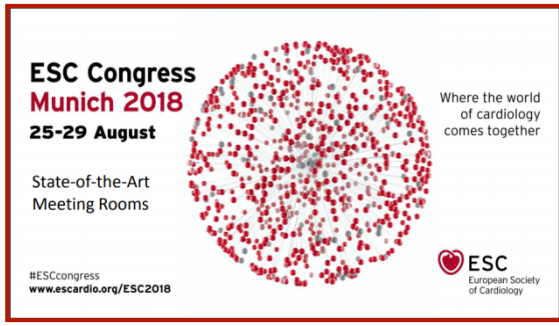


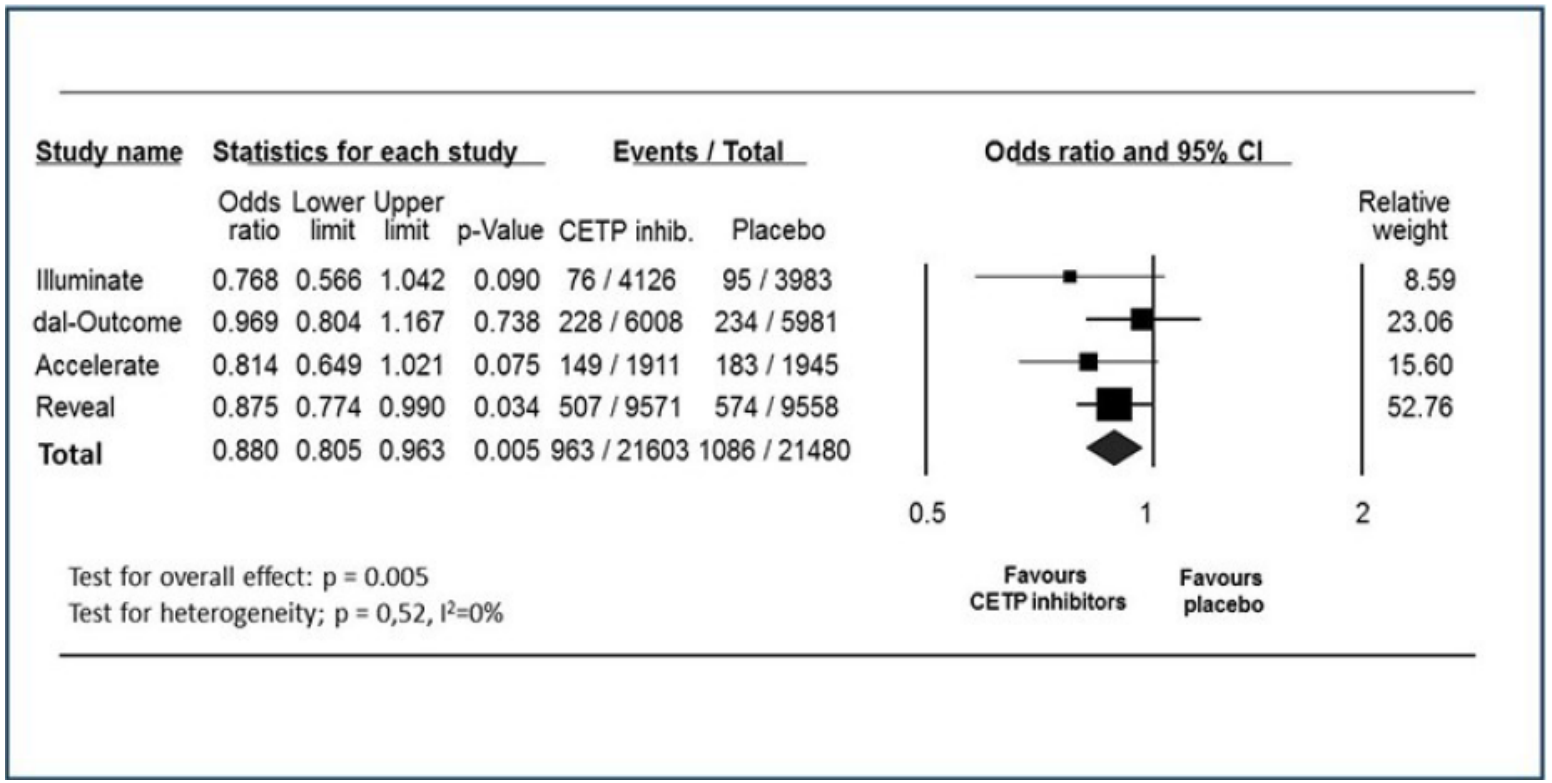
Background: Cholesteryl ester transfer protein (CETP) inhibitors are a drug class that target the enzyme CETP, increasing significantly serum high density lipoprotein cholesterol level (HDLC). Since HDLC has potential antidiabetic properties and the beneficial effect of these drugs on glucose homeostasis has not been sufficiently studied**, the aims of this study were: (1) to evaluate the effect of CETP inhibitors on the incidence of diabetes and (2) to assess the association between CETP inhibitors induced changes in HDLC levels and the incidence of diabetes**.

This year in … lipidi

Therapy with cholesteryl ester transfer protein (CETP) inhibitors and diabetes risk. A Metaanalysis

European Heart Journal (2018) 39 (Supplement), 4





Conclusions: CETP inhibitors reduced the incidence of diabetes. This improvement in glucose metabolism **may have been related, at least in part, to the increase in HDLC concentration.**

This year in … lipidi

LIPOPROTEINE HDL: non più solo «colesterolo buono»

High-Density Lipoproteins Effects on Vascular Function and Role in the Immune Response
Arash Haghikia, MD, Ulf Landmesser, MD Cardiol Clin 36 (2018) 317–327
doi.org/10.1016/j.ccl.2017.12.013 0733-8651/18/ 2017

High-density lipoprotein (HDL) metabolism and bone mass.
Papachristou NI, Blair et al. Endocrinol. 2017 May;233(2):R95-R107.
doi: 10.1530/JOE-16-0657. Epub 2017 Mar 17.

Therapy with cholesteryl ester transfer protein (CETP) inhibitors and diabetes risk. A Metaanalysis L.M. Lobo, W. Masson ET AL. European Heart Journal (2018) 39 (Supplement), 4

Electronic supplementary material:
The online version of this article contains supplementary material.

journal of global health

Effect of physician characteristics and knowledge on the quality of dyslipidemia management and LDL–C target goal achievement in China: Subgroup analysis of the Dyslipidemia International Study

Conclusion: Chinese **physicians' characteristics and knowledge** of LDL–C target goals were associated with patients' LDL–C goal achievement.

www.jogh.org • doi: 10.7189/jogh.07.020702December 2017 • Vol. 7 No. 2 • 020702

GRAZIE PER L'ATTENZIONE!