ACC Latin America Conference 2018

In partnership with:

Lipid Management 2018: Creating Harmony in an Ever-Changing Landscape of Guidelines

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Vice-Chair, ACC Annual Scientific Sessions

Disclosures

- *Advisory Board:* Akcea, Amgen, Sanofi/Regeneron

Objectives

- Provide overview of evidence for benefits of statin and non-statin therapies in ASCVD risk reduction
- Compare and contrast 2 major PCSK9 inhibitor CV outcomes trials
- Identify major groups of patients who have demonstrated benefit with non-statin therapies
- Discuss changes to new 2018 ACC/AHA lipid guidelines

Lowering LDL-C Reduces ASCVD

Study	Statin	Mean Baseline LDL-C	Mean LDL-C Reduction	% Reduction in Coronary Events
WOSCOP				
4S				1)
CARE	Pravastatin 40mg			24 (P = 0.003)
LIPID	Pravastatin 40mg	150	25	24 (P <0.0001)

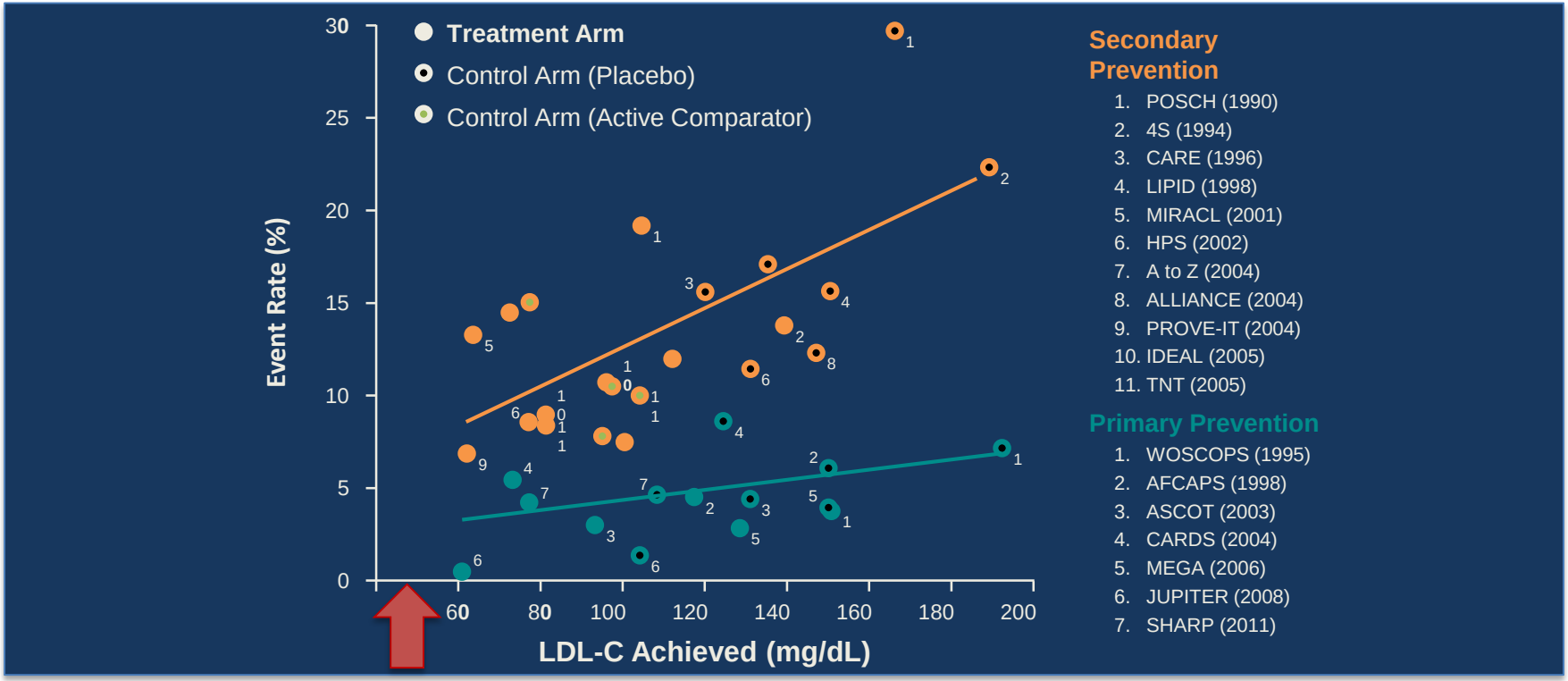
Statins are the mainstay of therapy.

CTTC meta-analysis showed ***20%-25%*** reduction in major CV end points for every ***1 mmol/liter (39 mg/dl)*** reduction in LDL-C*

Table adapted from Maron DJ, et al. *Circulation*. 2000;101:207-213

*CTTC. *Lancet*. 2010; 376(9753):1670-1681

Major Lipid Trials: LDL-C Achieved vs Rates of Coronary Events



Secondary Prevention

1. POSCH (1990)
2. 4S (1994)
3. CARE (1996)
4. LIPID (1998)
5. MIRACL (2001)
6. HPS (2002)
7. A to Z (2004)
8. ALLIANCE (2004)
9. PROVE-IT (2004)
10. IDEAL (2005)
11. TNT (2005)

Primary Prevention

1. WOSCOPS (1995)
2. AFCAPS (1998)
3. ASCOT (2003)
4. CARDS (2004)
5. MEGA (2006)
6. JUPITER (2008)
7. SHARP (2011)

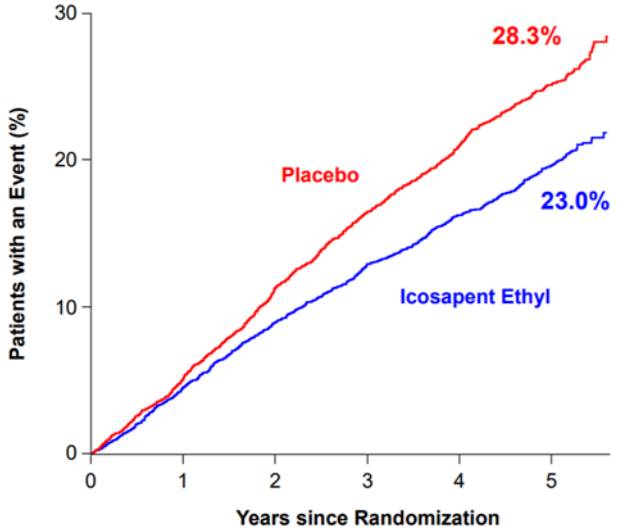
Adapted from Raymond C, et al. *Clev Clin J Med*. 2014;81:11-19.

Evolving Evidence, Evolving Guidance

Primary End Point:

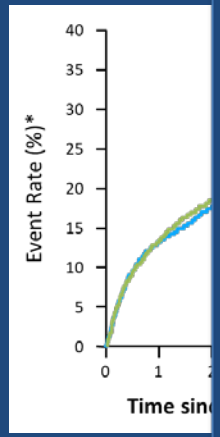
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

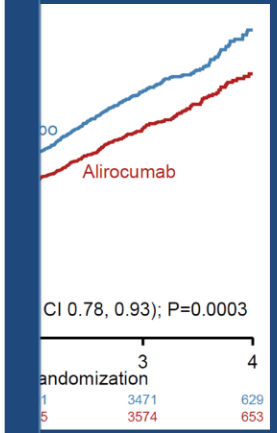
reduce-it



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018. Bhatt DL. AHA 2018, Chicago.





IMP

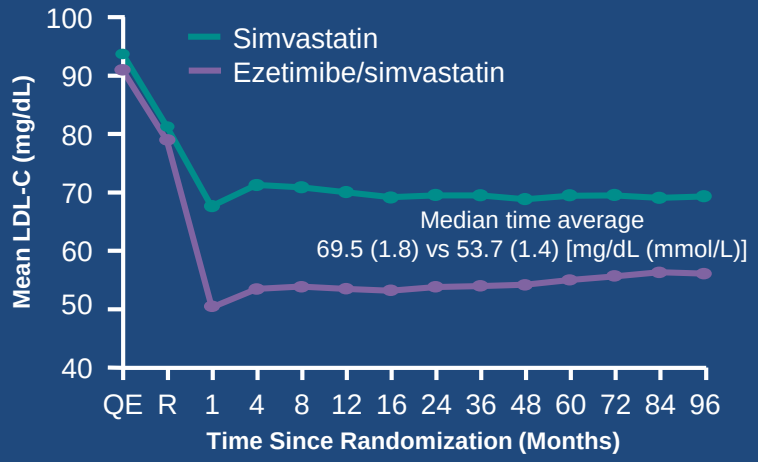
mes[3]

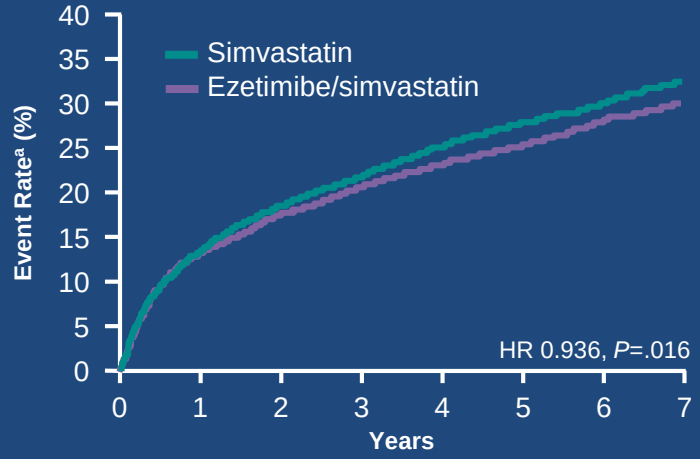
1. Cannon CP, et al. *N Engl J Me*
2. Sabatine MS, et al. *N Engl J M*
3. Steg PG. Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab - ODYSSEY OUTCOMES. March 10, 2018. http://www.acc.org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes.

Impact of Ezetimibe in ACS

IMPROVE-IT Study

18,144 ACS patients randomized to simvastatin (40 mg QHS) or simvastatin/ezetimibe (40 mg/10 mg QHS) for 7 years





Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-97.

