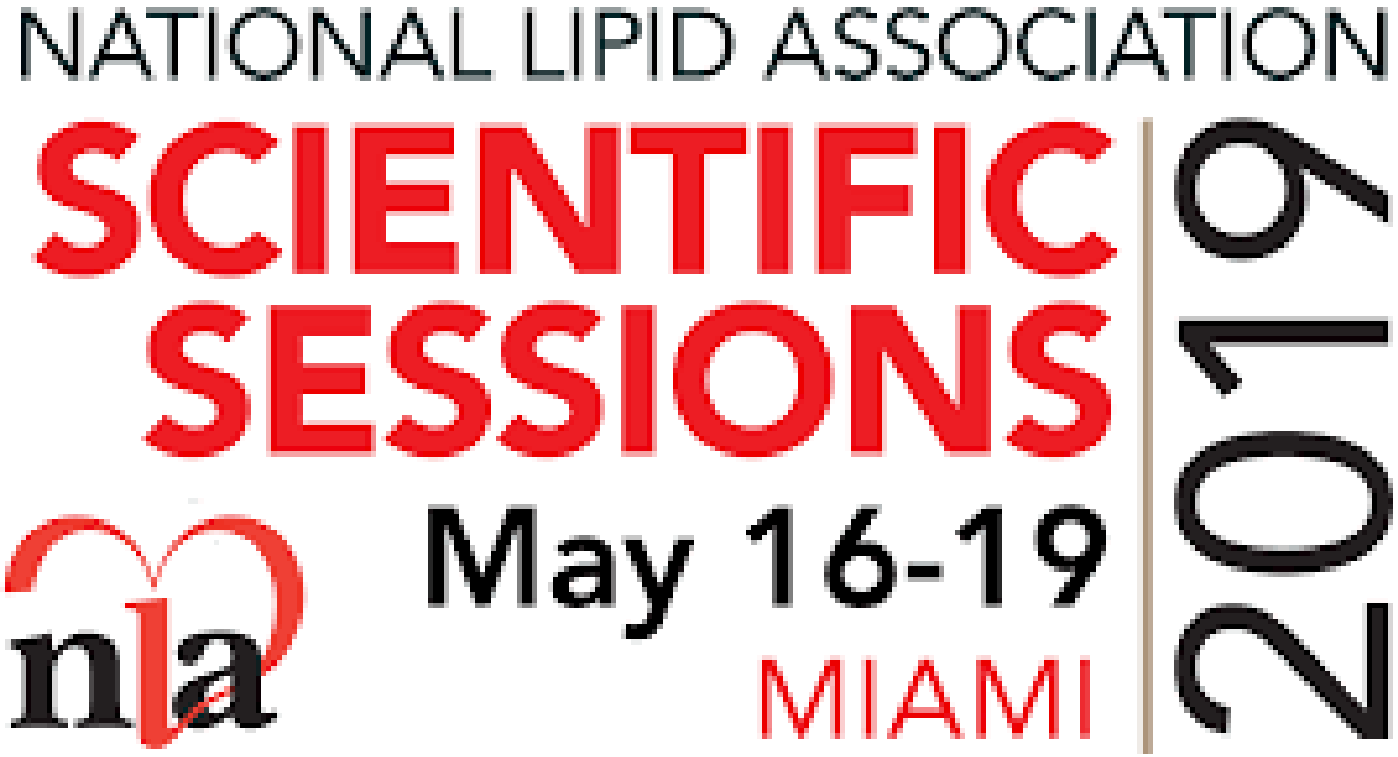

Jose M Garcia Mateo, MD, FACE
Diplomate of the American Board of Endocrinology, Diabetes and Metabolism
Diplomate of the American Board of Clinical Lipidology

Disclosure

•Dr. Jose M. Garcia Mateo, endocrinologist, declares that he serves as a speaker and consultant for the following pharmaceutical companies: ***Eli Lilly, Astra Zeneca, Sanofi , Amgen, Boehringer Ingelheim, Janseen, Akcea, Abbvie and Merck.***

Guidelines

Risk Assessment and Primary Prevention Emphasis

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL.

