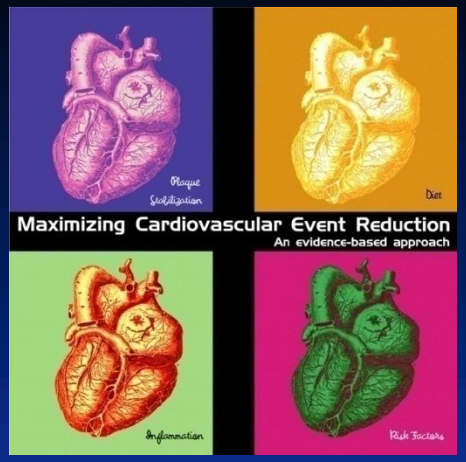

Intensive Lipid Intervention-Status 2021

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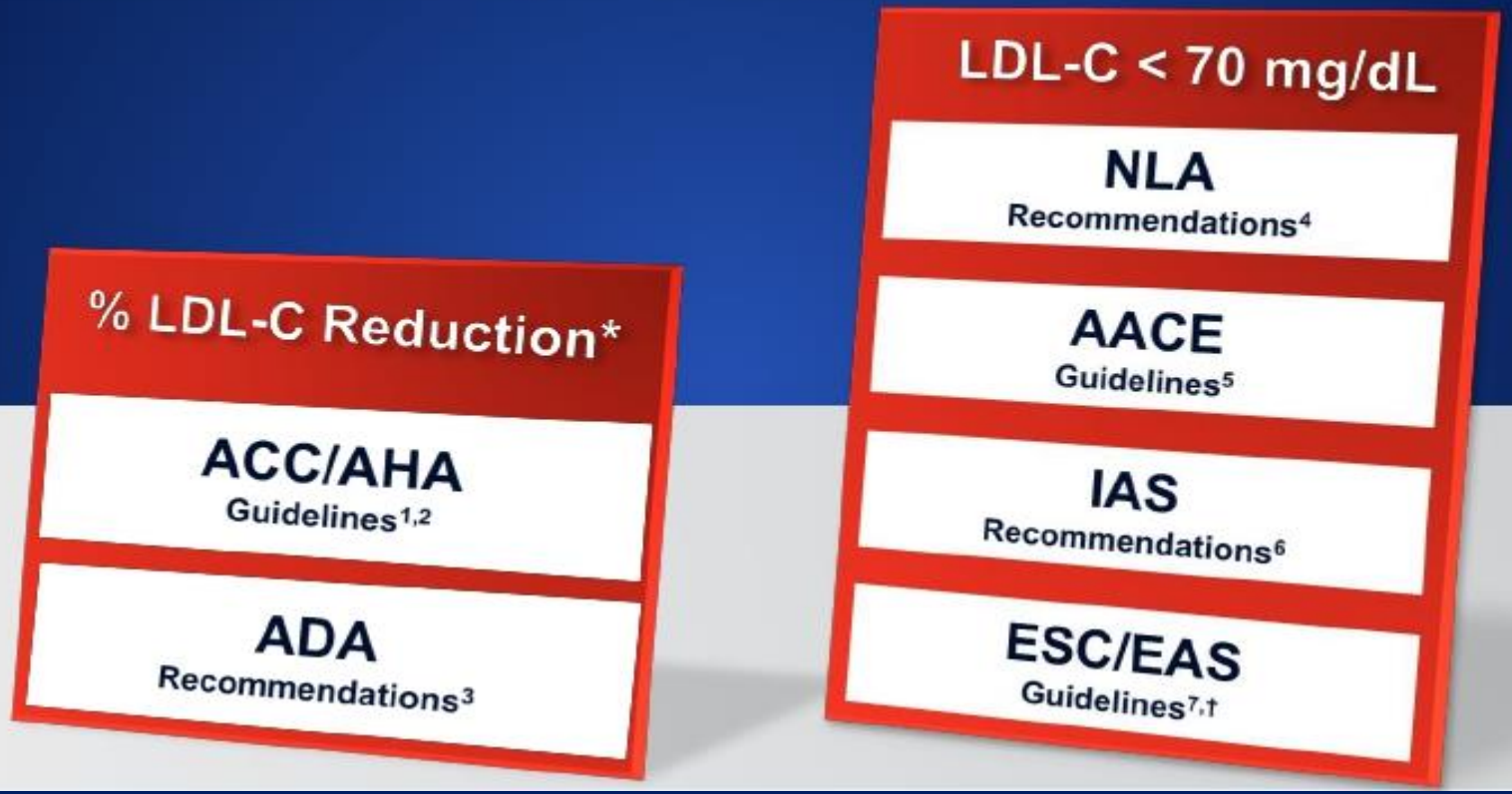
Fish Oil /Omega-3/ Lipid
Lavie COI/Disclosures

Speaker and Consultant for GOED and DSM and in the past for Amarin (Vascepa) ; Amgen (Repatha) and Sanofi/Regeneron (Praluent), Esperion (Nexletol and Nexlizet)

LDL-C Reduction Remains Fundamental to Major Cholesterol Treatment Guidelines and Recommendations

Recommendations for Patients With Clinical ASCVD



ASCVD = atherosclerotic cardiovascular disease; ACC = American College of Cardiology; AHA = American Heart Association; ADA = American Diabetes Association; NLA = National Lipid Association; AACE = American Association of Clinical Endocrinologists; IAS = International Atherosclerosis Society; ESC = European Society of Cardiology; EAS = European Atherosclerosis Society.

*Percent LDL-C reduction defines treatment intensity and assesses adherence;[1] †also includes percent LDL-C reduction as an efficacy metric.[7]

1. Stone NJ, et al. *J Am Coll Cardiol*. 2014;63:2889-2934. 2. Keaney JF, et al. *N Engl J Med*. 2014;370:275-278. 3. American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S1-S94. 4. Jacobson TA, et al. *J Clin Lipidol*. 2014;8:473-488. 5. Jellinger PS, et al. *Endocr Pract*. 2012;18(suppl 1):1-78. 6. Expert Dyslipidemia Panel, Grundy SM. *J Clin Lipidol*. 2013;7:561-565. 7. Reiner Z, et al. *Eur Heart J*. 2011;32:1769-1818.

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EXPERT CONSENSUS DECISION PATHWAY

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents

Endorsed by the National Lipid Association

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2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA

Guideline on the Management of Blood Cholesterol

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No Writing Group Members have COI/RWI Relevant to this Guideline

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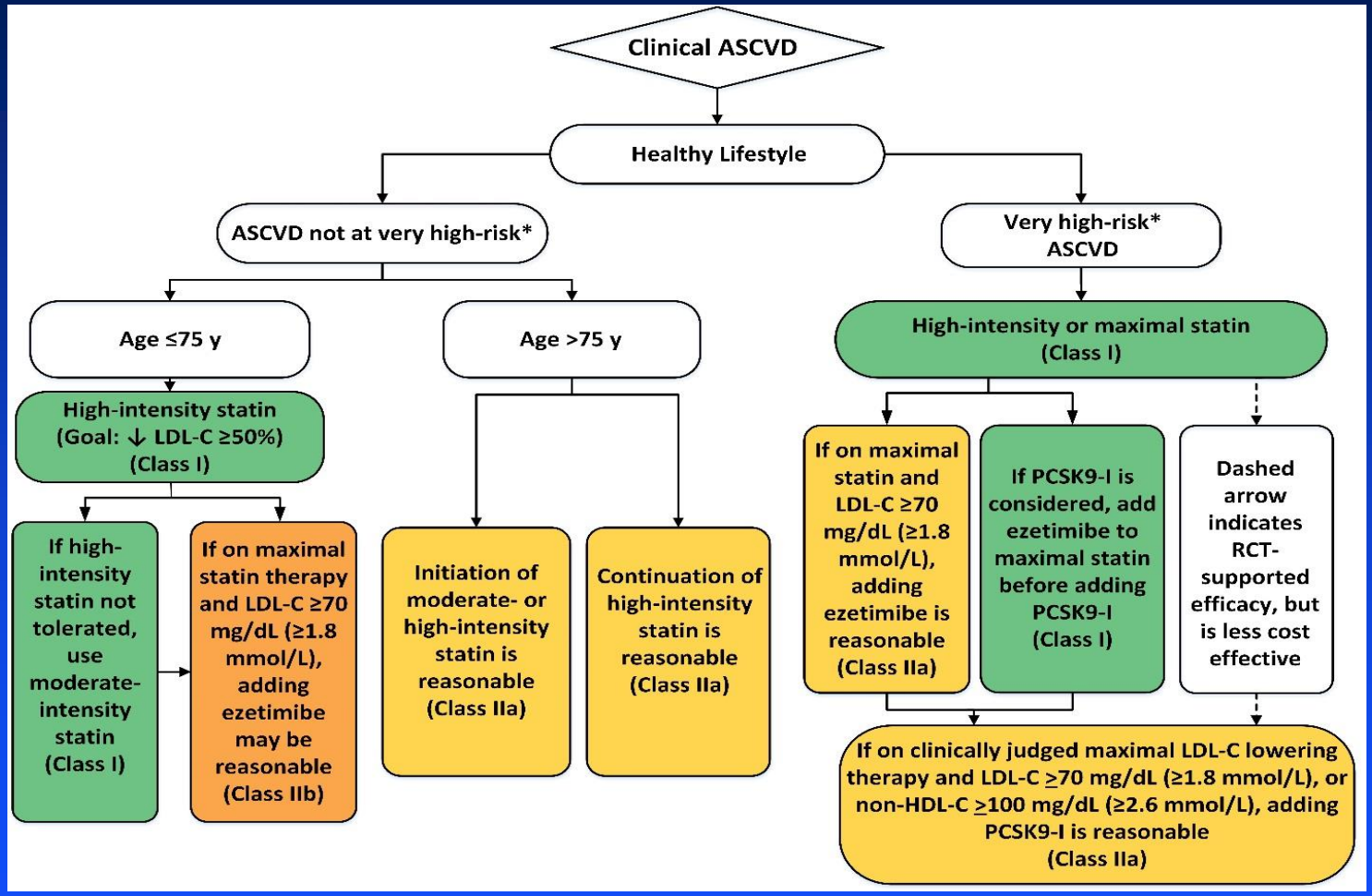
Secondary Prevention



Very High-Risk ASCVD Patients

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

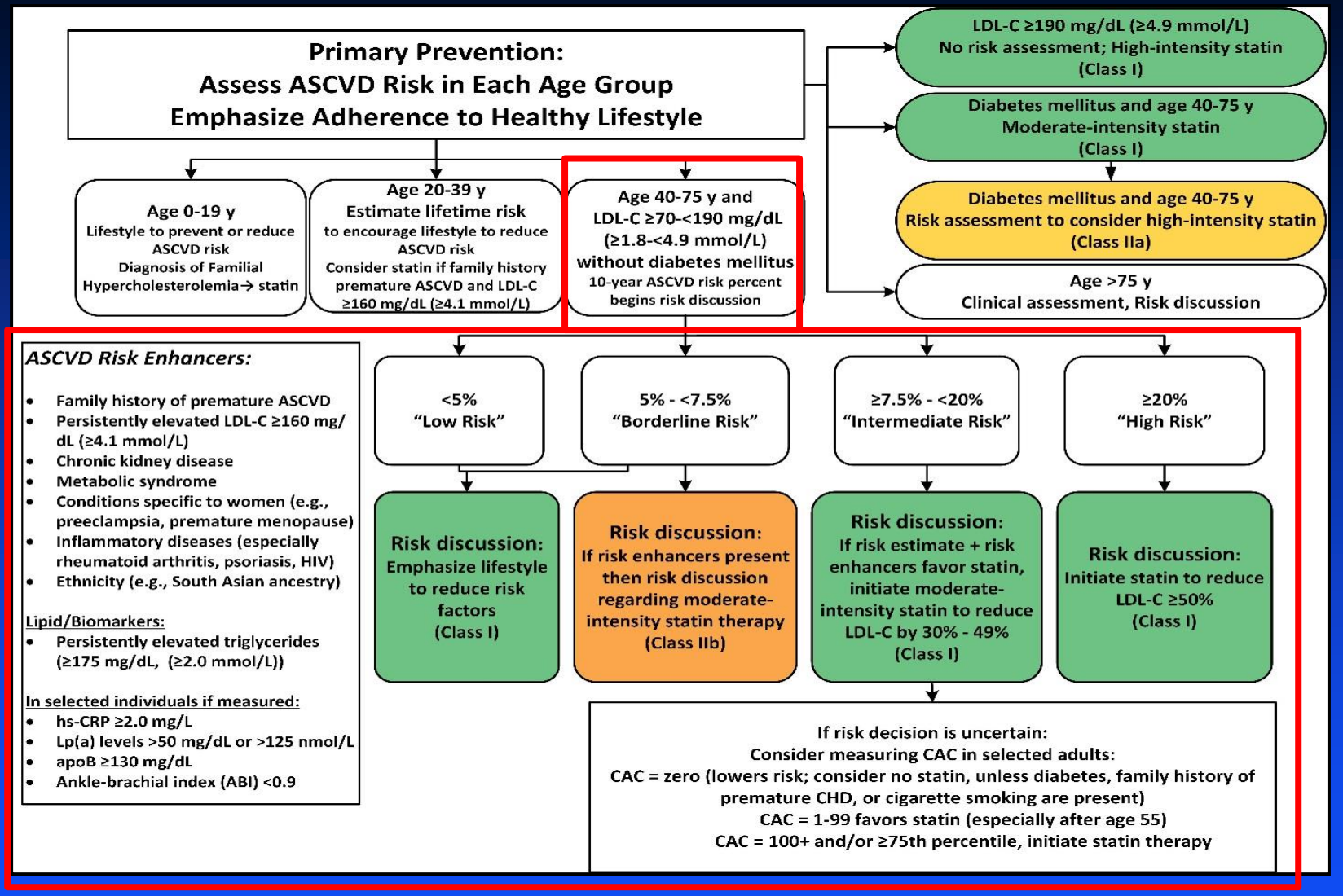
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

***Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.**

Conclusions:

Secondary Prevention

- **Lifestyle still important even with statin use**
- **Use High intensity statin (40-80 mg atorvastatin or 20-40 mg rosuvastatin)**
- **Lower LDL-C better with proven therapies**
- **If very high risk & LDL-C ≥70 mg/dL despite maximal tolerated statin, consider ezetimibe &/or PCSK9 inhibitor (and now maybe bempedoic acid.)**


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Questions on Primary Prevention in Diabetes Mellitus

Primary Prevention

- What about DM at age 39 and 76
- Should HSCRP and/or CAC impact intensity of statins in DM
- Should clinicians worry about statins worsening blood glucose in DM
- Should clinicians worry about higher intensity statins worsening glucose more than low intensity statins

Selected Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

- Patients reluctant to initiate statin who wish to understand their risk & potential for benefit more precisely
- Patients concerned about need to reinstitute statin after discontinuation for ? statin-associated symptoms
- Men, 55-80 y/o; women, 60-80 y/o with low burden of risk factors who question whether they would benefit Rx
- 40-55 y/o with 10-yr risk of ASCVD 5% - 7.4% with risk-enhancing factors

Limitations of Statins

- Muscle Side Effects-consider Coenzyme Q 10 and check and treat low D
- Many patients do not obtain all lipid goals despite intensive doses
- Considerable Residual Risk
- Concern about other Adverse Effects-Liver,Diabetes,Memory, etc
- Most effective in patients with higher CHD risk

Statins in Diabetes Mellitus

- Patients with DM need statins more than most other patients in primary prevention
- Statins increase blood sugar and increase prevalence of DM
- Higher dose/intensity statins worsen blood sugar mores so than do lower doses/intensity
- Patients who develop DM on statins have the same protection against CHD/stroke as do patients who do not develop DM
- Pitavastatin has least effects on glucose
- DM patients may need coQ10 and D

Ezetimibe Therapy
Implications of IMPROVE-IT

- Produces 15-20% reductions in LDL-C added to statins
- Negative results and publicity from ENHANCE
- IMPROVE-IT AHA Nov,2014
- Over 18,000 post-ACS;7 years;median LDL-C 69.9 to 53.2 md/dl
- Significant event reduction , absolute 2% and relative 6.4%;NNT 50 for 7 yr (or 350 per year)

DiNicolantonio J, Lavie CJ et al. Am J Med, on-line 2/27/15

JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients
The GLAGOV Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

IMPORTANCE Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.

OBJECTIVE To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

DESIGN, SETTING, AND PARTICIPANTS The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography.

INTERVENTIONS Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.

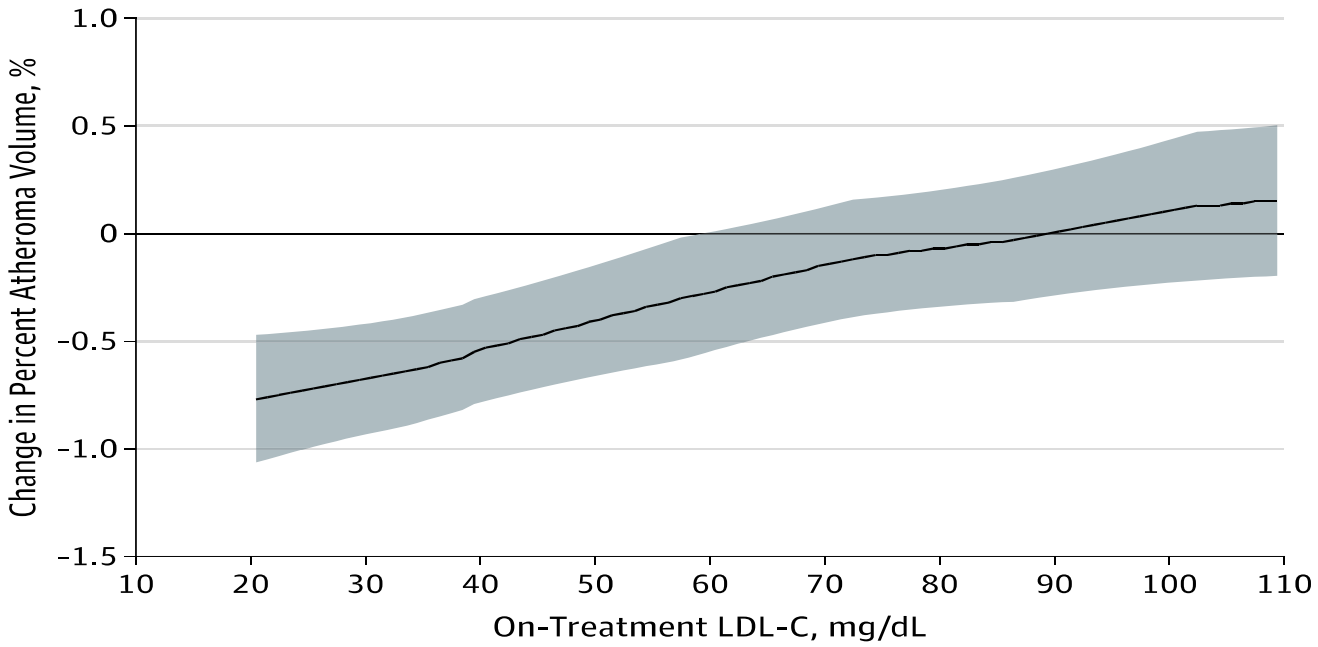
MAIN OUTCOMES AND MEASURES The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. Safety and tolerability were also evaluated.

Supplemental content

Nicholls, S. JAMA. doi:10.1001/jama.2016.16951

Evolucomab, LDL-C and Coronary Atheroma Progression

Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume



Local regression (LOESS) curve illustrating the post hoc analysis of the association (with 95% confidence intervals) between achieved low-density lipoprotein cholesterol (LDL-C) levels and the change in percent atheroma volume in all patients undergoing serial IVUS evaluation. Curve truncated at 20 and 110 mg/dL owing to the small number of values outside that range. To convert LDL-C values to mmol/L, multiply by 0.0259.

Nicholls, S. JAMA. doi:10.1001/jama.2016.16951

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.

RESULTS

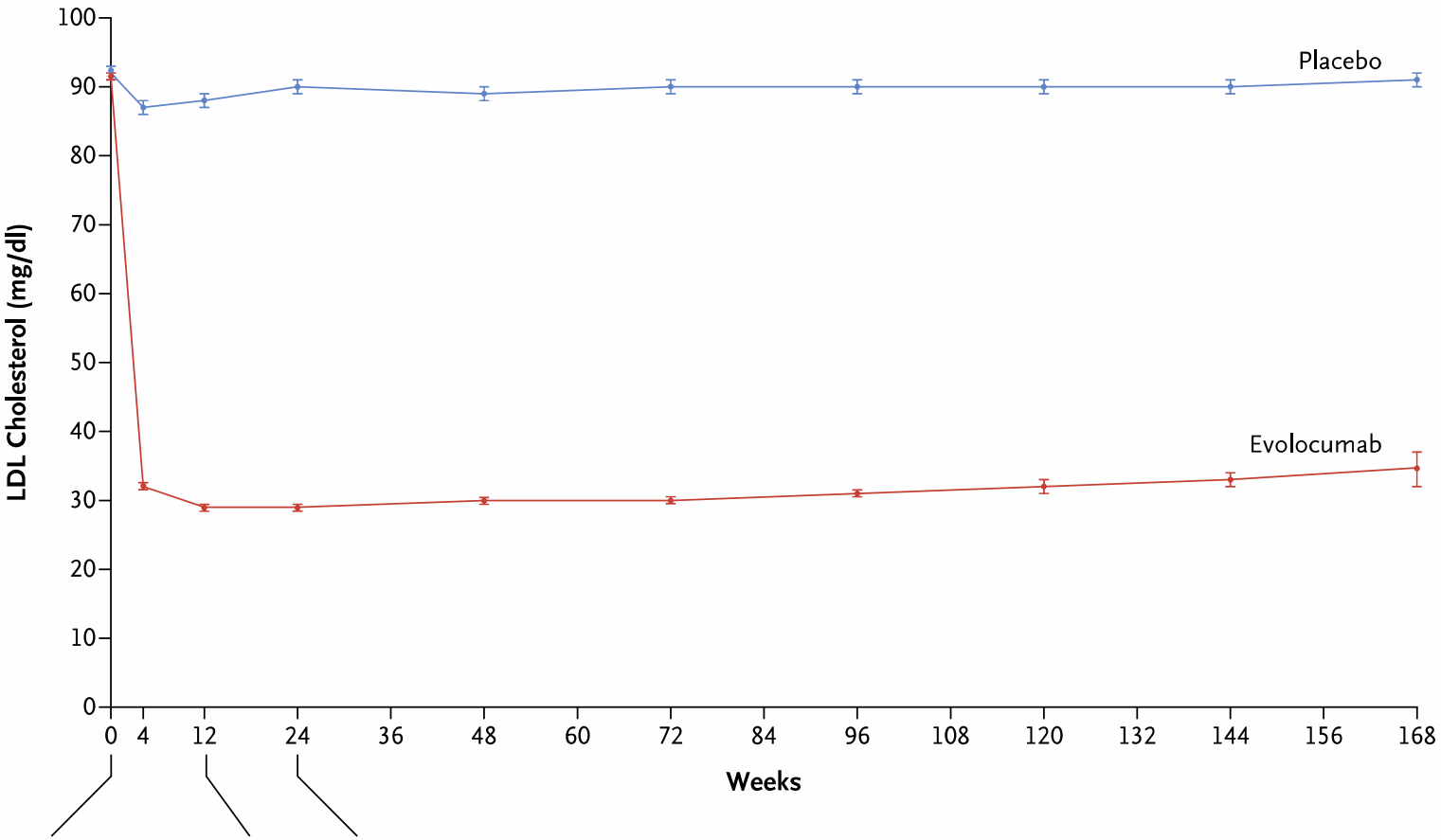
At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) ($P<0.001$). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; $P<0.001$) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88;

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W., S.A.M., J.F.K.); Sydney Medical School, National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (A.C.K.); Amgen, Thousand Oaks, CA (N.H., H.W., T.L., S.M.W.); International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London (P.S.S.); and Oslo University Hospital, Ullevål and Medical Faculty, University of Oslo, Oslo (T.R.P.). Address reprint requests to Dr. Sabatine at the TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 60 Fenwood Rd., Boston, MA 02115, or at msabatine@partners.org.

*A complete list of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) steering committee and investigators is provided in the Supplementary Appendix, available at NEJM.org.

Sabatine MS et al. NEJM 2017; 376: 1713-1722

Evolocumab and Major CVD Events

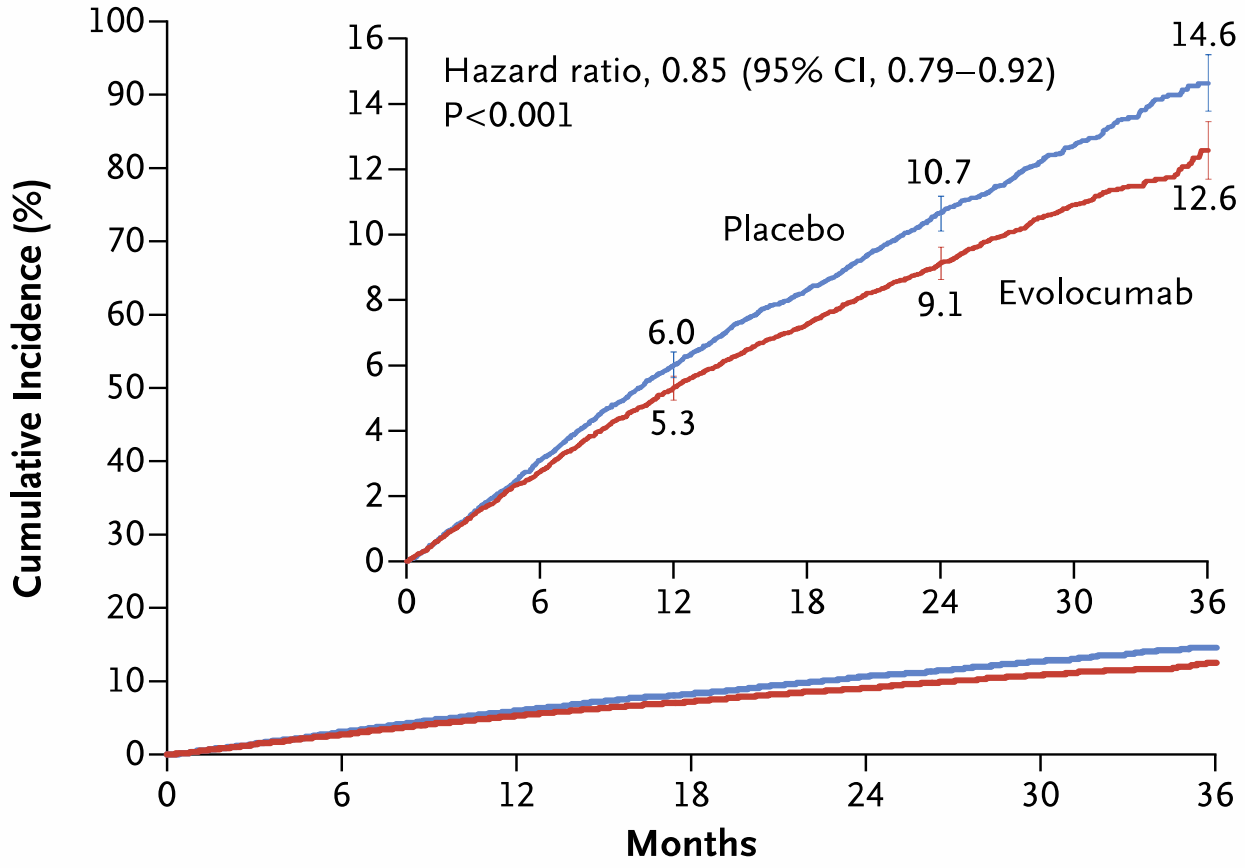


No. at Risk										
Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768
Absolute difference (mg/dl)		54	58	57	56	55	54	52	53	50
Percentage difference		57	61	61	59	58	57	55	56	54
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Sabatine MS et al. NEJM 2017; 376: 1713-1722