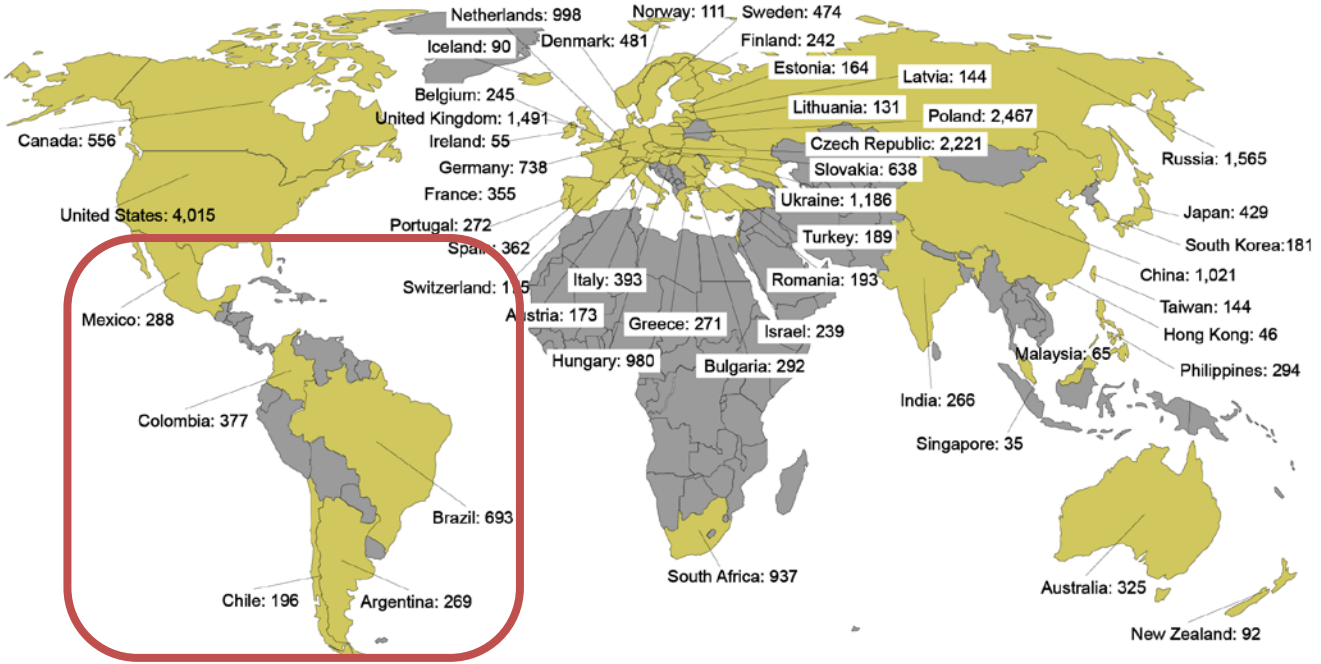
Key PCSK9 Inhibitor CV Outcomes Trials

	Evolocumab (AMG 145)	Alirocumab (SAR236553 / REGN727)
Trial	**FOURIER**	**ODYSSEY Outcomes**
Sample size	27,564	18,924
Patients	Stable ASCVD (MI, stroke, or PAD) with high-risk features	4-52 weeks post-ACS
Age	63	58
Statin **High-intensity statin** **No statin**	Atorvastatin ≥20 mg or equivalent 69% 0.2%	Evidence-based medical Rx 89% 2.5%
LDL-C mg/dL (mmol/L): inclusion **Baseline LDL-C mg/dL (mmol/L)**	≥70 (≥1.8) 92 (2.4)	≥70 (≥1.8) 87 (2.3)
PCSK9 inhibitor dosing	Q2W or Q4W	Q2W
Endpoint	1°: CV death, MI, stroke, revascularization, or hospitalization for UA Key 2°: CV death, MI, or stroke	CHD death, MI, ischemic stroke, or hospitalization for UA
Follow-up	26 months	34 months

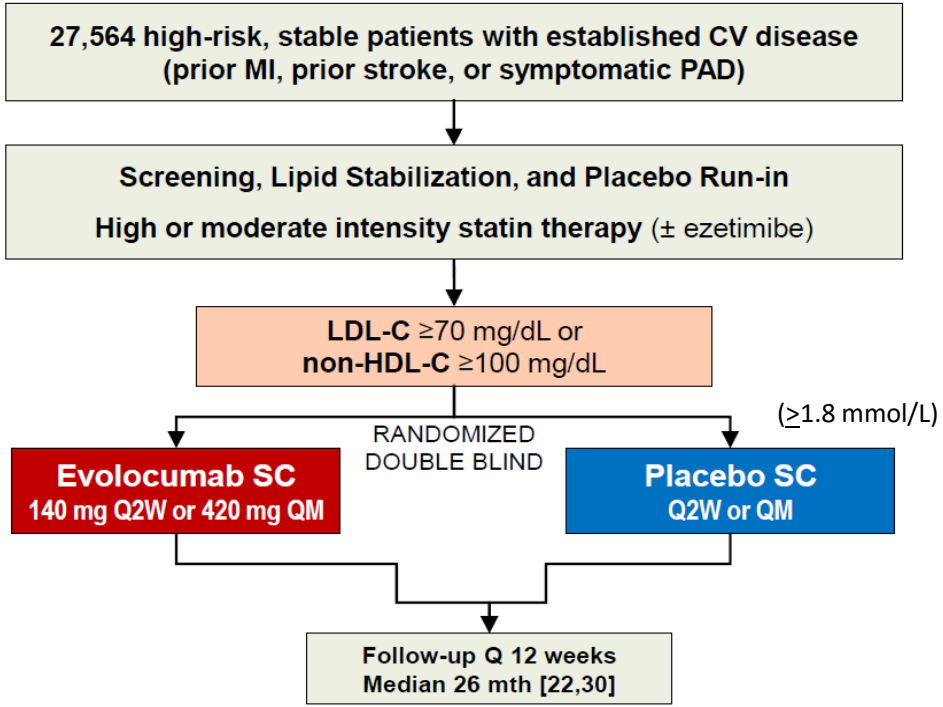
Ridker PM, et al. *N Engl J Med*. 2017;376(16):1527-39; Sabatine MS, et al. *Am Heart J.* 2016;173:94-101; DOI: 10.1056/NEJMoa1801174

Global Enrollment

27,564 patients randomized at 1242 sites
in 49 countries between 2/2013 – 6/2015

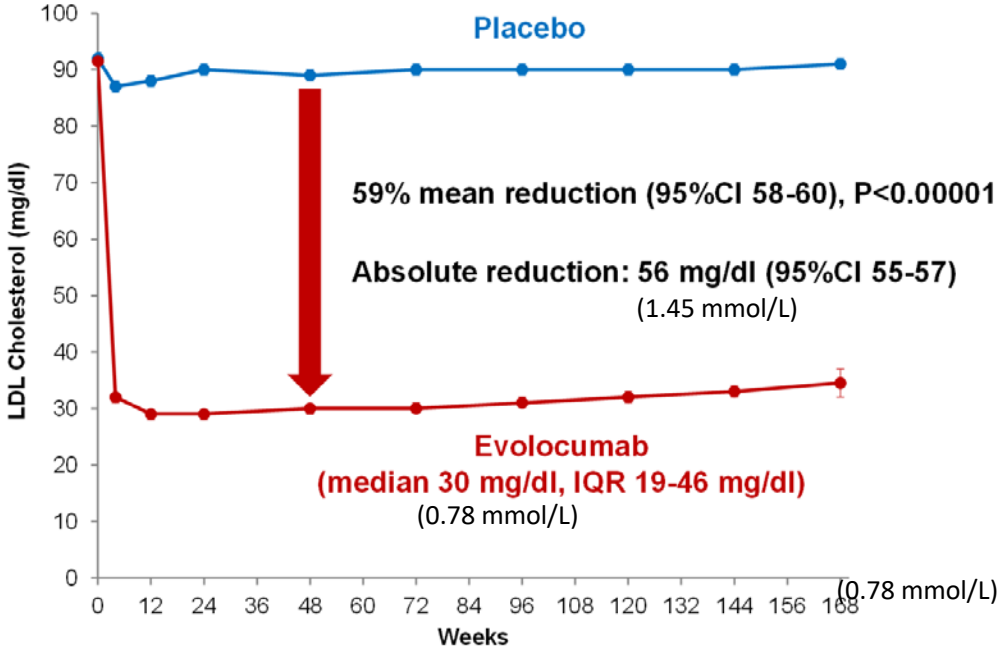


FOURIER Trial Design



Sabatine MS et al. *Am Heart J* 2016;173:94-101

LDL Cholesterol

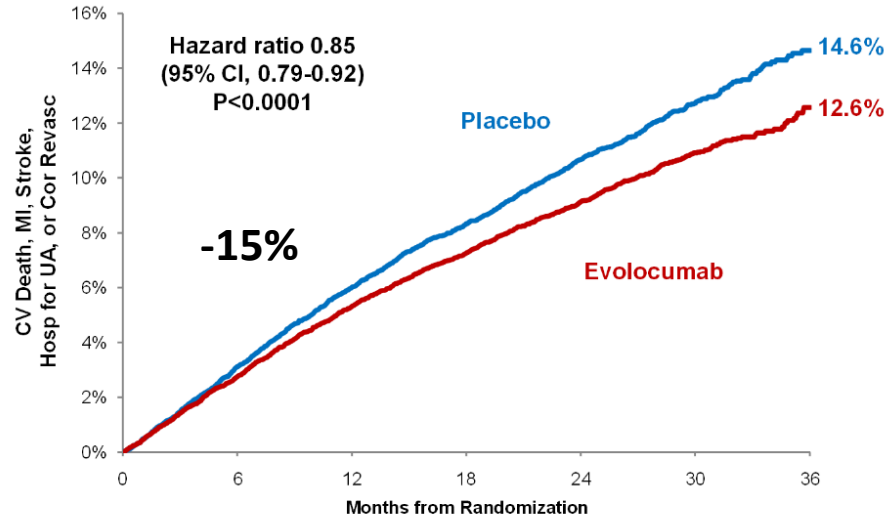


(0.78 mmol/L)

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

Sabatine MS et al. *N Engl J Med.* 2017;376:1713-22.

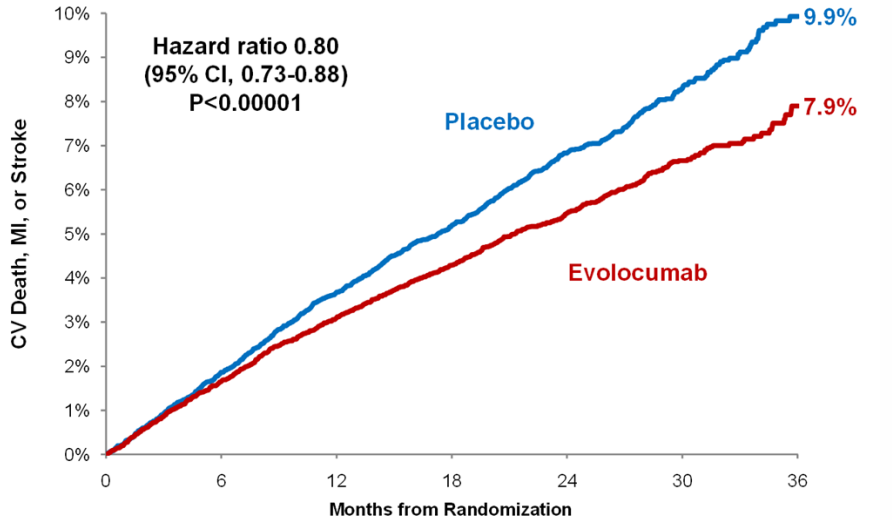
Primary Endpoint



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

Sabatine MS et al. *N Engl J Med.* 2017;376:1713-22.

Key Secondary Endpoint

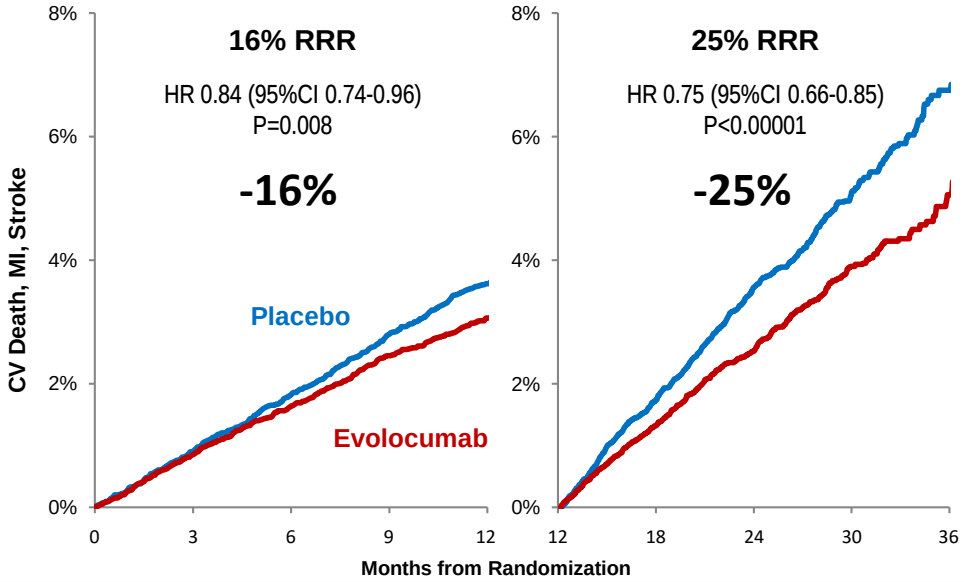


An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

Sabatine MS et al. *N Engl J Med.* 2017;376:1713-22.