PUBLISHED BY ELSEVIER

AHA/ACC SPECIAL REPORT

Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease

A Special Report From the American Heart Association and American College of Cardiology

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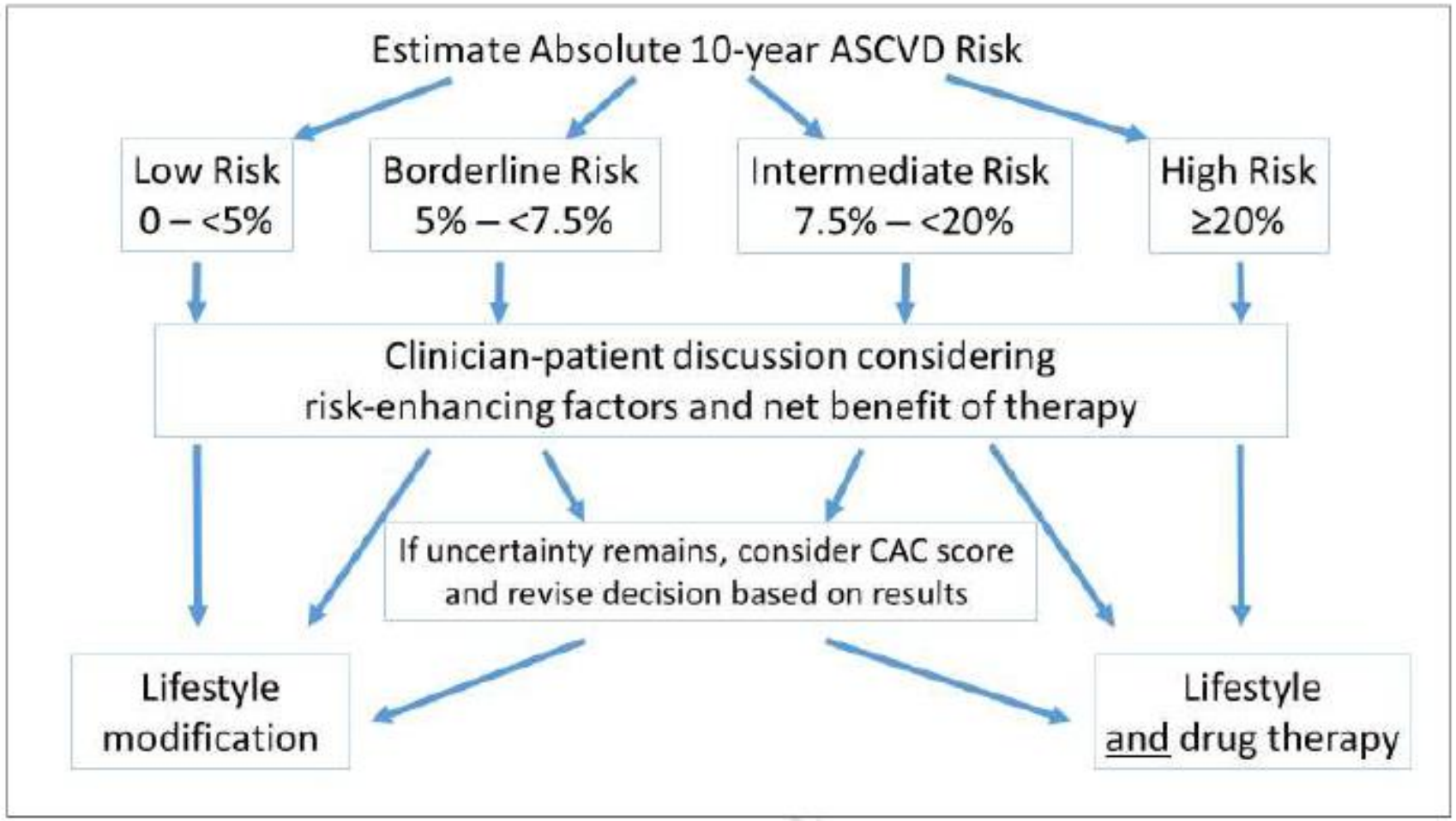
Figure 2. Overall conceptual approach to risk assessment and decision-making regarding the intensity of prevention efforts and use of drug therapy in primary prevention of ASCVD.