Evolocumab and Major CVD Events

Primary Efficacy End Point



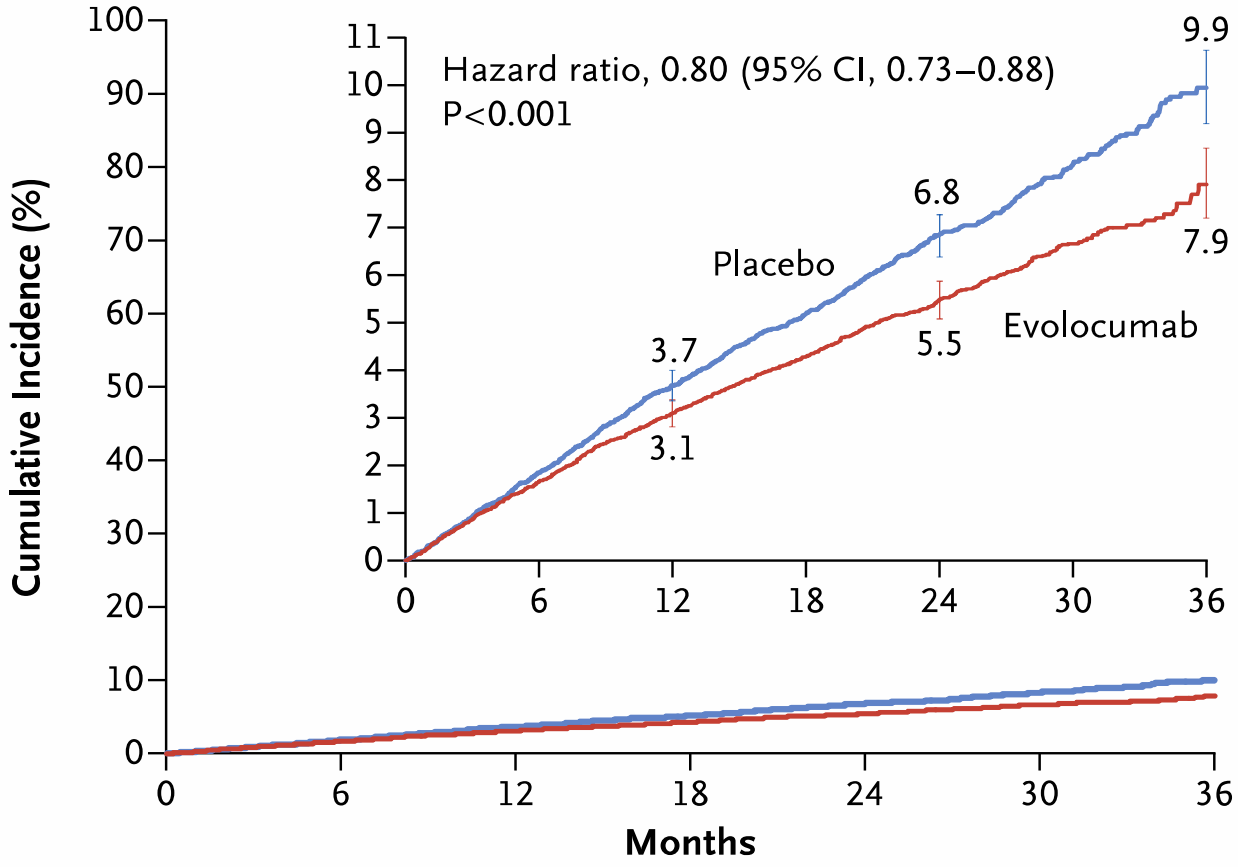
No. at Risk

Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

Sabatine MS et al. NEJM 2017; 376: 1713-1722

Evolocumab and Major CVD Events

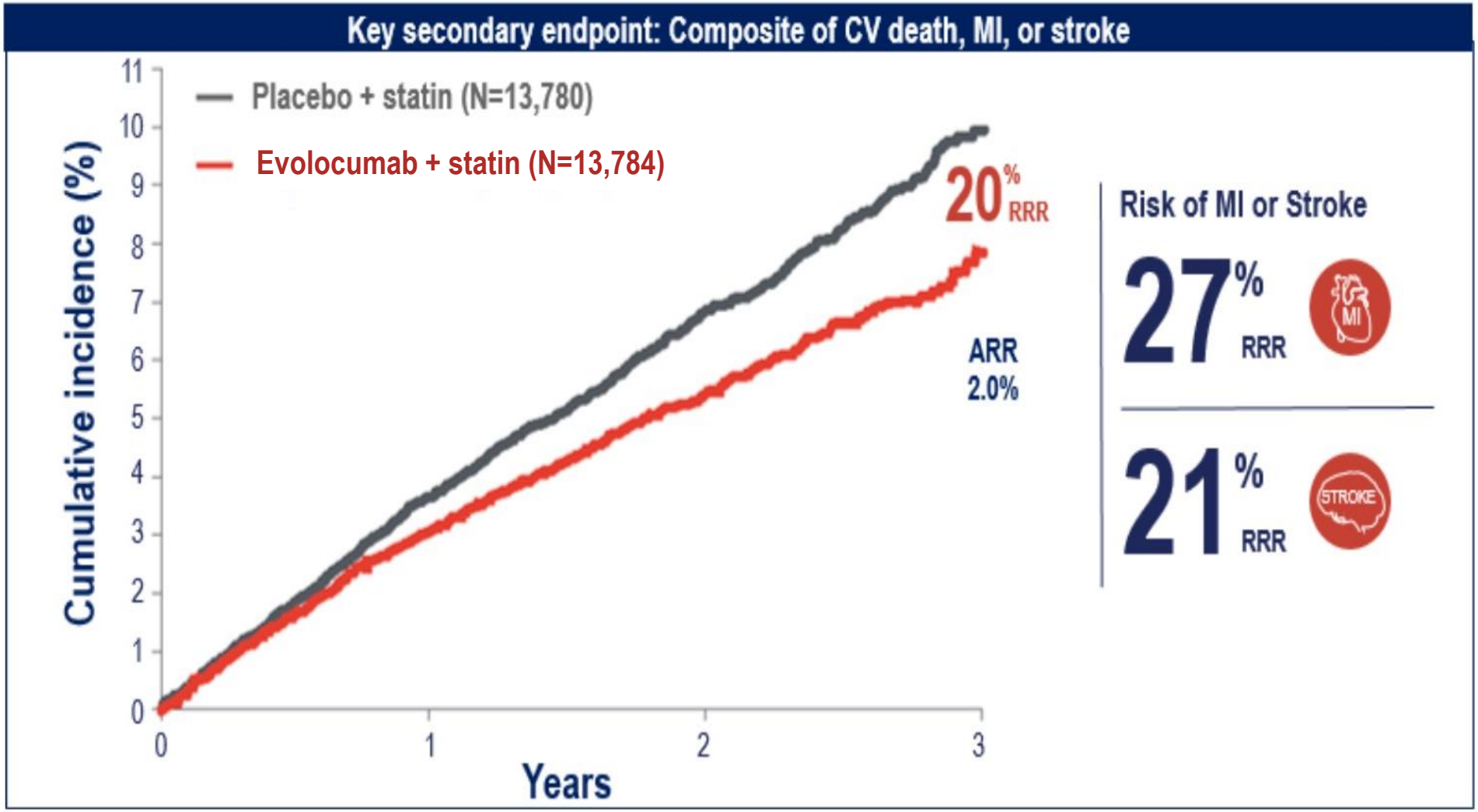
Key Secondary Efficacy End Point



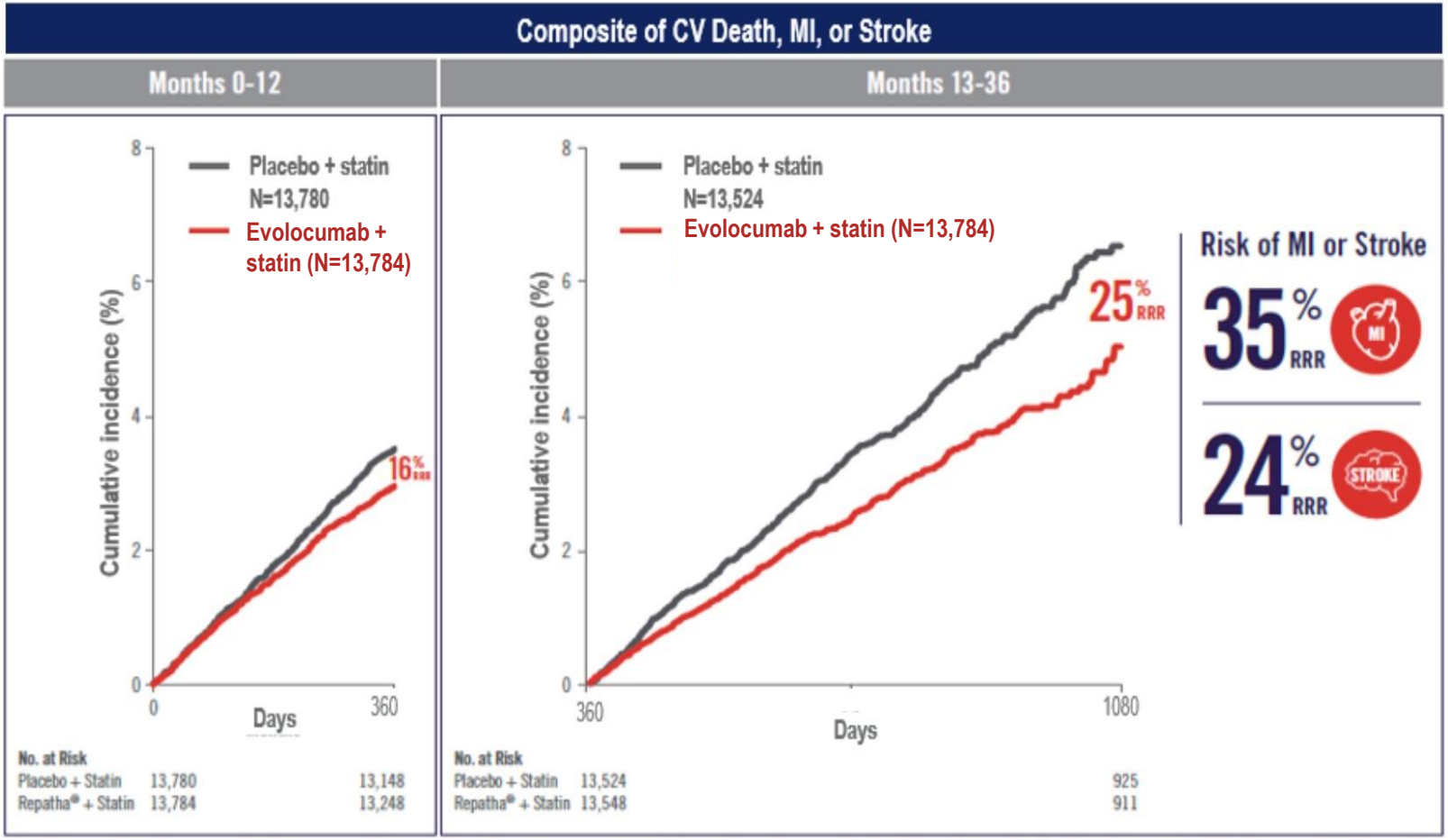
No. at Risk							
Placebo	13,780	13,449	13,142	12,288	7944	3893	731
Evolocumab	13,784	13,501	13,241	12,456	8094	3935	724

Sabatine MS et al. NEJM 2017; 376: 1713-1722

Evolocumab Reduced Risk of Composite CV Events by 20% in a Median of Only 2.2 Years[1,2]