Evolocumab in Stable, High-Risk ASCVD

Landmark Analysis



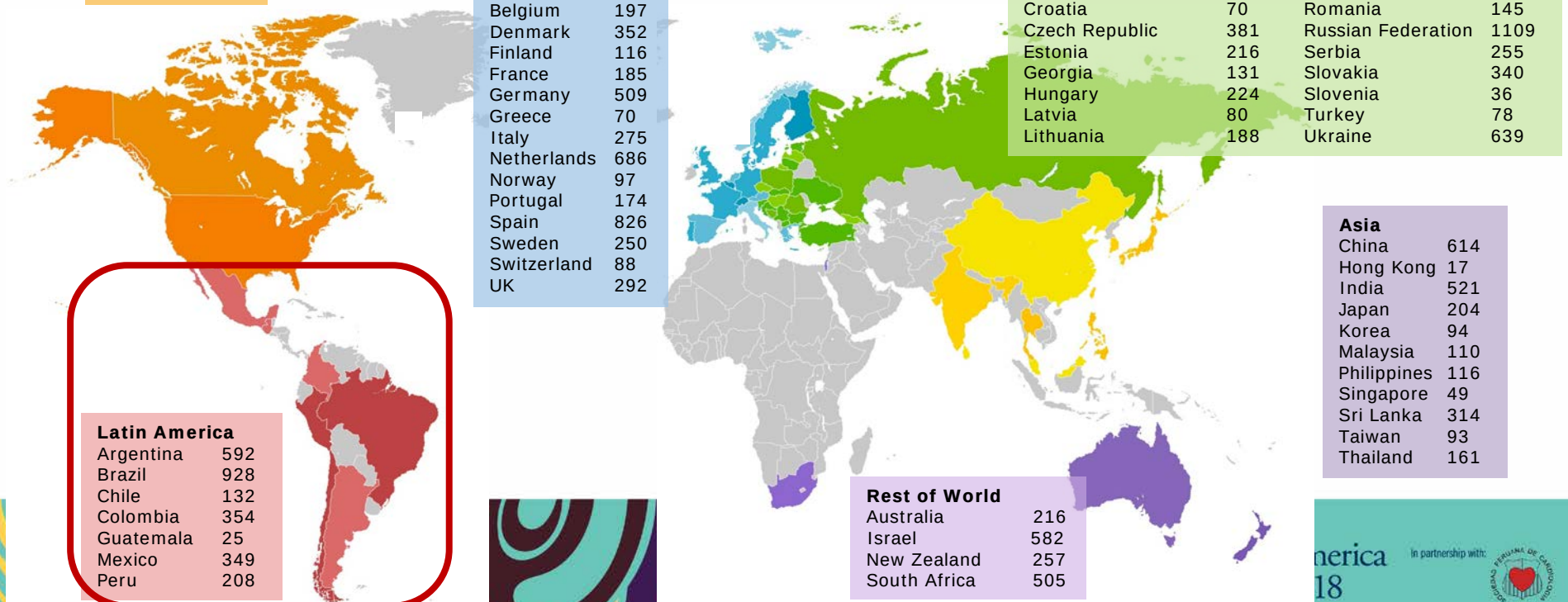
Sabatine MS, et al. *N Engl J Med*. 2017;376(18):1713-22.

ODYSSEY OUTCOMES:

18,924 patients randomized at 1315 sites in 57 countries

Nov 2, 2012 – Nov 11, 2017

ODYSSEY OUTCOMES



Canada / USA	
Canada	361
US	2511

Western Europe	
Austria	58
Belgium	197
Denmark	352
Finland	116
France	185
Germany	509
Greece	70
Italy	275
Netherlands	686
Norway	97
Portugal	174
Spain	826
Sweden	250
Switzerland	88
UK	292

Central / Eastern Europe			
Bosnia–Herzegovina	156	Macedonia	132
Bulgaria	333	Poland	926
Croatia	70	Romania	145
Czech Republic	381	Russian Federation	1109
Estonia	216	Serbia	255
Georgia	131	Slovakia	340
Hungary	224	Slovenia	36
Latvia	80	Turkey	78
Lithuania	188	Ukraine	639

Asia	
China	614
Hong Kong	17
India	521
Japan	204
Korea	94
Malaysia	110
Philippines	116
Singapore	49
Sri Lanka	314
Taiwan	93
Thailand	161

Latin America	
Argentina	592
Brazil	928
Chile	132
Colombia	354
Guatemala	25
Mexico	349
Peru	208

Rest of World	
Australia	216
Israel	582
New Zealand	257
South Africa	505

nerica
18

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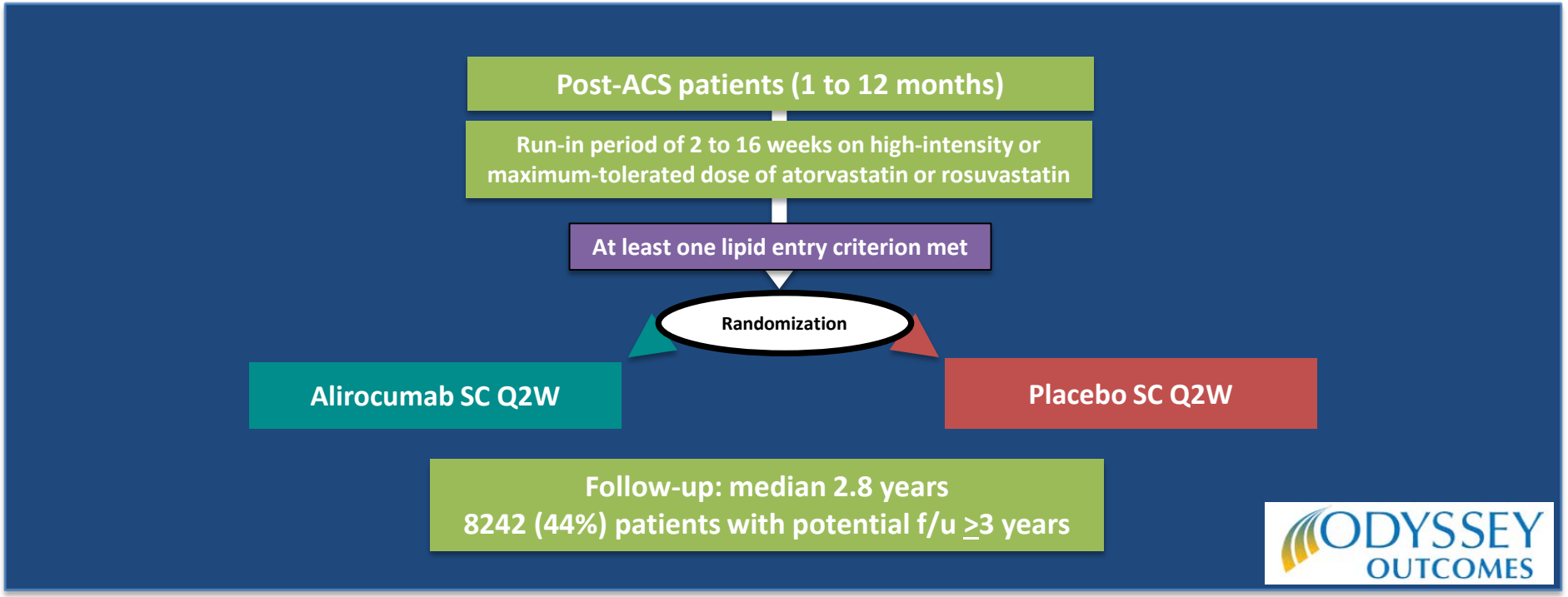
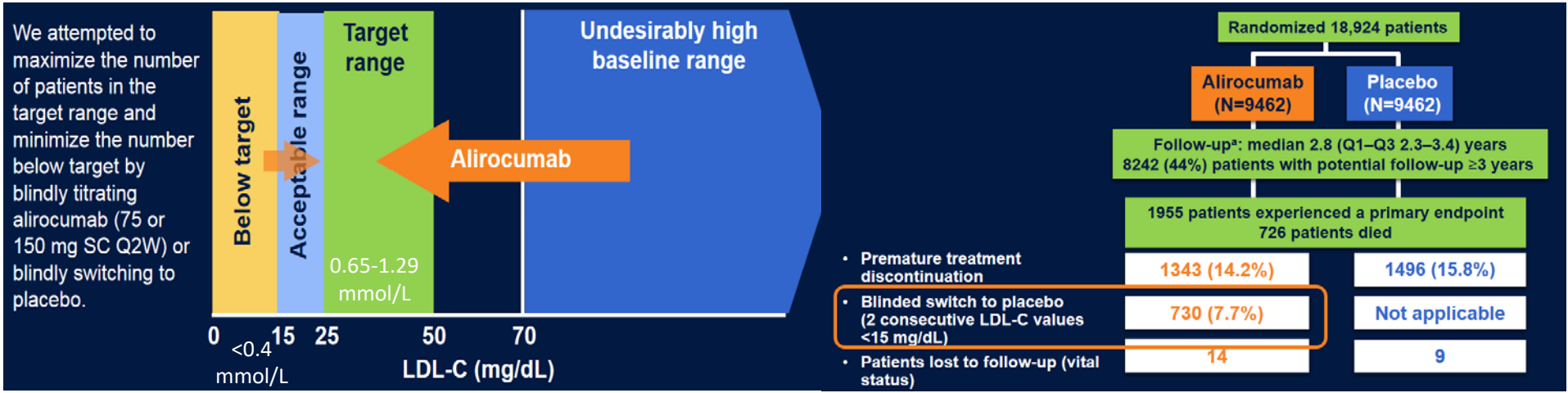
ODYSSEY Outcomes: Treatment Assignment



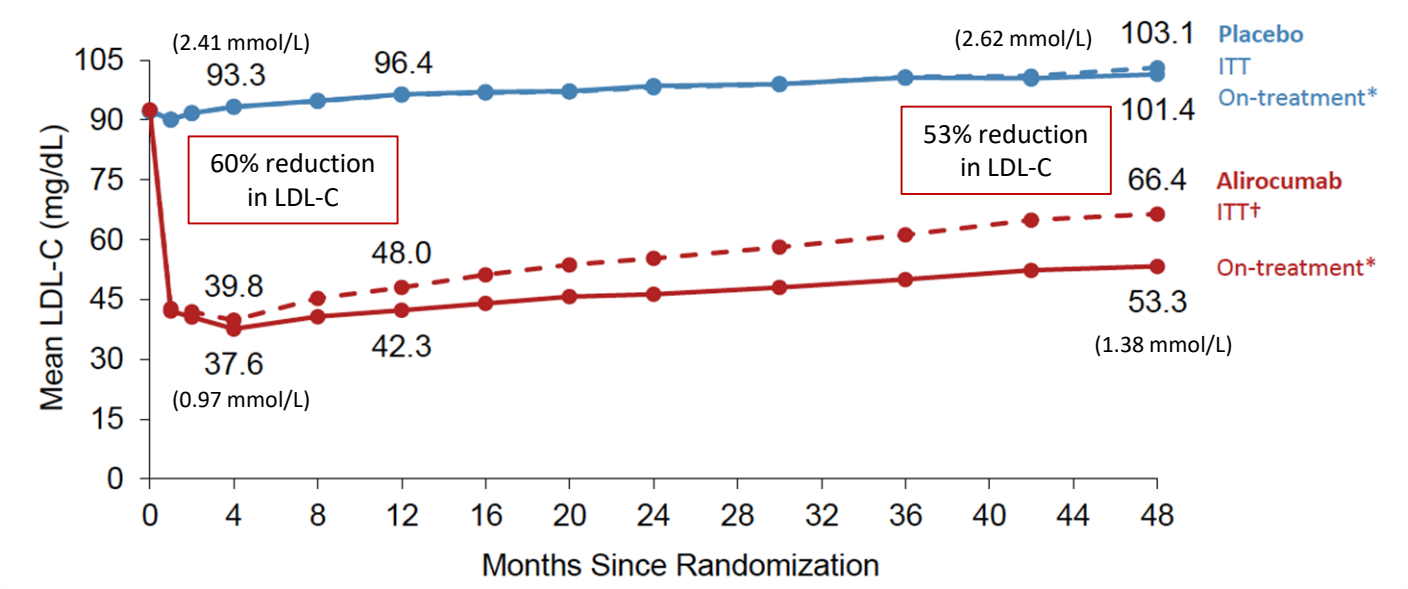
OPEN ACCESS: Schwartz GG, et al. *Am Heart J.* 2014;168(5):682-9.e1.