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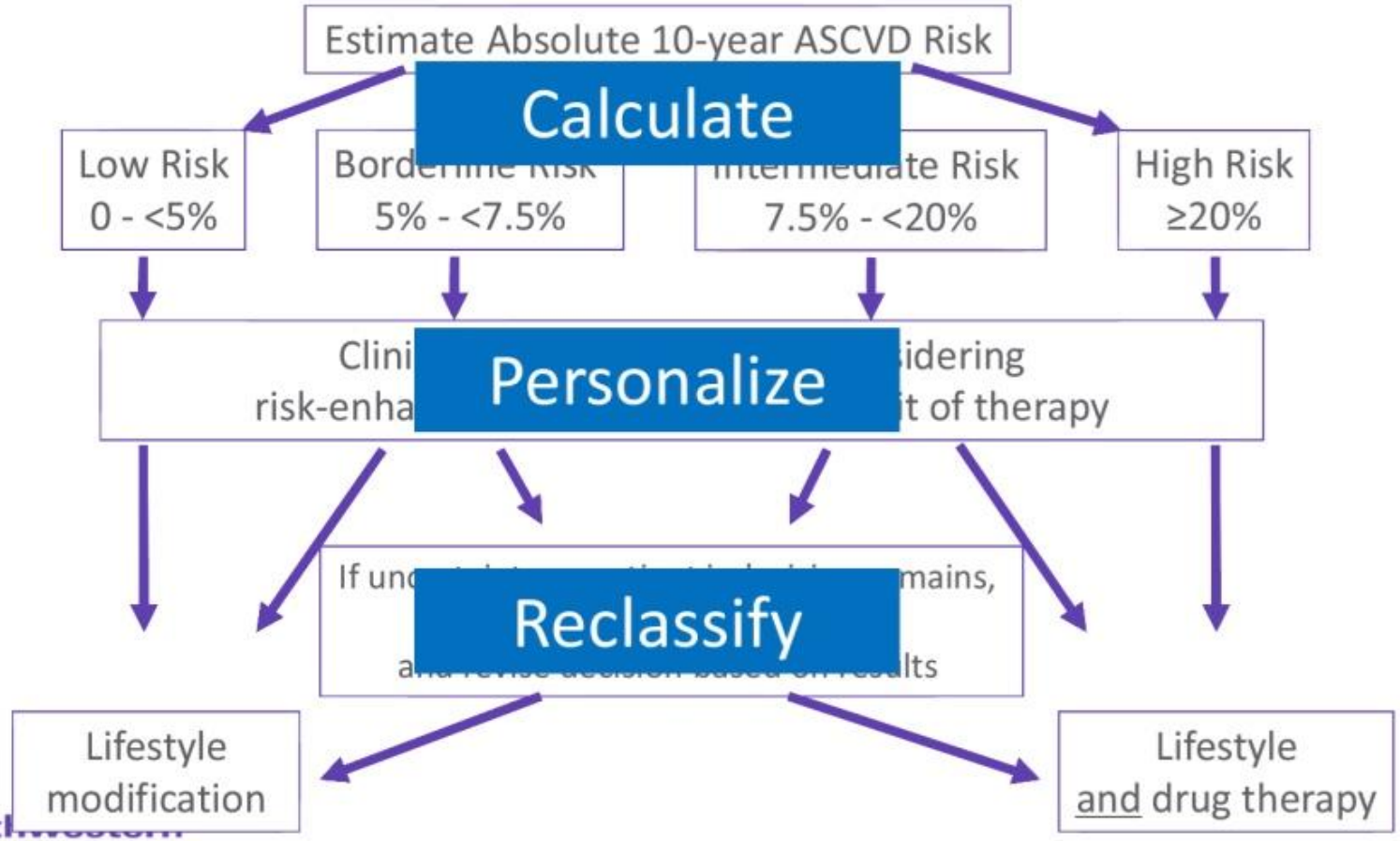
Approach to Risk Assessment in 1° Prevention: CPR