Post-hoc exploratory analysis
Risk Reduction with Evolocumab Changes Between Months 0-12 and Months 13-36



Considerations:

- For months 0-12, all patients in the study were included[2]
- For months 13-36, the analysis excluded those patients who died in the first year, but included patients even if they experienced non-fatal events during the 0-12 month period. Patients were not re-randomized after the landmark time of 12 months.[2]

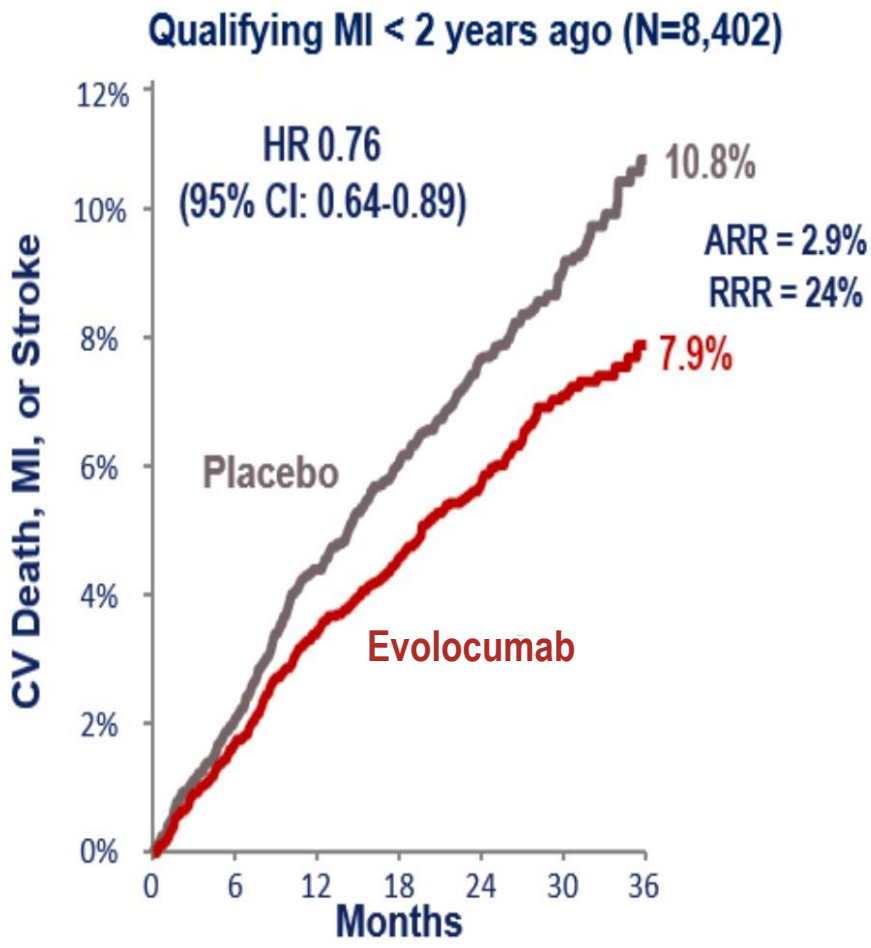
- This exploratory analysis was performed to inform assessments on the demonstrated treatment effect in the period before and after a landmark time of 12 months and supports the importance of maintaining patients on therapy[2]
- For this analysis the relative risk reduction for the composite endpoint from months 13-36 was driven by a reduction in the risk of MI HR: 0.65 (0.55-0.77) and stroke HR: 0.76 (0.60-0.97). **Observed HR for CV death: 1.12 (0.88-1.42)**[1]

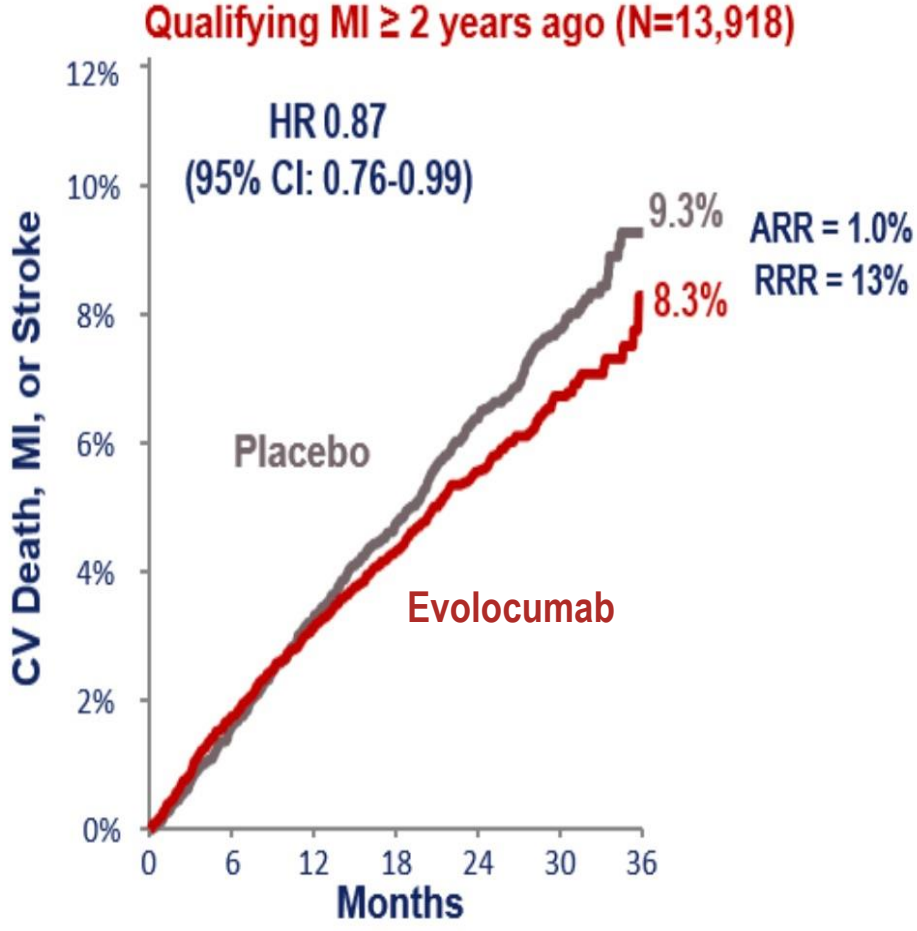
1. Supplement to: Sabatine MS, et al. N Engl J Med. 2017;376:1713-1722. 2. Data on file, Amgen.

Post-hoc analysis

Patients With a More Recent MI Are at Higher Risk of a Subsequent Event

Analysis of the 81% of patients in FOURIER with MI as their qualifying event





Mean time from MI to enrollment in FOURIER was 3.4 years.
The observed HR for CV death was 1.05 (95% CI, 0.88-1.25) from the primary analysis.

Sabatine MS, et al. Presented at The American Heart Association Annual Conference, November 2017.

Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease

Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)

Editorial, see p XXX

BACKGROUND: The PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor evolocumab reduced low-density lipoprotein cholesterol and cardiovascular events in the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). We investigated the efficacy and safety of evolocumab in patients with peripheral artery disease (PAD) as well as the effect on major adverse limb events.

METHODS: FOURIER was a randomized trial of evolocumab versus placebo in 27 564 patients with atherosclerotic disease on statin therapy followed for a median of 2.2 years. Patients were identified as having PAD at baseline if they had intermittent claudication and an ankle brachial index of <0.85 or if they had a prior peripheral vascular procedure. The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularization. The key secondary end point was a composite of cardiovascular death, myocardial infarction, or stroke. An additional

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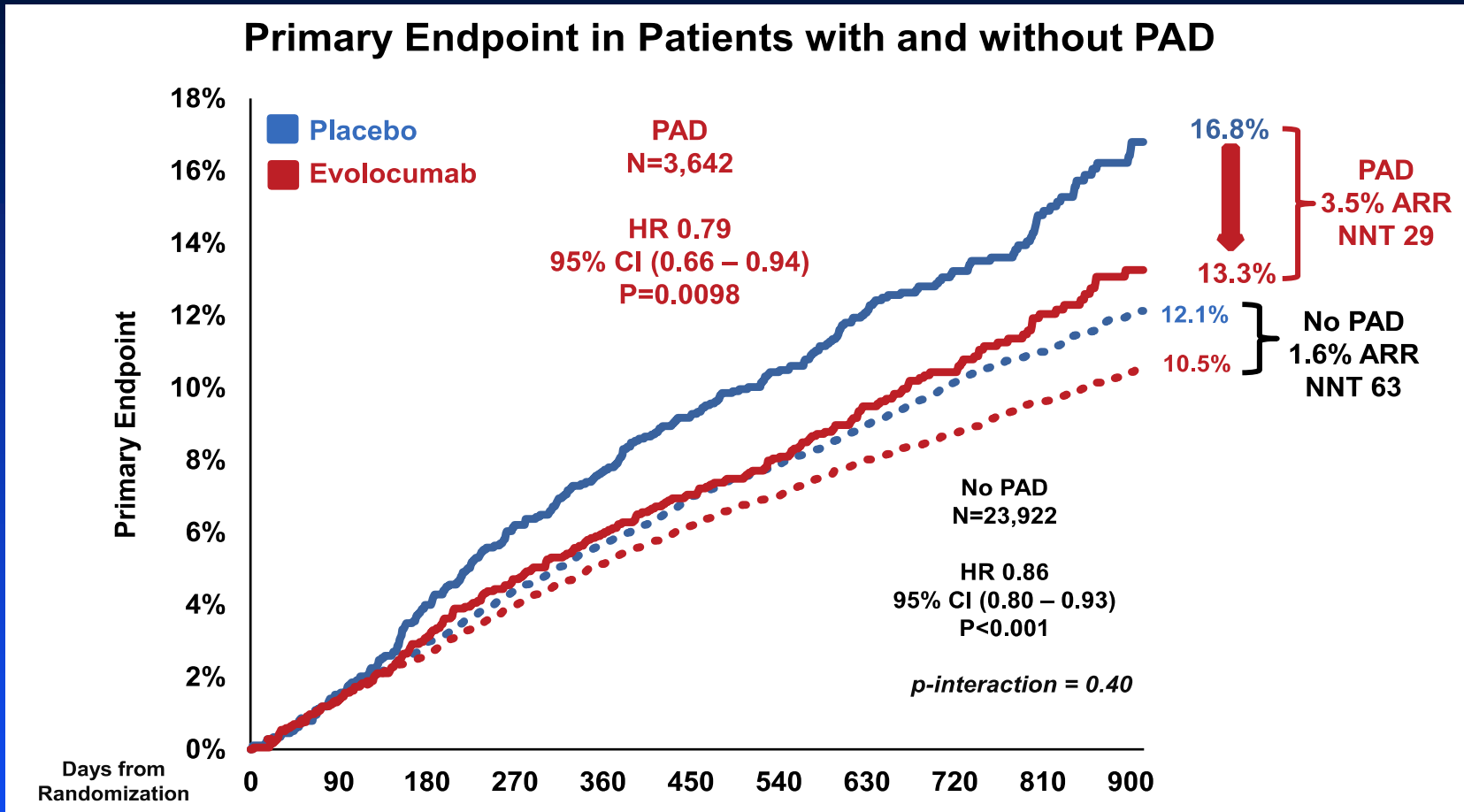
Bonaca MP et al. Circulation 2017:137: 338-350