ODYSSEY Outcomes: A Target Range for LDL-C



OPEN ACCESS: Schwartz GG, et al. *Am Heart J.* 2014;168(5):682-9.e1.

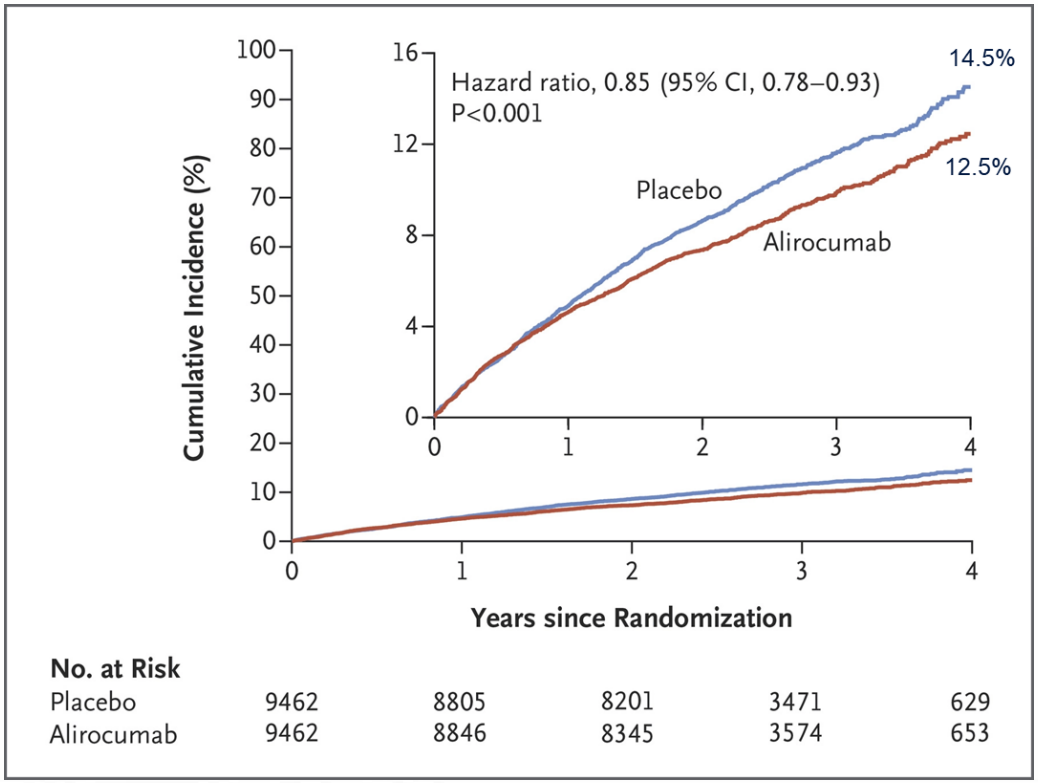
LDL-C: Intent-to-Treat and On-Treatment Analyses



DOI: 10.1056/NEJMoa1801174

Primary Efficacy Endpoint: MACE

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



RRR: -15%

ARR[a]: 2.0%

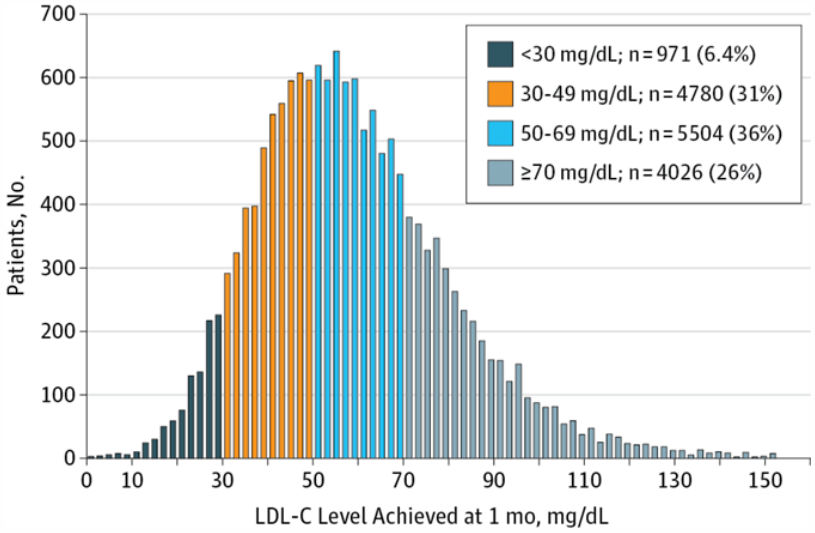
[a]Based on cumulative incidence

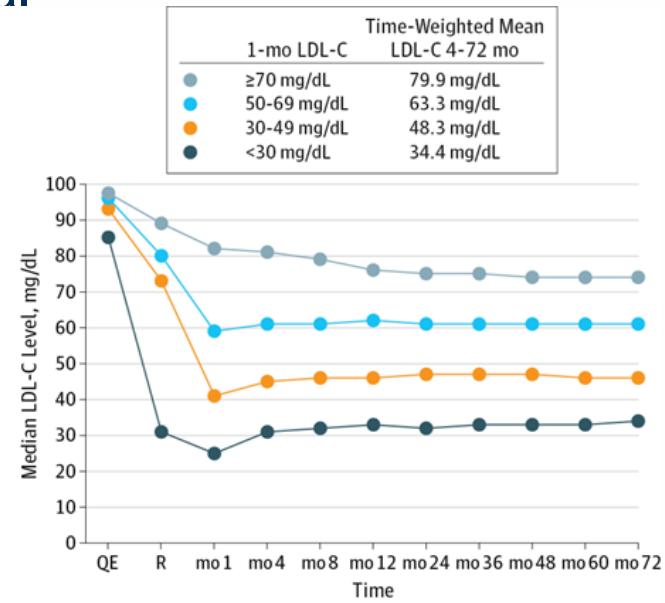
DOI: 10.1056/NEJMoa1801174

Evolving Evidence and Identifying the High-risk Patient

- Achieved LDL-C level
- Diabetes
- Prior MI
- MI Size and Type
- Extent of CAD
- PAD
- Lp(a)

Long-term Safety and Efficacy of Achieving Very Low Levels of LDL-C
A Prespecified Analysis of the IMPROVE-IT Trial





No. at risk

≥70 mg/dL	3992	3951	4026	3697	3427	3221	2848	2568	2404	2006	1547
50-69 mg/dL	5472	5430	5504	5229	4941	4728	4273	3940	3636	3062	2318
30-49 mg/dL	4744	4733	4780	4528	4283	4073	3730	3414	3167	2638	2066
<30 mg/dL	961	964	971	916	868	832	755	699	661	525	411

JAMA Cardiol. 2017;2(5):547-555. doi:10.1001/jamacardio.2017.0083

Long-term Safety and Efficacy of Achieving Very Low Levels of LDL-C
A Prespecified Analysis of the IMPROVE-IT Trial

Table 2. Safety Events by Achieved LDL-C Level at 1 Month[a]

Prespecified Safety End Points	Achieved LDL-C Level (mg/dL) at 1 mo, No. (%) of Patients				*P* Value for Trend
	<30 (n = 971)	30-49 (n = 4780)	50-69 (n = 5504)	≥70 (n = 4026)	
Adverse event leading to drug discontinuation	92 (9.5)	451 (9.4)	470 (8.5)	354 (8.8)	.21
Rhabdomyolysis, myopathy, or myalgias with CK elevation >5 times ULN[b]	4 (0.4)	30 (0.6)	26 (0.5)	25 (0.6)	.81
Rhabdomyolysis or myopathy[b]	0	13 (0.3)	9 (0.2)	15 (0.4)	.12
Rhabdomyolysis[b]	0	6 (0.1)	7 (0.1)	8 (0.2)	.16
AST or ALT above 3 times ULN	21 (2.2)	97 (2.0)	97 (1.8)	84 (2.1)	.88
Gall bladder adverse event	35 (3.6)	155 (3.2)	200 (3.6)	145 (3.6)	.48
Neurocognitive adverse events	20 (2.1)	121 (2.5)	158 (2.9)	91 (2.3)	.95
Short-term[c]	12 (1.2)	61 (1.3)	91 (1.7)	48 (1.2)	.98
Longer-term[d]	8 (0.8)	60 (1.3)	67 (1.2)	43 (1.1)	.89
Hemorrhagic stroke[b]	3 (0.3)	41 (0.9)	23 (0.4)	25 (0.6)	.50
Hospitalization for heart failure	45 (4.6)	200 (4.2)	189 (3.4)	148 (3.7)	.06
Noncardiovascular death[b]	56 (5.8)	244 (5.1)	310 (5.6)	197 (4.9)	.50
Cancer[b]	87 (9.0)	413 (8.6)	477 (8.7)	300 (7.5)	.04

JAMA Cardiol. 2017;2(5):547-555. doi:10.1001/jamacardio.2017.0083

FOURIER: Efficacy and safety of very low levels of LDL-C with evolocumab

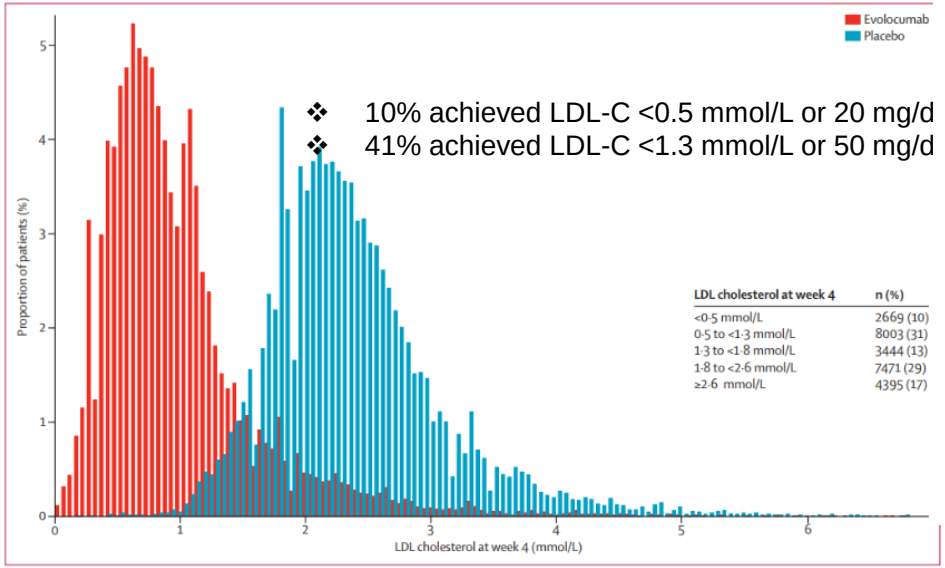
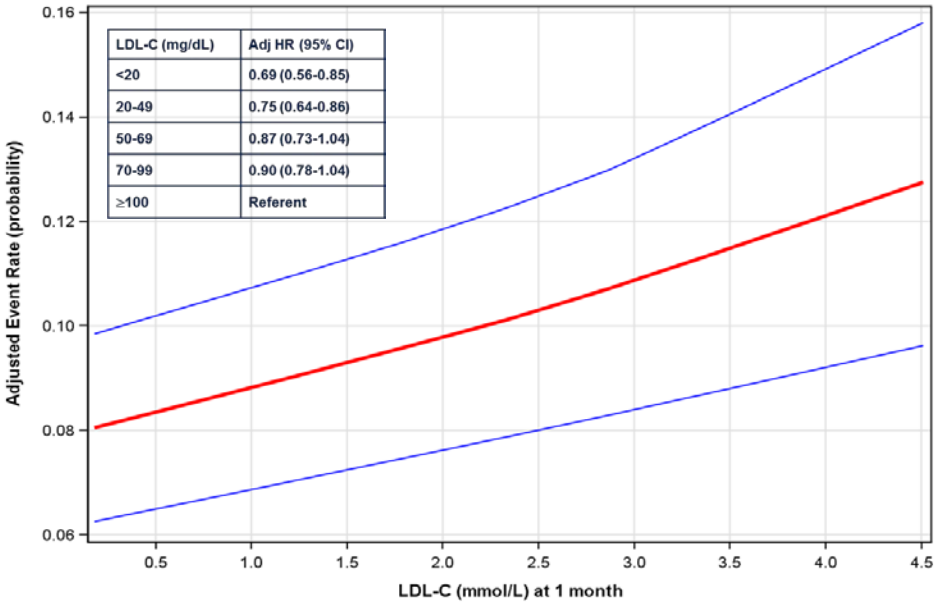


Figure 1: Distribution of achieved LDL-cholesterol concentrations at 4 weeks in patients who did not have a primary efficacy or prespecified safety event before the study
Red bars are evolocumab (median 0·8 mmol/L, IQR 0·5–1·2). Blue bars are placebo (median 2·2 mmol/L, IQR 1·9–2·7).