Benefits of Evolocumab in PAD



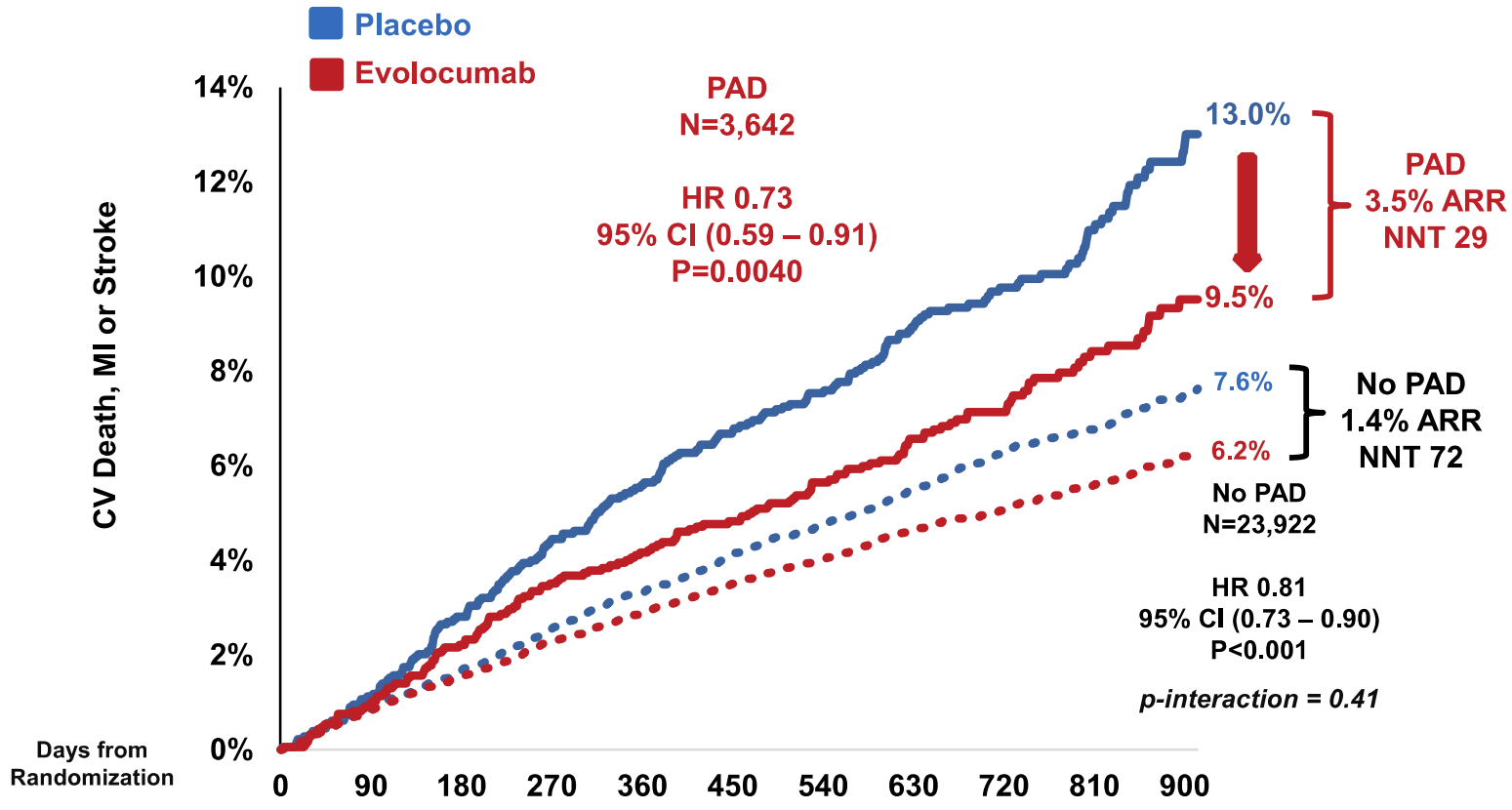
Number at risk

Placebo PAD	1784	1749	1700	1654	1617	1588	1536	1281	973	695	432
Evolocumab PAD	1858	1827	1790	1753	1726	1701	1651	1378	1050	749	460
Placebo no PAD	11996	11793	11582	11390	11217	11039	10400	8759	6864	5173	3443
Evolocumab no PAD	11926	11736	11568	11384	11224	11081	10486	8807	6972	5242	3476

Bonaca MP et al. Circulation 2017:137: 338-350

Benefits of Evolocumab in PAD

CV Death, MI or Stroke in Patients with and without PAD



Number at risk

Placebo PAD	1784	1756	1721	1685	1654	1632	1587	1332	1014	729	452
Evolocumab PAD	1858	1834	1806	1774	1758	1740	1692	1427	1091	779	480
Placebo no PAD	11996	11861	11732	11606	11494	11375	10767	9099	7167	5429	3636
Evolocumab no PAD	11926	11802	11699	11583	11490	11397	10828	9138	7258	5474	3649

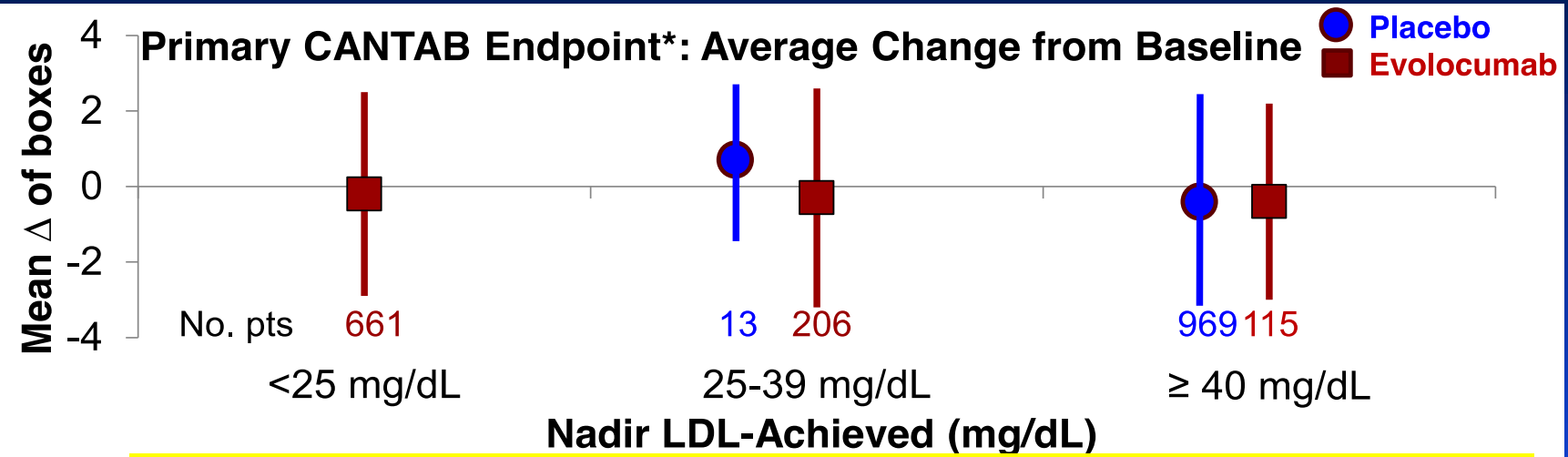
Bonaca MP et al. Circulation 2017:137: 338-350

EBBINGHAUS: A Cognitive Study of Patients Enrolled in the FOURIER Trial

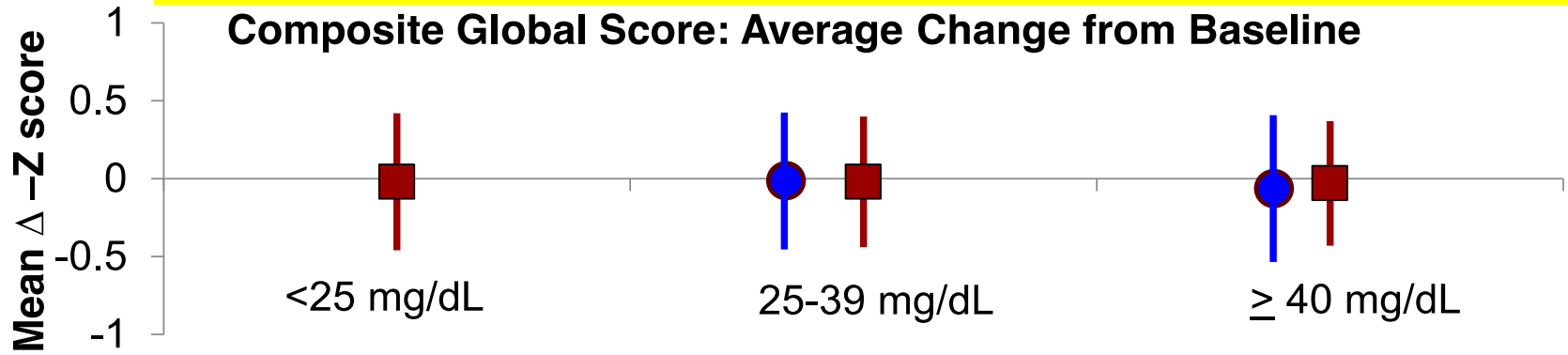
RP Giugliano, F Mach, K Zavitz, AC Keech, TR Pedersen,
MS Sabatine, P Sever, C Kurtz, N Honarpour, BR Ott,
on behalf of the EBBINGHAUS Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 18, 2017

Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)



P=NS across LDL values achieved and also between treatments

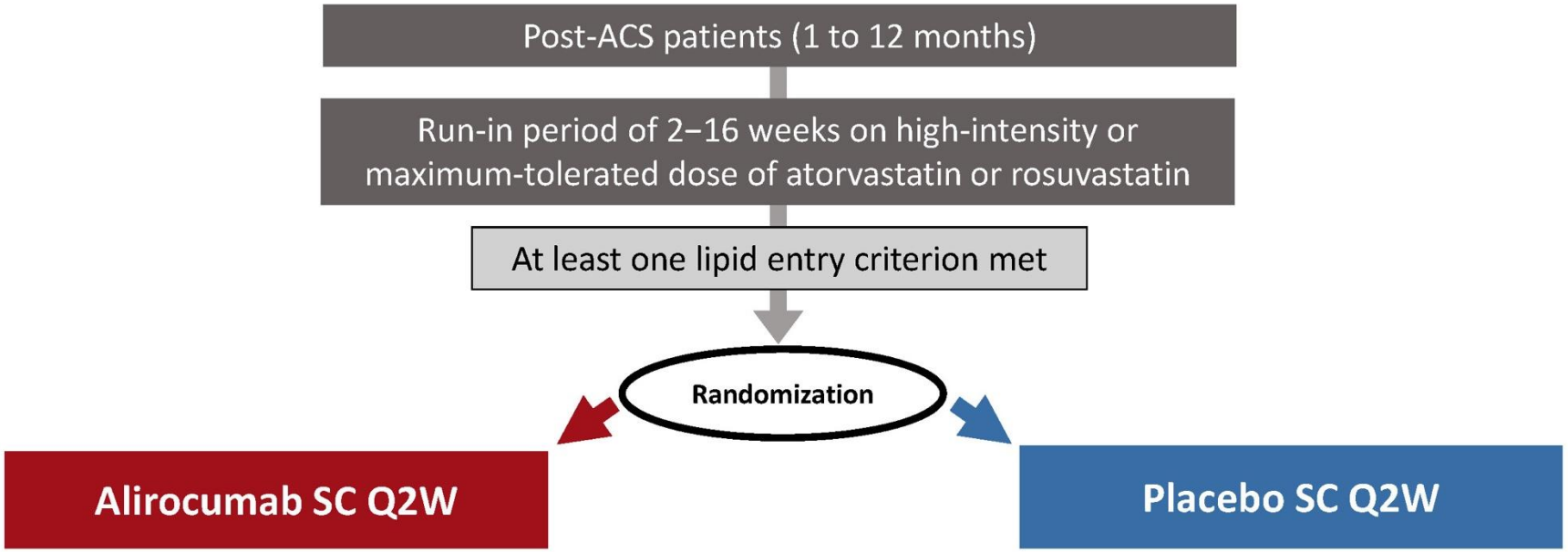


Negative score -> improvement
Lower scores are better

*Spatial working memory strategy index of executive function, raw score

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Treatment Assignment

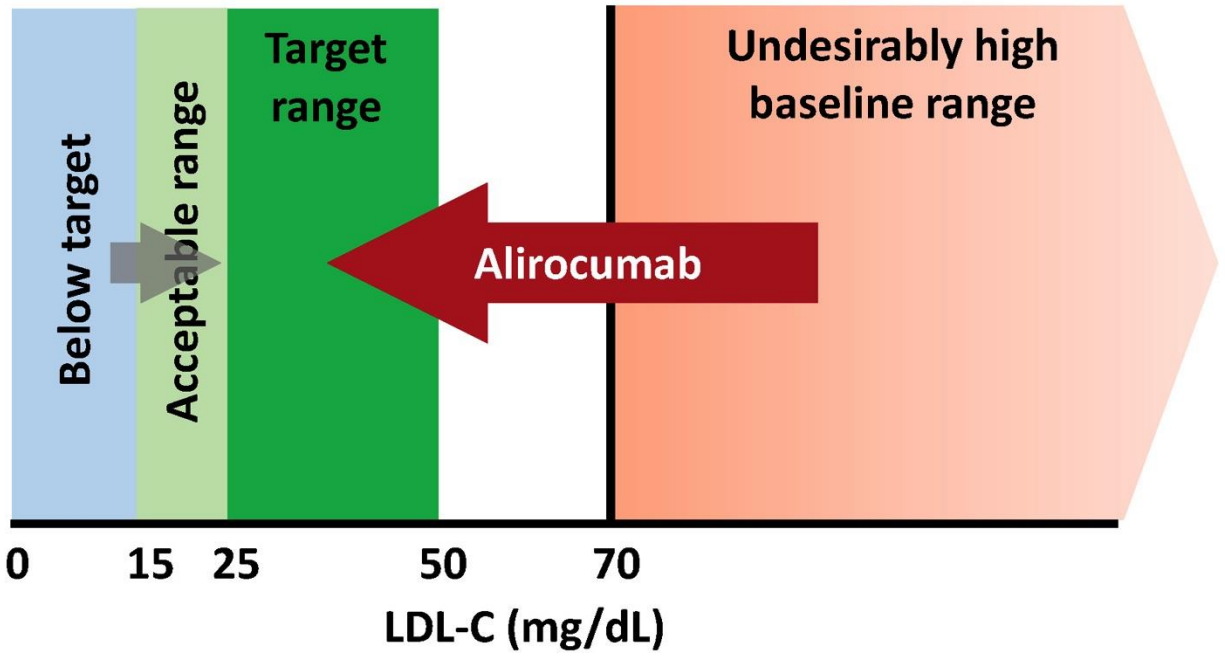


Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

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

A Target Range for LDL-C

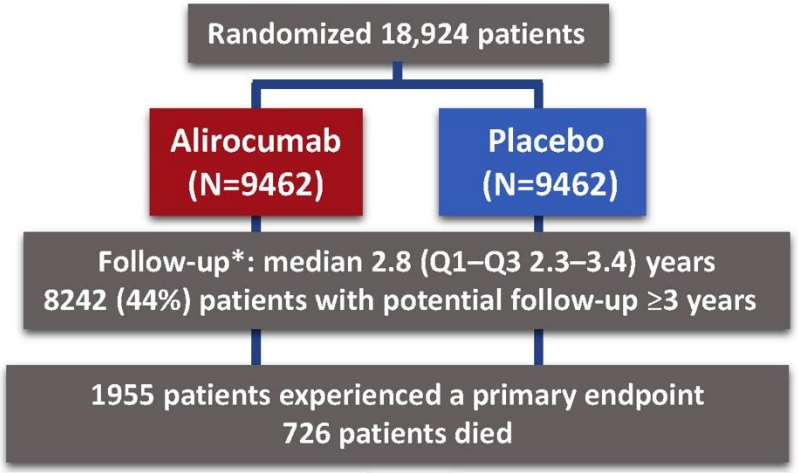
We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



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

ODYSSEY OUTCOMES

Patient Disposition

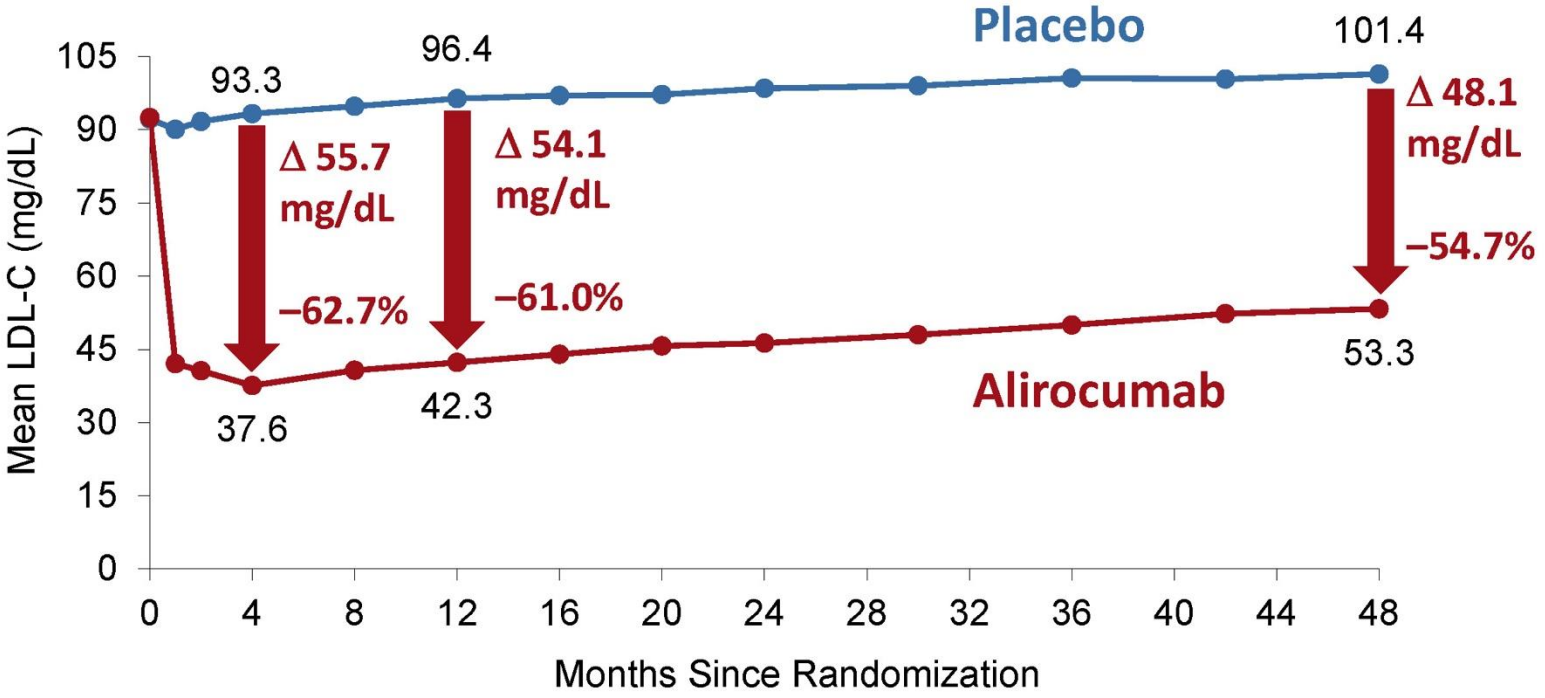


• **Premature treatment discontinuation**	1343 (14.2%)	1496 (15.8%)
• **Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)**	730 (7.7%)	Not applicable
• **Patients lost to follow-up (vital status)**	14	9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

ODYSSEY OUTCOMES

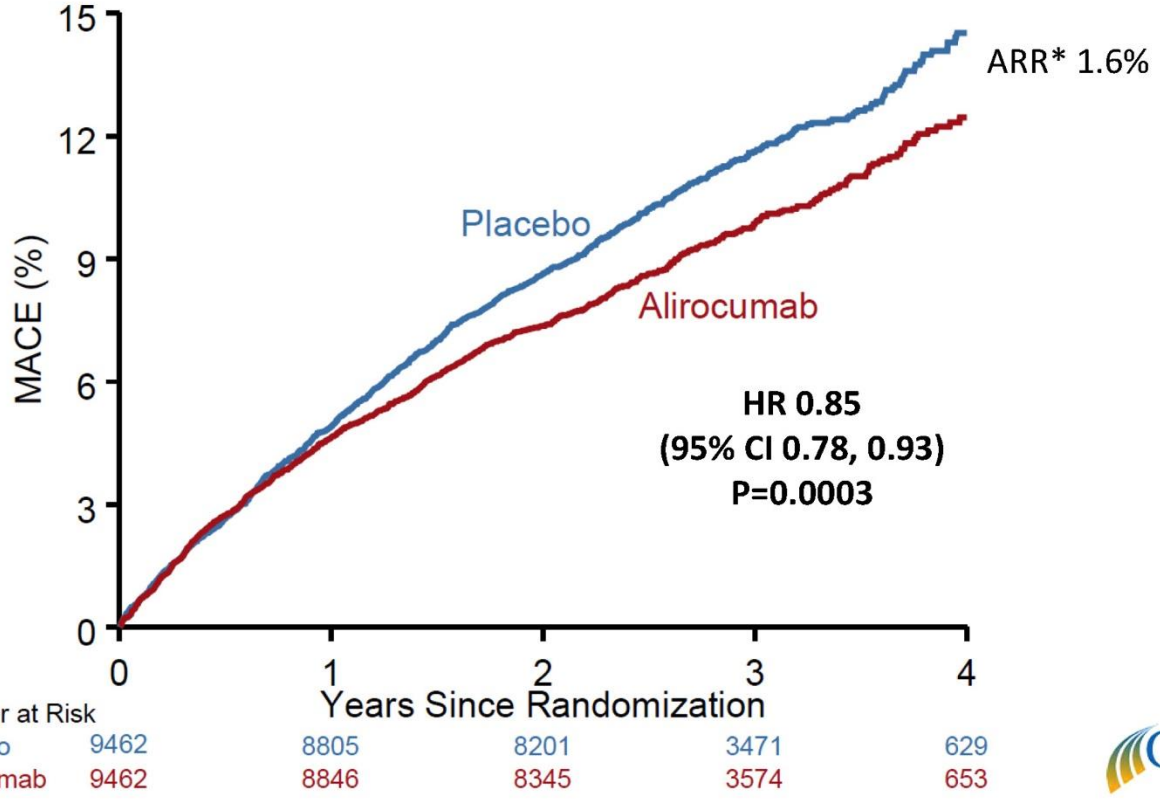
LDL-C: On-Treatment Analysis



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

*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

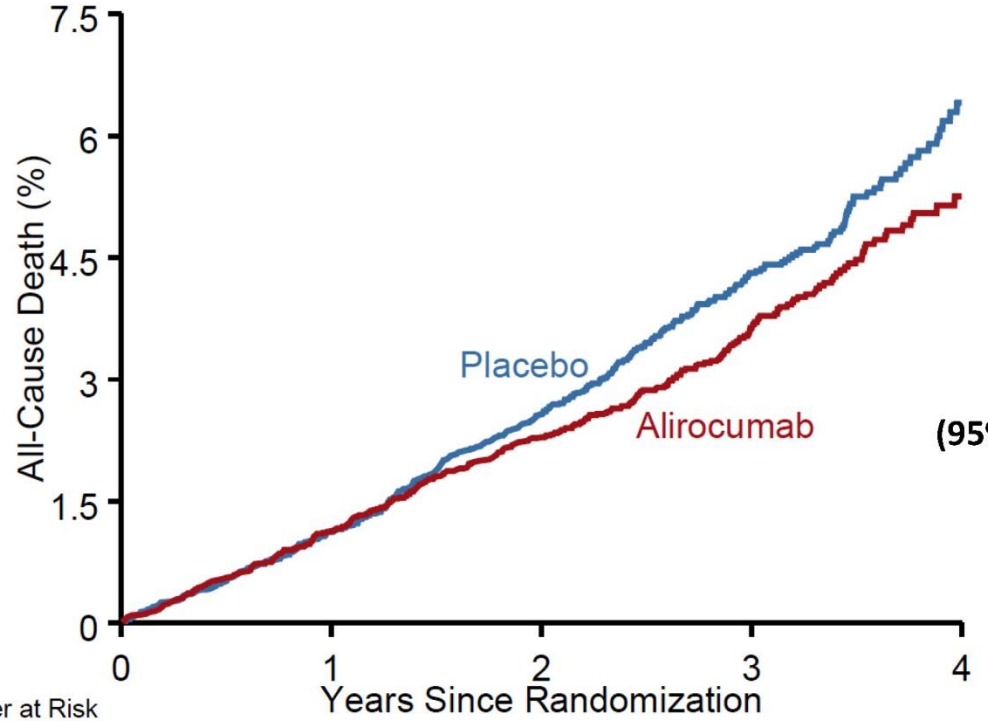
Main Secondary Efficacy Endpoints:
Hierarchical Testing

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

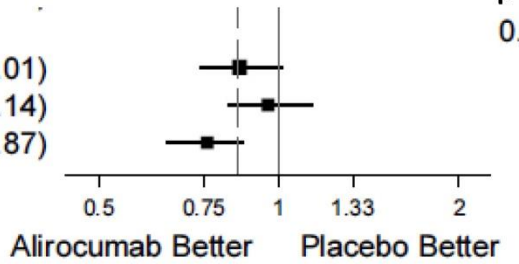


*Nominal P-value
†Based on cumulative incidence

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

Primary Efficacy in Main Prespecified Subgroups

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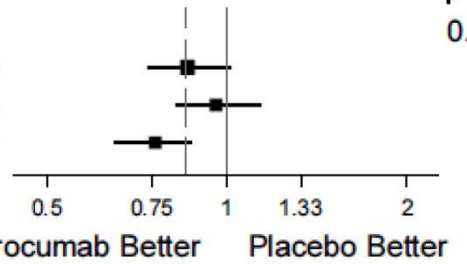
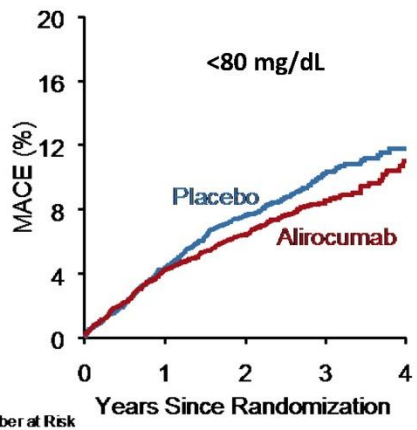
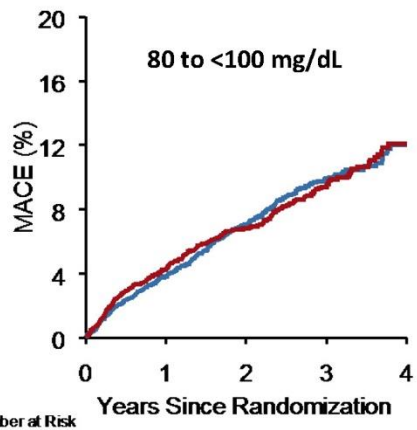