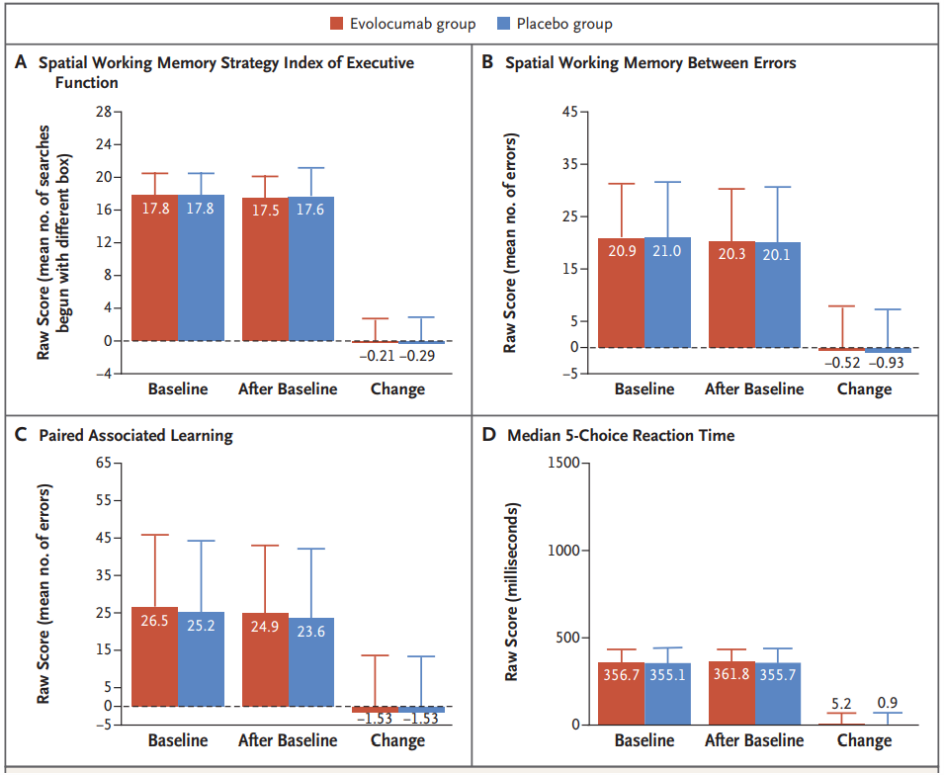
Giugliano RP, et al. *Lancet*. 2017;390(10106):1962-71.



- Monotonic relationship between achieved LDL-C and CVOTs down to LDL-C <0.2 mmol/L (<10 mg/dL).
- No safety concerns with very low LDL-C levels over a median of 2.2 years.

EBBINGHAUS Study of cognitive function during treatment with evolocumab

- Subgroup of FOURIER
- 1204 patients, 19 months
- Assessed cognitive function during treatment
  - Cambridge Neuropsychological Test Automated Battery
- No significant differences

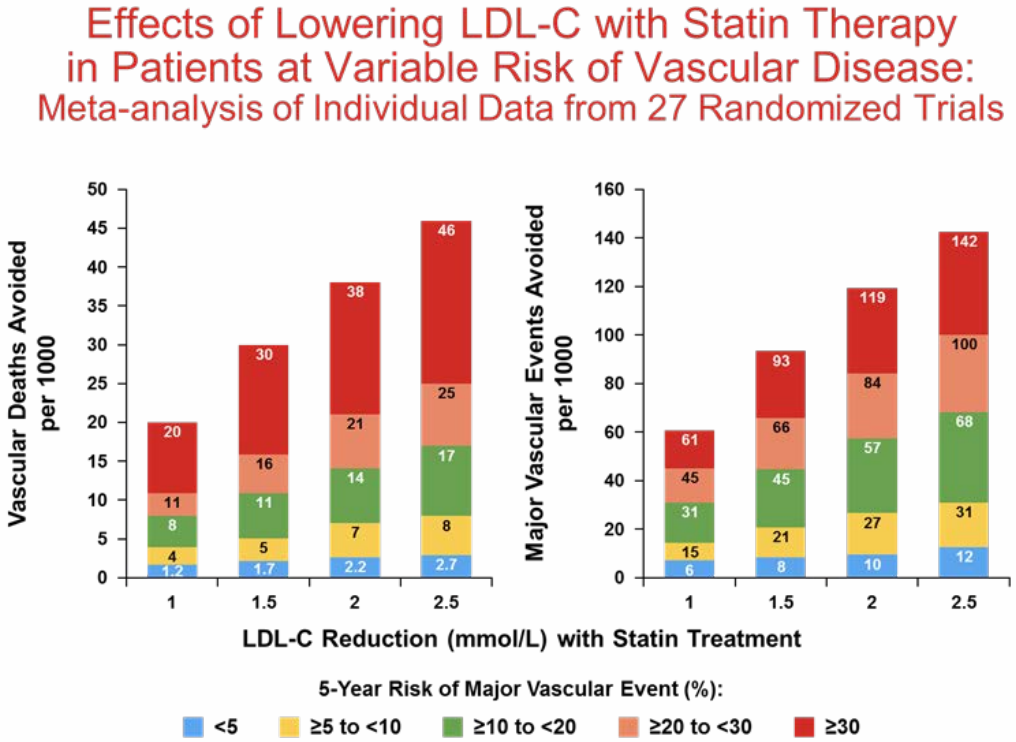


N Engl J Med 2017;377:633-43.

What did the RCTs demonstrate? Identifying the high-risk patient

ASCVD Risk Reduction Is Proportional To Baseline Risk

- Reduction in ASCVD events is related to the
  - Extent of LDL-C reduction
  - Baseline level of risk
- Greatest *absolute* number of events avoided in pts at greatest risk



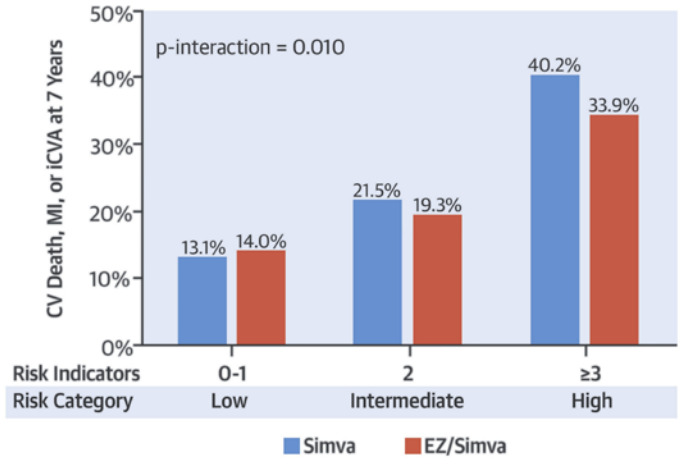
Cholesterol Treatment Trialists' (CTT) Collaborators, et al. Lancet. 2012;380:581-590.

IMPROVE-IT: Addition of ezetimibe to moderate-intensity statin post-ACS

- Characteristics that identified patients most likely to benefit
  - History of CHF
  - HTN
  - Age ≥75 yrs
  - Diabetes
  - Prior stroke
  - Prior CABG
  - PAD
  - eGFR <60
  - Smoking

CENTRAL ILLUSTRATION: TRS 2°P

TRS 2°P Risk Indicators	Points
CHF	1
HTN	1
Age ≥75	1
DM	1
Prior Stroke	1
Prior CABG	1
PAD	1
eGFR <60	1
Smoking	1
Maximum Possible	9



Bohula, E.A. et al. J Am Coll Cardiol. 2017;69(8):911-21.