*P-values for interaction



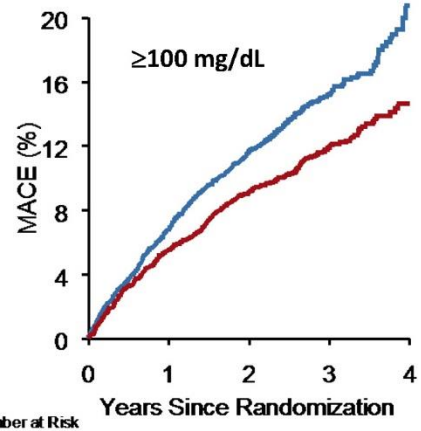
Number at Risk

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



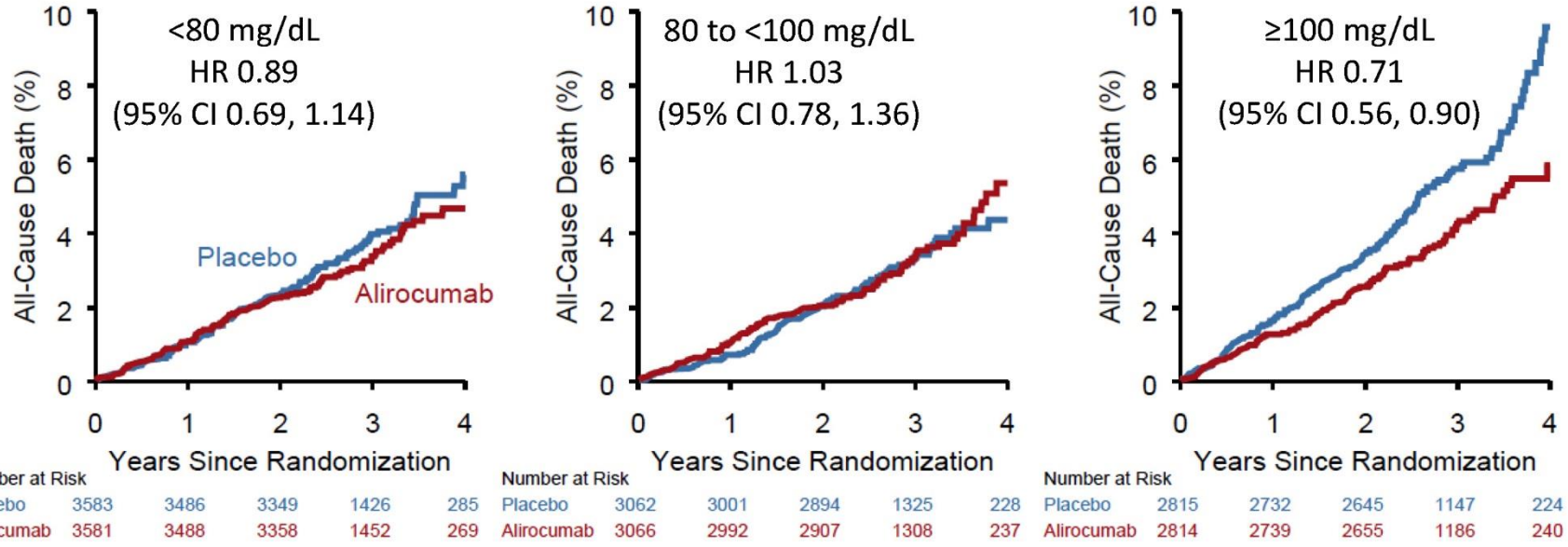
Number at Risk

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

ODYSSEY OUTCOMES

Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR* 1.7% $P_{interaction}$=0.12



*Based on cumulative incidence

ODYSSEY OUTCOMES

Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

Hypertriglyceridemia and Low HDL

- **The subgroup of high TGs and low HDL had benefits with fenofibrate in ACCORD-Lipid even with statins and low LDL**
- **Several recent trials and meta-analyses suggest modest benefits with Omega-3 PUFAs in patients with dyslipidemia**
- **The results with pure EPA in REDUCE-IT were particularly impressive , with 25% reduction in major events and 20% reduction in CV death.**

Bhatt DC et al.NEJM 2018

Elagizi A, Lavie CJ et al.PCVD 2018;61: 76-85

ACCORD Lipid NEJM 2010

REVIEW

MAYO CLINIC

Sea Change for Marine Omega-3s: Randomized Trials Show Fish Oil Reduces Cardiovascular Events

Evan L. O'Keefe, MS; William S. Harris, PhD; James J. DiNicolantonio, PharmD; Andrew Elagizi, MD; Richard V. Milani, MD; Carl J. Lavie, MD; and James H. O'Keefe, MD

Abstract

Recently, 3 large randomized controlled trials (RCTs) have assessed the effects of supplementation with marine omega-3 fatty acids on the occurrence of cardiovascular disease (CVD) events. We reviewed this evidence and considered it in the context of the large and growing body of data on the CV health effects of marine omega-3s. One RCT examining 8179 patients, most with coronary heart disease (CHD), reported that 4 grams/day of a highly purified omega-3 product containing eicosapentaenoic acid (EPA) reduced the risk for major adverse CV events by 25% ($P<.001$). Two other recent RCTs in primary prevention populations showed that approximately 1 gram/day of purified fish oil containing 840 mg/day of EPA and docosahexaenoic acid (DHA) significantly reduced risks of CHD and CV death, especially in individuals who did not consume fish and seafood frequently. The American Heart Association (AHA) continues to emphasize the importance of marine omega-3s as a nutrient for potentially reducing risks of congestive heart failure, CHD, ischemic stroke, and sudden cardiac death. Marine omega-3s should be used in high doses for patients with CHD on statins who have elevated triglycerides and at about 1 gram/day for primary prevention for individuals who do not consume at least 1.5 fish or seafood meals per week.

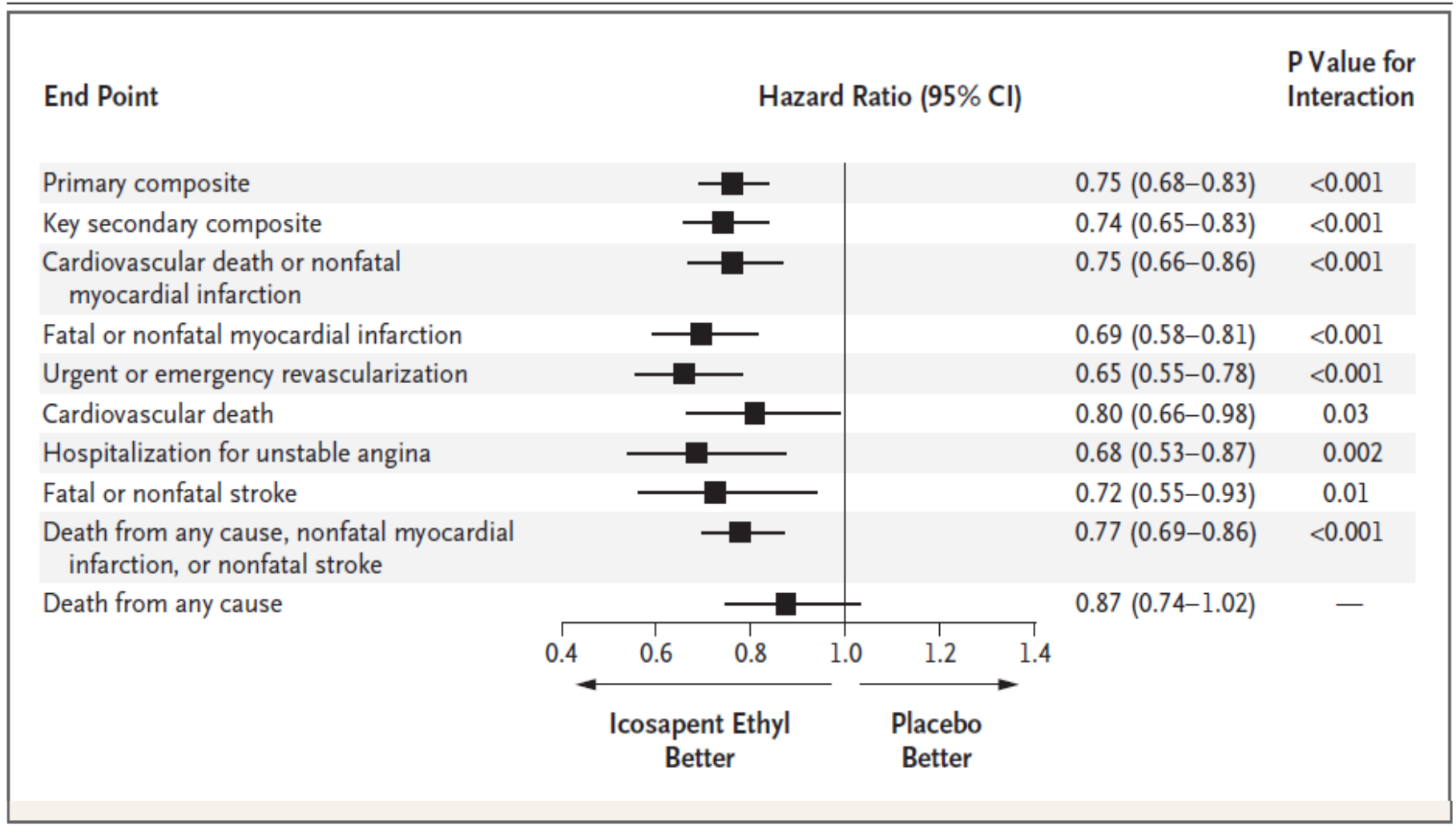
Recent Major Omega-3 RCTs

NEJM

- REDUCE-IT-probably the strongest of all recent lipid trials with agents added to statins
- VITAL-reported as negative , but with some important CHD findings
- ASCEND-also reported as negative in a DM cohort but with some important vascular findings

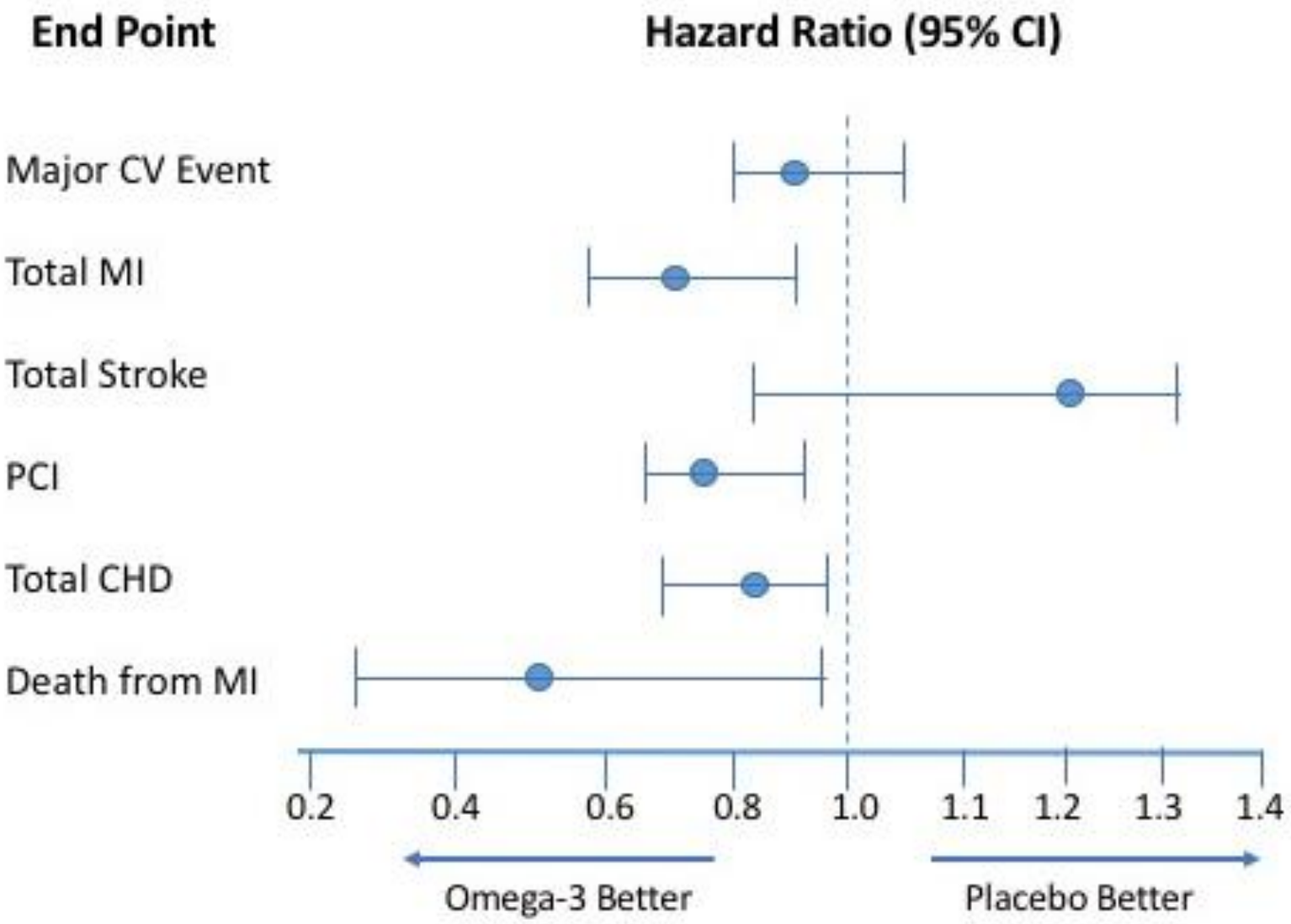
O'Keefe EL, Lavie CJ et al. Mayo Clinic Proc 2019,;94:2524-2533