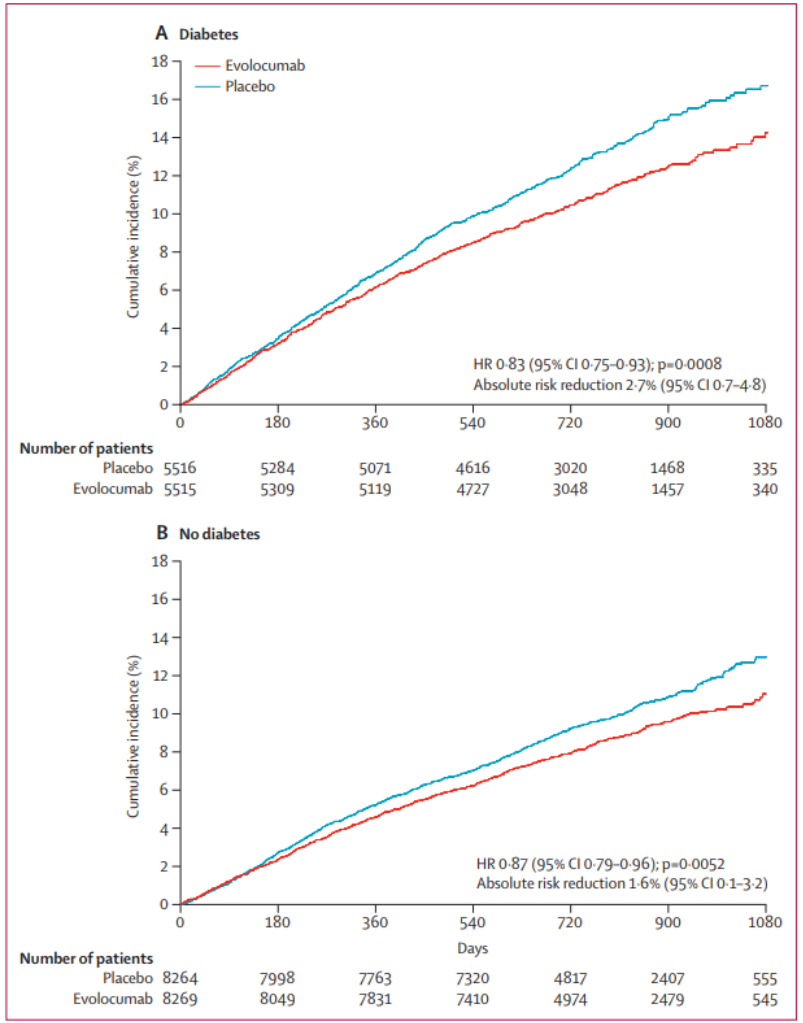


Figure 2: Primary endpoint

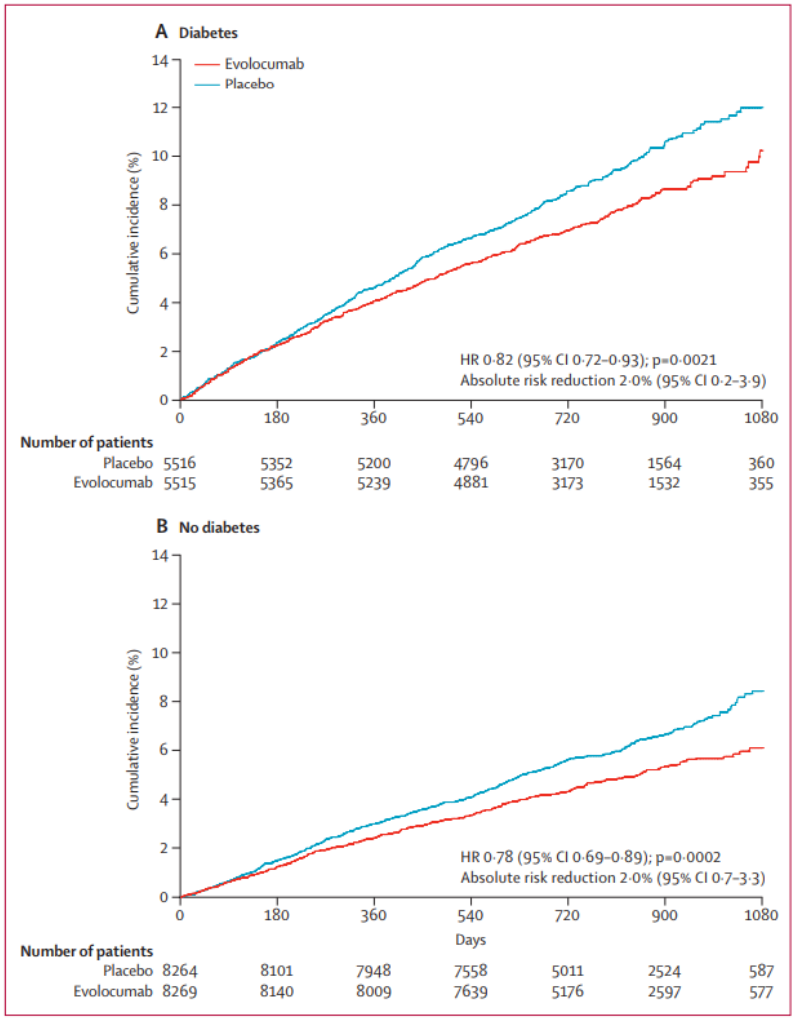
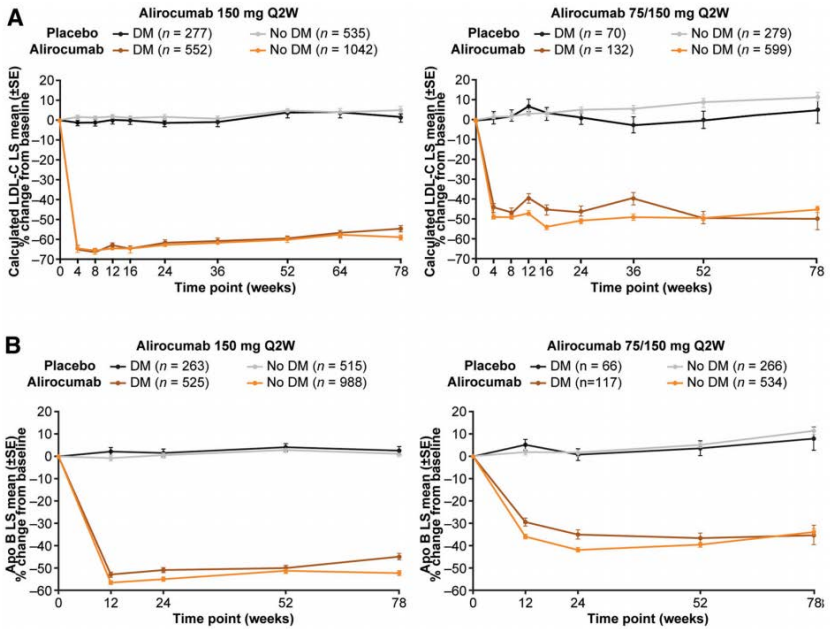


Figure 3: Key secondary endpoint

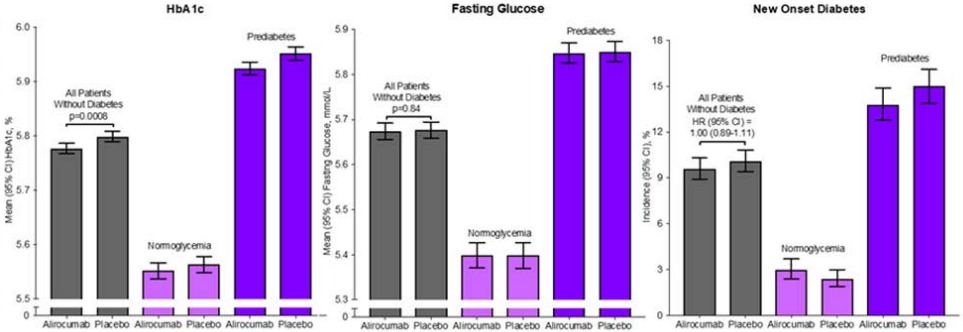
;5(12):941-950.

Efficacy and safety of alirocumab in DM: Pooled analyses from phase 3 trials



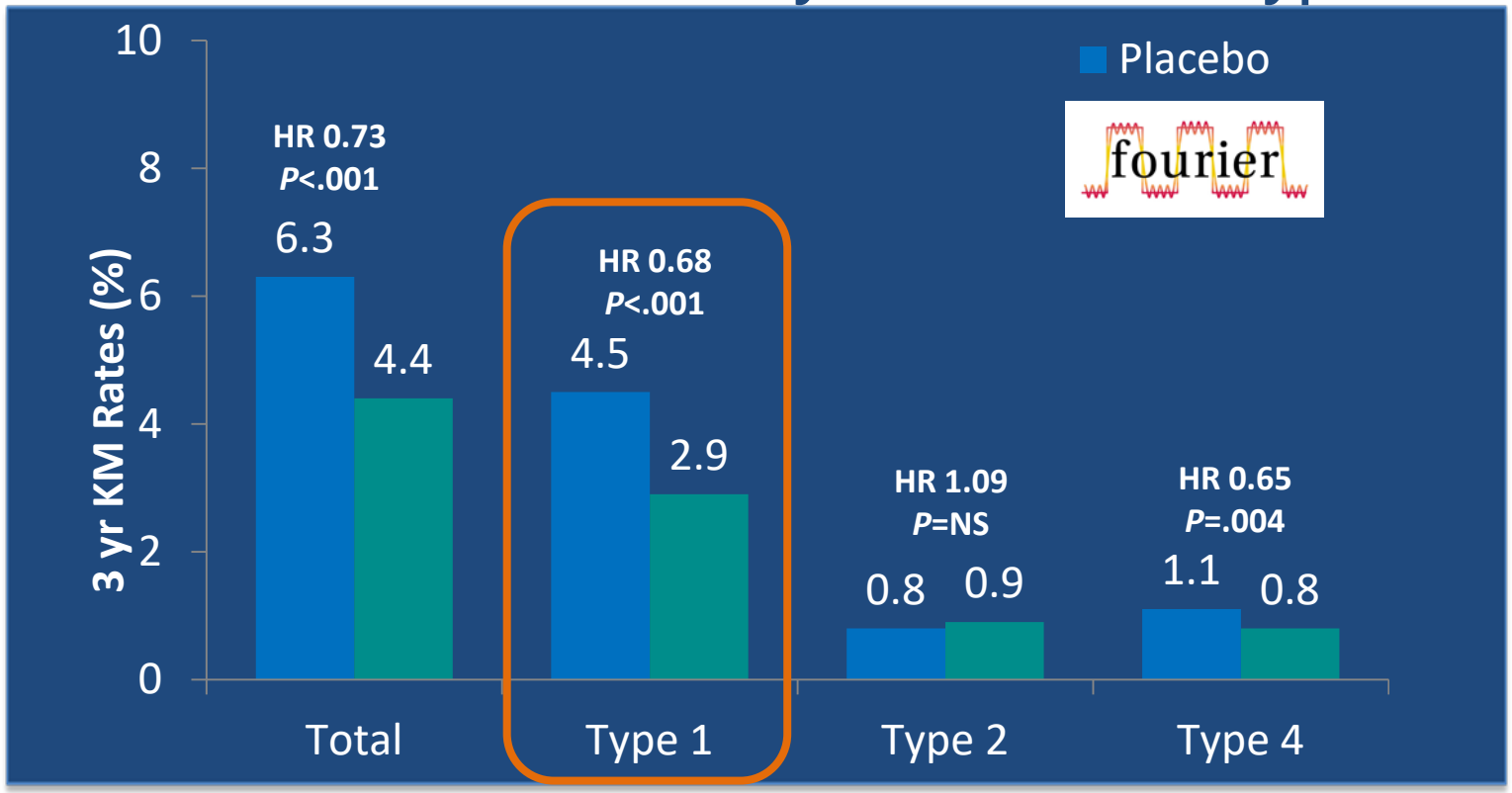
Diabetes Therap 2018;9:1317-1334

Post-randomization A1c, Fasting Glucose, and New-onset Diabetes by Baseline Glucometabolic Status



Ray KK, American Diabetes Association 2018 (Orlando, FL)

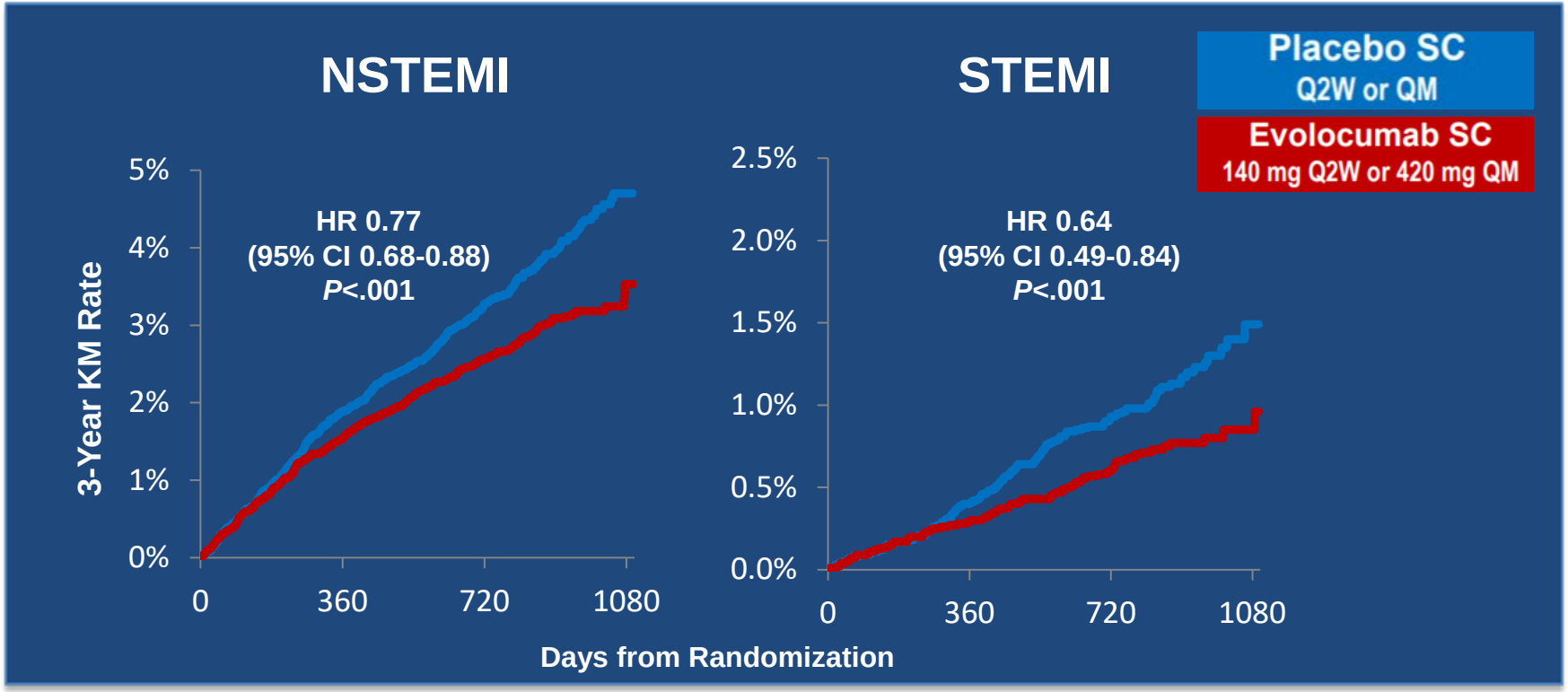
Effect of Evolocumab by Universal MI Type



Wiviott SD, et al. *Circulation* 2017;136:A16714.