Benefits of EPA in REDUCE-IT



Bhatt DL et al. NEJM 2018;380:11-22

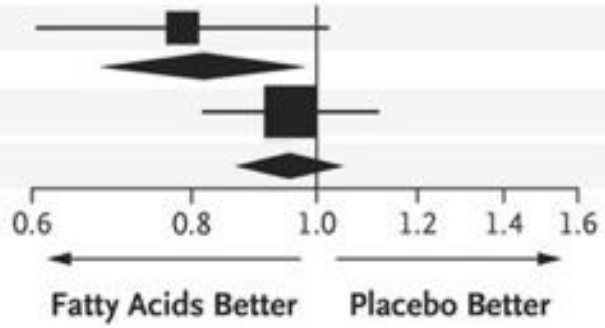
Benefits of Omega-3 in VITAL



Manson JE et al. NEJM 2018; 380: 23-32

Benefits of Omega-3 in ASCEND

Cause of Death	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)
	no. of patients with event (%)		
Coronary	100 (1.3)	127 (1.6)	0.79 (0.61–1.02)
Vascular	**196 (2.5)**	**240 (3.1)**	**0.82 (0.68–0.98)**
Cancer	305 (3.9)	319 (4.1)	0.95 (0.82–1.12)
All causes	**752 (9.7)**	**788 (10.2)**	**0.95 (0.86–1.05)**



Bowmam L et al. NEJM 2018; 379:1540-1550

Bempedoic Acid-New Therapy to Lower LDL-C

- ACL (ATP-Citrate Lyase) inhibitor which reduces LDL-C 15-20% in patients on intensive statins and over 20% in patients not on statins
- Combination of Bembedoic Acid 180 mg with Ezetimide 10 mg, LDL-C is reduces by close to 40%
- Clinical Event Trials on-going with Bempedoic Acid
- Potential less expensive and non-injectable alternative to PCSK9Is for those not meeting LDL-C goals or statin intolerance

Lipids and Diabetes Mellitus

- Patients with DM really need vigorous lipid treatment
- Despite adverse effects on blood sugar, DM patients have profound benefits from statins and intense statins
- Almost all lipid therapies produce greater risk reductions in patients with higher baseline risk
- Generally patients with DM have greater clinical event reductions with statins , fibrates, ezetimibe , PCSK9Is , and EPA, because patients with DM have higher risk
- Clasically, the patient with DM and PAD would particularly benefit from more aggressive lipid therapy

Summary and Conclusions

- The Guidelines emphasize evidence based therapy, especially with statins
- Statins have tremendous evidence in primary and especially secondary prevention
- The Guidelines may lead to under-treatment in the "young elderly" and in high-risk Combined Dyslipidemia and do not emphasize non-statin therapies (including Ezetimibe and PCSK9Is) , but the latter 2 receive attention in recent updates.
- PCSK9Is now have robust clinical data , with quite marked lowering of LDL-C and reduction in clinical events, including mortality and along with ezetimbe are emphasized to get LDL-C < 70 mg/DL

Lipid Case Study

A 55 yo male with DM on metformin, HTN on Ramipril, and former smoker had LAD stent for MI and moderate other disease.Lipids include TC 320, TG280, HDL 30, LDL 244. He did not tolerate Rosuvastatin 20 mg due to myalgias/ myopathy

Non-Lipid Therapies Indicated

- DAPT-Ticagrelor and Baby ASA
- Beta Blocker-Carvedilol
- ACEI/ARB
- SL NTG
- Cardiac Rehab and Exercise
- SGLT2I

Lipid Abnormalities Needing Treatment

- LDL Goal< 70 mg/Dl
- TGs
- HDL
- Non-HDL

Therapies Available for LDL-C

- Statins
- Ezetimide
- Bempedoic Acid
- PCSK9Is

Statins Available for LDL-C

- Intense Statins-Atorvastatin40- 80 mg or Rosuvastatin 20-40 mg
- Did not tolerate Rosuva 20
- Now he REALLY needs statins

Statin Intolerance

- Lower Dose
- Different Agent
- Pravastatin, Fluvastatin, or Pitavastatin may be tolerated but not “potent”
- Try Atorvastatin
- Coenzyme Q 10 200-400 mg/d
- Check Vitamin D (Level 10) and treat

Initial Lipid Therapy

- Vit D 50,000 IU twice weekly for 2 weeks, weekly 6 weeks, biweekly for 6 weeks, then D3 4000 IU daily
- Co Q 10 200-400 mg/d
- Atorvastatin 40 mg, later 80 if tolerated
- Ezetimide 10 mg daily

Repeat Lipids

- On Atorvastatin 80 mg and Ezetimide 10 mg
- TC 195, TG 220, HDL 29, LDL122
- Bempedoic Acid 180 mg/d added
- Repeat lipids TC 165, TG 205, HDL 30, LDL 94

Other Options for LDL-C

- Very Intensive Low Fat Diet
- Evolocumab-140 mg every 2 weeks or 420 mg monthly
- Alirocumab -75 or 150 mg every 2 weeks

PCSK9 Inhibitor Added

- Evolocumab-420 mg monthly added
- TC 95,TG 210, HDL31, LDL22
- Consider reducing lipid intensity???
- Bempedoic Acid could be first eliminated as currently there is no proven event reduction
- Acceptable , however, to leave LDL< 25!

What About TGs

- Lipids off Bempedoic Acid now TC 112, TG 225, HDL 30, LDL 37
- Combined EPA/DHA
- Pure EPA
- Fenofibrate

Omega-3 and Major Cardiovascular Outcomes

MAYO CLINIC

ORIGINAL ARTICLE

Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials

Aldo A. Bernasconi, PhD; Michelle M. Wiest, PhD; Carl J. Lavie, MD; Richard V. Milani, MD; and Jari A. Laukkanen, MD, PhD

Abstract

Objectives: To quantify the effect of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on cardiovascular disease (CVD) prevention and the effect of dosage.

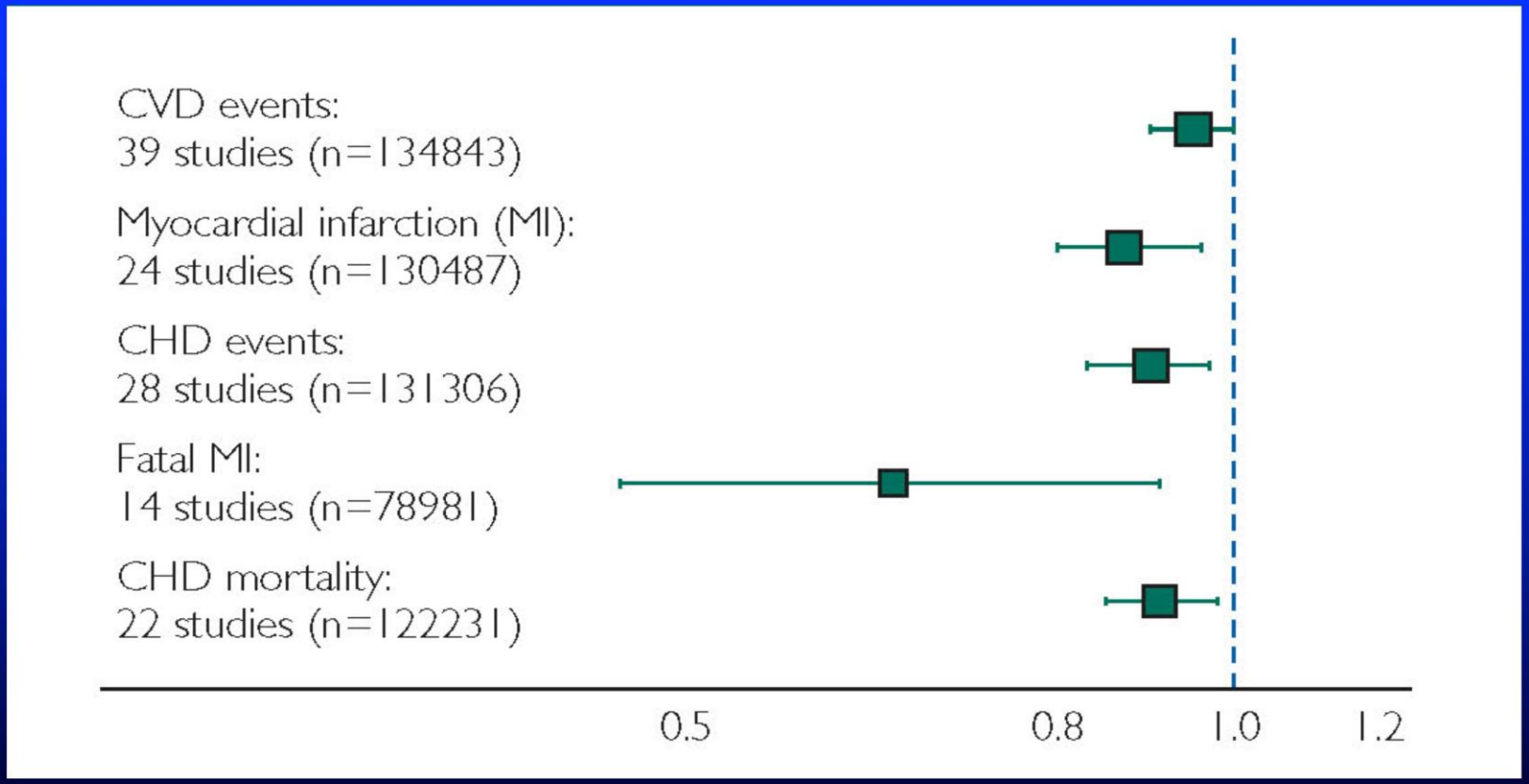
Methods: This study is designed as a random effects meta-analysis and meta-regression of randomized control trials with EPA/DHA supplementation. This is an update and expanded analysis of a previously published meta-analysis which covers all randomized control trials with EPA/DHA interventions and cardiovascular outcomes published before August 2019. The outcomes included are myocardial infarction (MI), coronary heart disease (CHD) events, CVD events (a composite of MI, angina, stroke, heart failure, peripheral arterial disease, sudden death, and non-scheduled cardiovascular surgical interventions), CHD mortality and fatal MI. The strength of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation framework.

Results: A total of 40 studies with a combined 135,267 participants were included. Supplementation was associated with reduced risk of MI (relative risk [RR], 0.87; 95% CI, 0.80 to 0.96), high certainty number needed to treat (NNT) of 272; CHD events (RR, 0.90; 95% CI, 0.84 to 0.97), high certainty NNT of 192; fatal MI (RR, 0.65; 95% CI, 0.46 to 0.91]), moderate certainty NNT = 128; and CHD mortality (RR, 0.91; 95% CI, 0.85 to 0.98), low certainty NNT = 431, but not CVD events (RR, 0.95; 95% CI, 0.90 to 1.00). The effect is dose dependent for CVD events and MI.

Conclusion: Cardiovascular disease remains the leading cause of death worldwide. Supplementation with EPA and DHA is an effective lifestyle strategy for CVD prevention, and the protective effect probably increases with dosage.

 ■ Mayo Clin Proc. 2020;■■(■):1-10

Omega-3 EPA/DHA and Major Cardiovascular Outcomes



Benasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2020; online Sept 17

Meta-Analysis of Omega-3 RCTs of Supplements

- Major Reductions in Clinical Events
- 35 % reduced risk of Fatal MI (NNT=128)
- 13% reduced risk of MI (NNT= 272)
- 10% reduced risk of CHD Events(NNT=192)
- 9 % reduced risk of Fatal CHD (NNT=431)
- CVD events reduced 5% (CI 0.90-1.00)

Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2021;96:304-313

Updated Meta-Analysis of Omega-3 RCTs of Supplements
EPA vs EPA/DHA

- Added STRENGTH and OMEMI; 42 studies; N=149,359
- Only CVD events and CHD Events changed
- CVD Events now reduced 4% ; p=0.05
- CHD events reduced 9%; p< 0.05
- Each 1 g/d EPA/DHA reduced MI by an additional 9 %

Bernasconi AA, Lavie CJ, et al. Mayo Clin Proc 2021, In Press

Updated Meta-Analysis of Omega-3 RCTs of Supplements
EPA vs EPA/DHA

- Added STRENGTH and OMEMI; 42 studies; N=149,359
- Reduced Fatal MI 35%
- Reduced MI 13%
- Reduced both CHD events and CHD mortality 9%
- Borderline 4% reduction in CVD events
- Still VERY SIGNIFICANT Omega-3 Benefits

Bernasconi AA, Lavie CJ, et al. Mayo Clin Proc 2021, In Press

What About TGs

- Lipids off Bempedoic Acid now TC 112, TG 225, HDL 30, LDL 37
- Combined EPA/DHA
- Pure EPA
- Fenofibrate

What About HDL

- Probably not nicotinic acid
- Exercise, weight loss
- Low dose alcohol??


T
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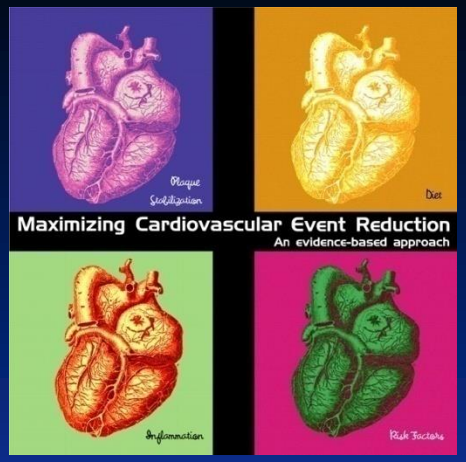
WELLS FARGO
We're on Track For a Cure



Intensive Lipid Intervention-Status 2021

Carl J. Lavie, MD,FACC,FACP,FCCP

Professor of Medicine

Medical-Director, Preventive Cardiology

John Ochsner Heart and Vascular Inst.

Ochsner Clinical School-The UQ School of Medicine, New Orleans, LA