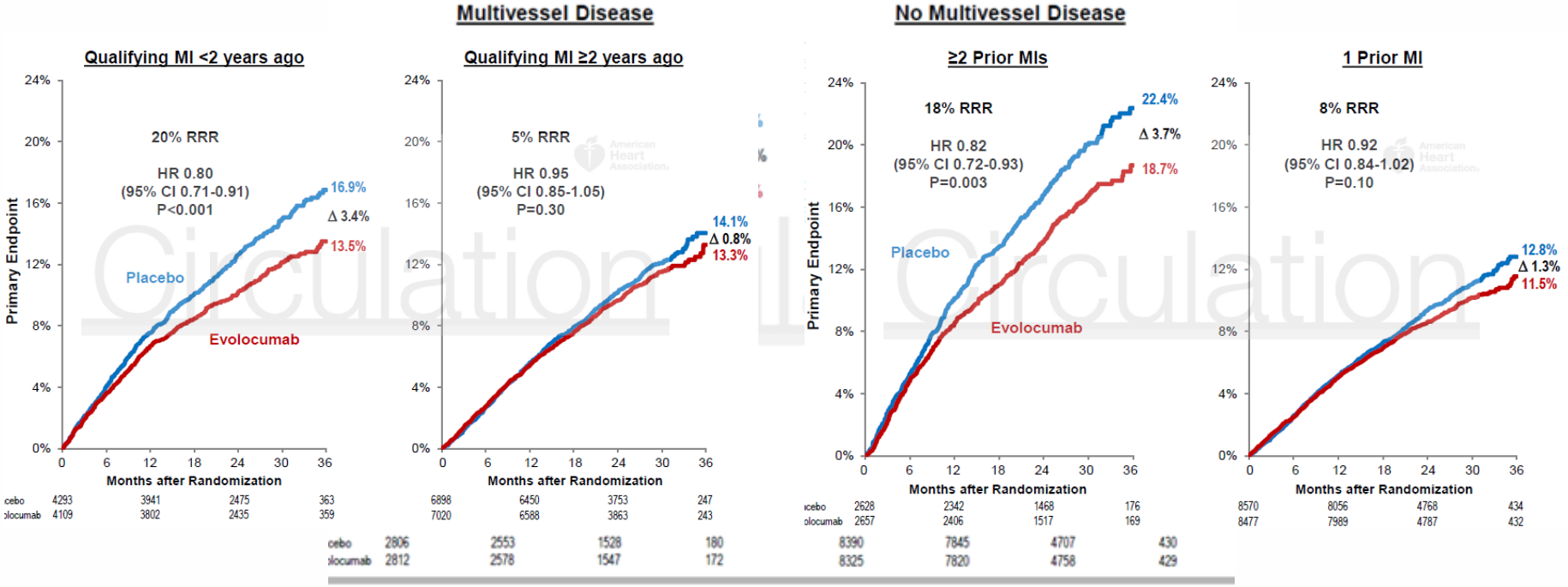
Due to small numbers, Types 3 and 5 are not presented individually

Effect of Evolocumab by MI Type: NSTEMI and STEMI



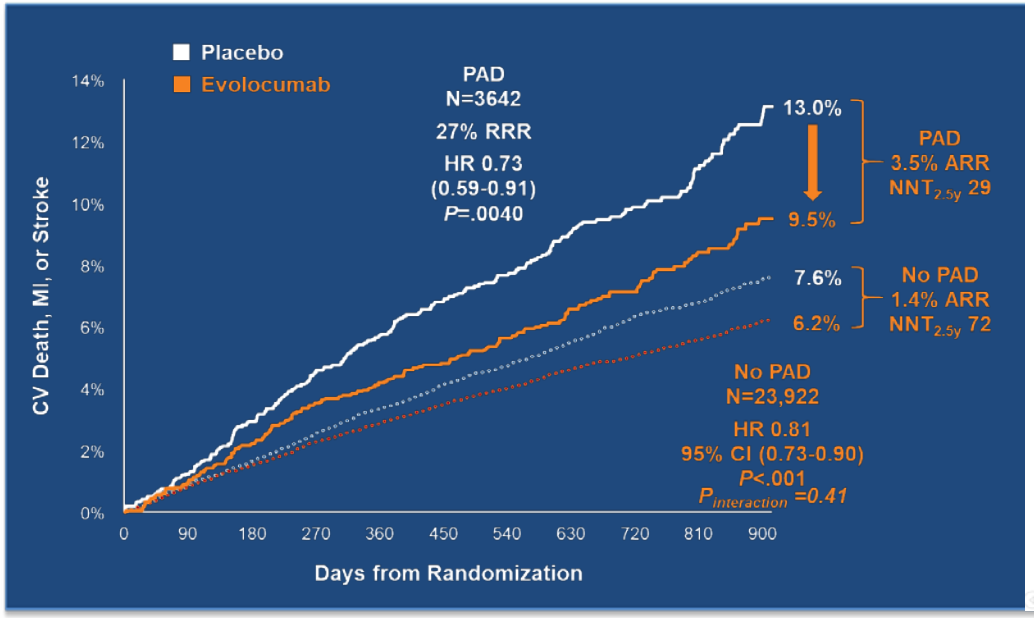
Wiviott SD, et al. *Circulation* 2017;136:A16714.

Clinical Benefit of Evolocumab by Extent of CAD

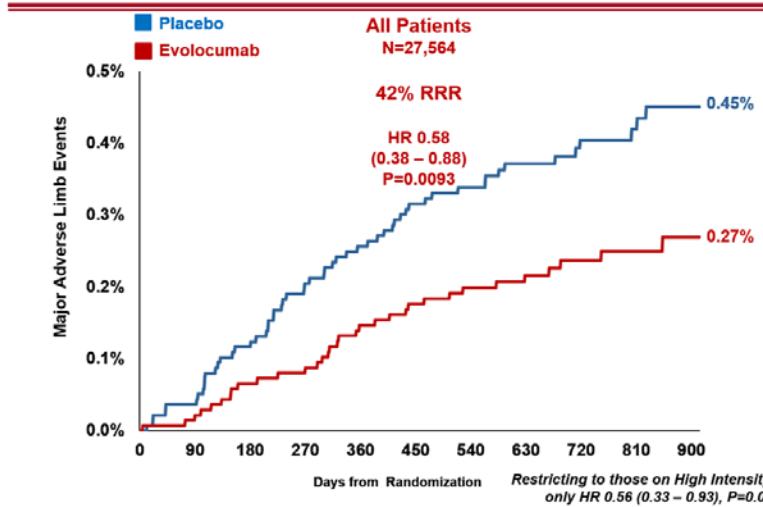


Sabatine MS, et al. *Circulation.* 2018 Apr 6. pii: CIRCULATIONAHA.118.034309.

CV death, MI, stroke, and MALE in patient with and without PAD



Major Adverse Limb Events

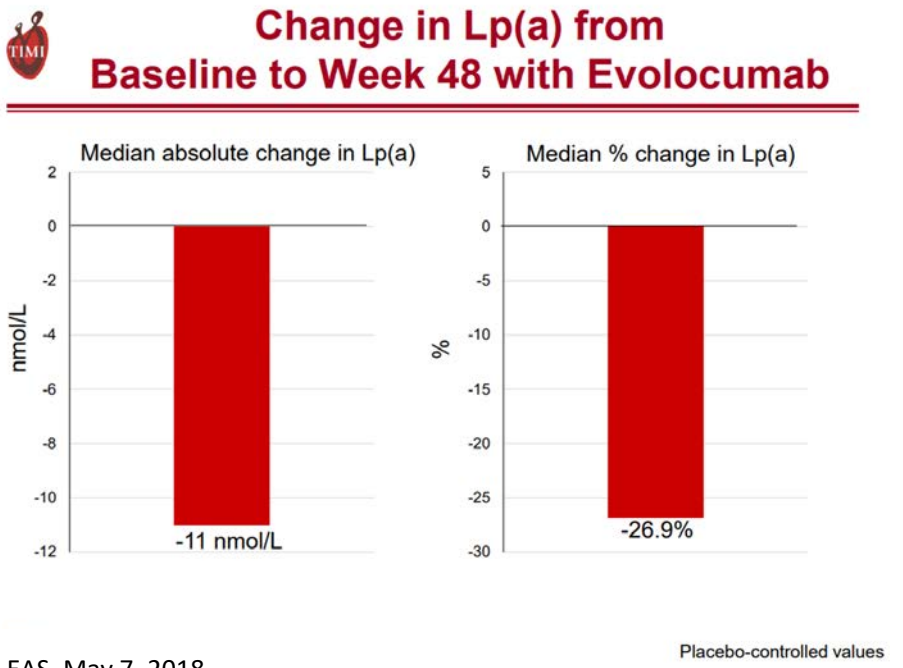


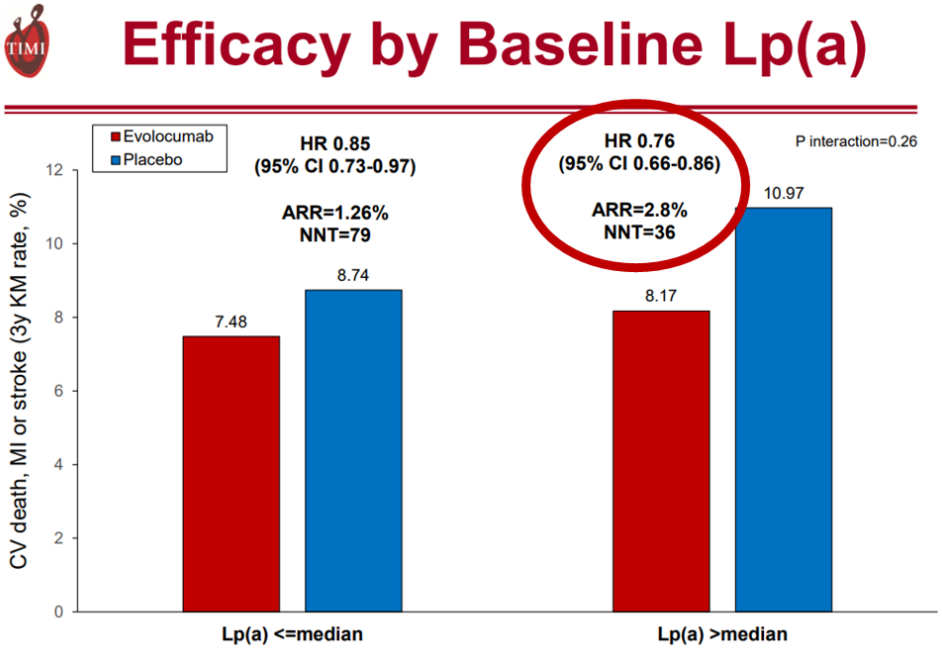
Restricting to those on High Intensity Statin only HR 0.56 (0.33 – 0.93), P=0.022

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

Bonaca MP, *Circulation* 2018;;137(4):338-50

Lp(a), CV risk, and evolocumab: FOURIER



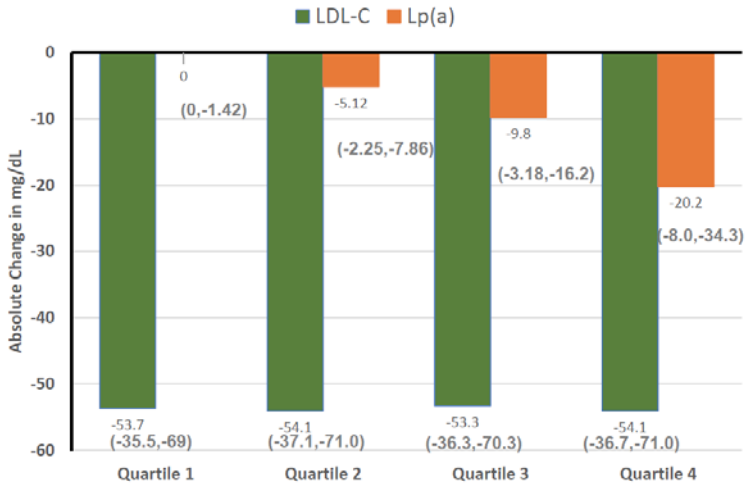


EAS, May 7, 2018

Lp(a) and alirocumab: ODYSSEY Outcomes

Median LDL-C and Lp(a) Change Across Lp(a) Quartiles (Alirocumab Group)

Change between baseline and Month 4; median (IQR)



Bittner VA, presented 2018 – Toronto, Canada, June 12, 2018

ODYSSEY OUTCOMES

Bittner VA, presented ISA, 2018. Toronto, Canada, June 12, 2018

CLINICAL PRACTICE GUIDELINES

Evolving evidence: Non-statin trials in the 2010s

2013 **No data that nonstatin therapy added to statin therapy provided incremental reduction in CHD events

2014 IMPROVE-IT (n=18,144)

2017 FOURIER (n=27,564)

2017 SPIRE 1 and SPIRE 2 (27,438)

2017 REVEAL (n=30,624)

2018 ODYSSEY Outcomes (n=18,924)

2018 REDUCE-IT (n=8,179)

2018 **7 major trials with non-statins recently completed, enrolling 130,873 patients

2018 ACC/AHA BLOOD CHOLESTEROL GUIDELINES

2018
ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624


AGREE
AGREE
AGREE
AGREE
AGREE
AGREE
AGREE
AGREE

What remains the same?

- Response to therapy based on % LDL-C reduction
- Reiterated the importance of monitoring response to therapy
- 4 statin benefit groups
  - ASCVD
  - LDL-C ≥190 mg/dL
  - Diabetes
  - High-risk primary prevention
- Inadequate response to therapy should be addressed, particularly in higher risk patients

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

What has been refined or revised?

- Role of non-statin therapies
  - New large RCTs since 2013 guidelines
  - Provides evidence-based guidance on ezetimibe, PCSK9 inhibitors (and BAS in LDL-C ≥190 mg/dL)

- Includes LDL-C "thresholds" for intensification of therapy
  - "In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy."
  - In agreement with the 2017 ACC Expert Consensus Decision Pathway on the role of non-statin therapies

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

What has been refined or revised?

- Class I (LOE B-NR) that ezetimibe should be considered prior to addition of PCSK9 inhibitor

I	B-NR	3. In patients with clinical ASCVD who are judged to be very high risk and *considered for PCSK9 inhibitor therapy,* maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (S4.1-14, S4.1-15).

- Includes value statement on PCSK9 inhibitors for ASCVD and LDL-C ≥190 mg/dl

Value Statement: Low Value (LOE: B-NR)	6. At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY) (Section 7 provides a full discussion of the dynamic interaction of different prices and clinical benefit) (S4.1-21–S4.1-23).

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

What has been refined or revised?

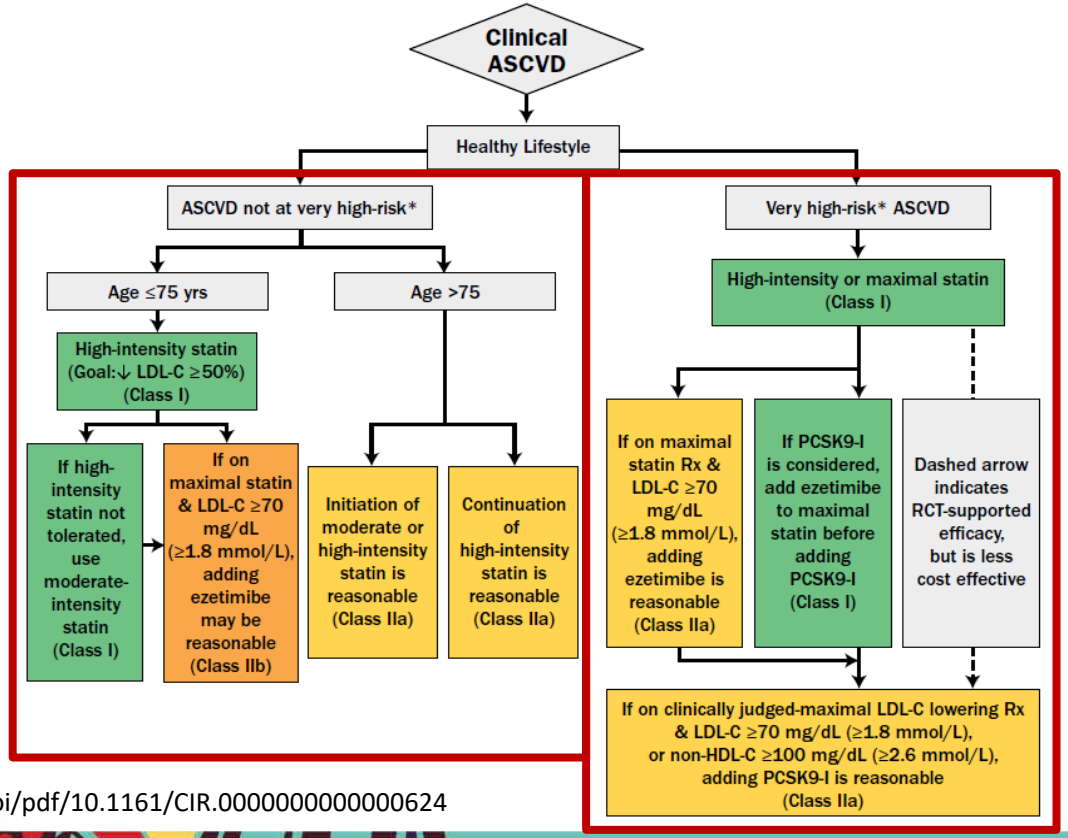
Like the 2017 ACC ECDP on non-statin therapies

- ASCVD not at very high risk
  - "ASCVD without comorbidities"
- ASCVD at very high risk
  - "ASCVD with comorbidities"

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 (S4.1-39))
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) (S4.1-15, S4.1-17)
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 one major ASCVD event and multiple high-ri onditions.

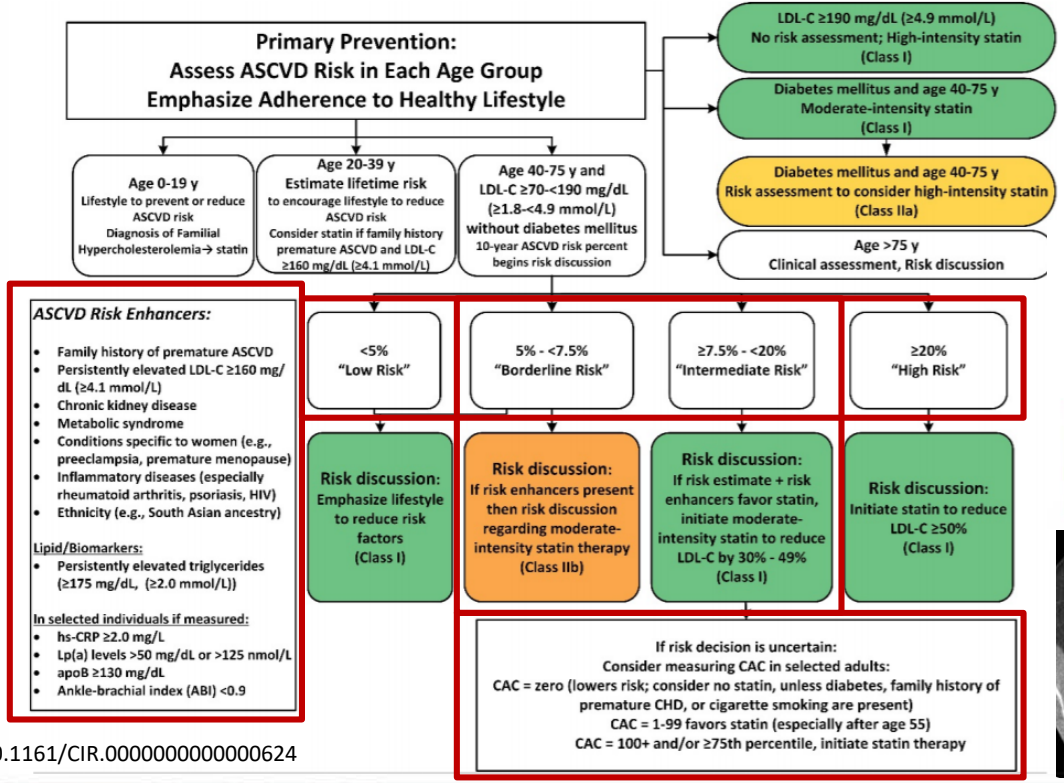
https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

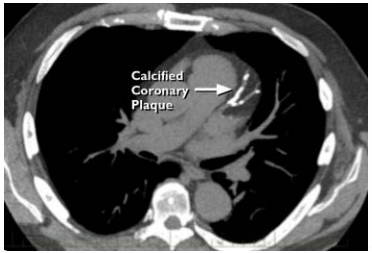
Secondary Prevention in Patients with Clinical ASCVD



https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

What has been refined or revised?





https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

New or expanded…

- Hypertriglyceridemia
- Chronic kidney disease
- Chronic inflammatory disorders and HIV
- Special patient populations
  - Older adults
  - Children and adolescents
  - Ethnicity (Asian Americans, Hispanic/Latino Americans, Blacks)
  - Women

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624

Summary

- Lifestyle intervention remains the foundation of ASCVD risk reduction.
- Statins are the mainstay of lipid-lowering therapy for ASCVD risk reduction.
- Evolving evidence has now defined a role for non-statin therapies in very high- and high-risk patients with inadequate lowering of LDL-C on maximally tolerated statin therapy.
- Analysis of RCTs for ezetimibe and PCSK9 inhibitors help to define those highest risk patients who are most likely to benefit from combination therapy.

Case Challenge and Discussion

Case Discussion

The patient is a 62 year old WM with a history of diabetes, symptomatic PAD, and ASCVD s/p AWMI 18 months ago. He has been on atorvastatin 80 mg since his MI, and was doing well until 6 months ago when he developed recurrent exertional CP. He has now undergone cardiac catheterization and stenting of a new LAD lesion with resolution of symptoms.

Case Discussion

At the time of intervention his lipid profile on atorva 80 mg was:

- Total Cholesterol 188 mg/dL
- LDL-C (calculated) 115 mg/dL
- HDL-C 45 mg/dL
- TG- 140 mg/dL
- 40% reduction in LDL-C from baseline

Case Discussion

- What are your recommendations for next steps in management of this patient?
    - Continue current therapy
    - Change to rosuvastatin 40 mg daily
    - Add ezetimibe 10 mg daily
    - Add PCSK9 inhibitor
    - Add bile acid sequestrant
    - Other?

Case Discussion

- The patient is changed to rosuvastatin 40 mg, with the subsequent development of bilateral thigh pain and weakness approximately 10 days later. This resolves within one week of stopping medication and restarts three days after beginning the same dose of rosuvastatin.

- The patient is placed back on atorvastatin 80 mg and repeat LDL-C level at 2 months is 117 mg/dL.

Case Discussion

- What would be your next step in management of this patient?
    - Continue current therapy
    - Diagnose patient with statin intolerance and use non-statin therapy only
    - Resume treatment with atorvastatin 80 mg and add ezetimibe
    - Resume treatment with atorvastatin 80 mg and add PCSK9 inhibitor
    - Switch to simvastatin 40 mg daily and ezetimibe
    - Other?

Case Challenge

The patient is started on ezetimibe 10 mg with reduction of LDL-C to 95 mg/dL.

Evolocumab 140 mg SQ/2 weeks is started. 8 weeks later his lipid panel is

- TC 76 mg/dL
- LDL-C (calculated) 30 mg/dL
- HDL-C 40 mg/dL
- TG 30 mg/dL

The patient is concerned about his low LDL-C and asks if this is dangerous, could it cause harm and is hesitant to adhere to his current treatment.

Case Challenge

Which of the following next steps would you recommend?

- Stop ezetimibe
- Decrease evolocumab dose to every 4 weeks 140 mg sq
- Decrease atorvastatin to 20 mg/day
- No change in current treatment
- Other?

Thank you!