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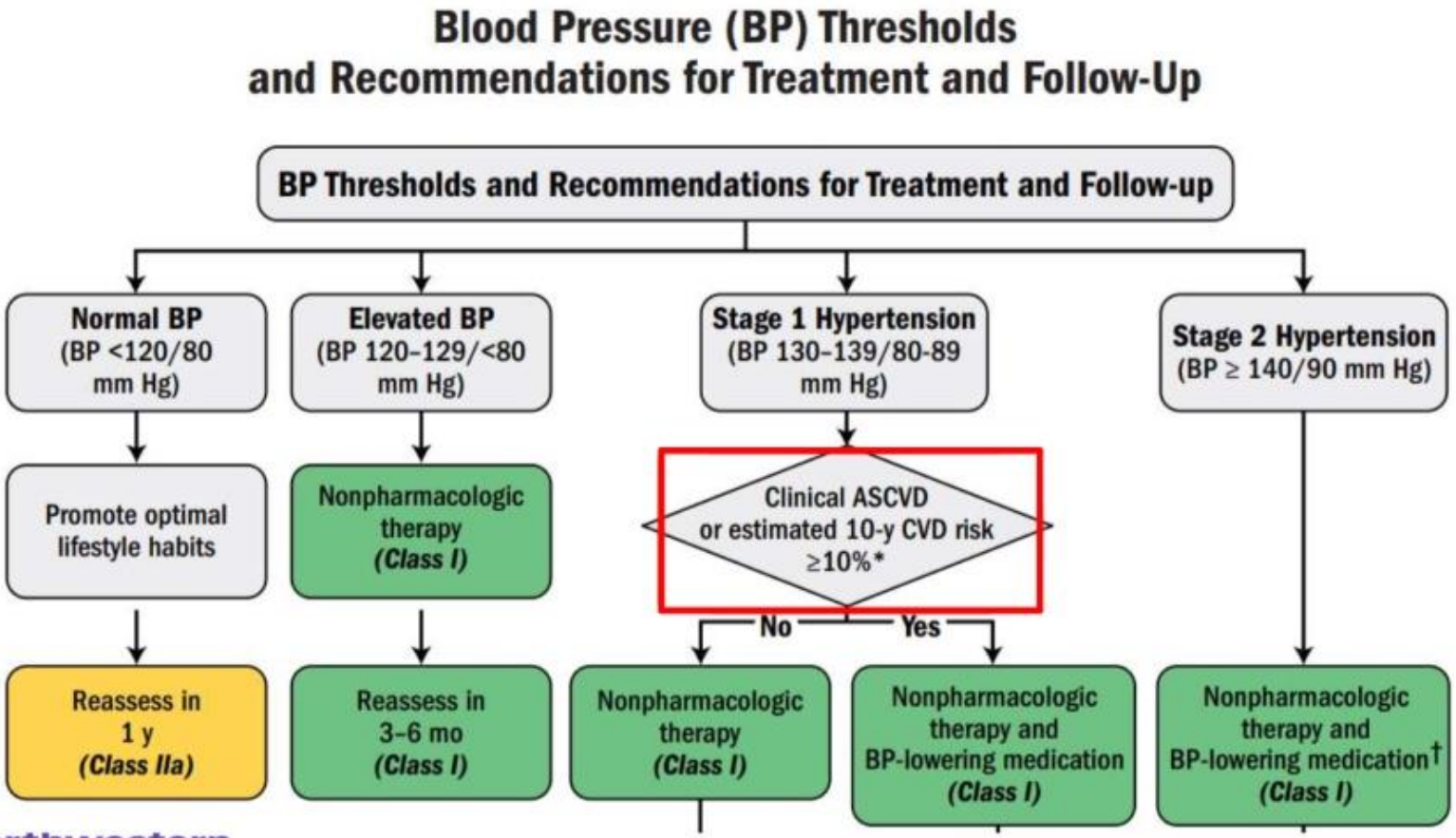
2017 ACC/AHA Hypertension Guidelines



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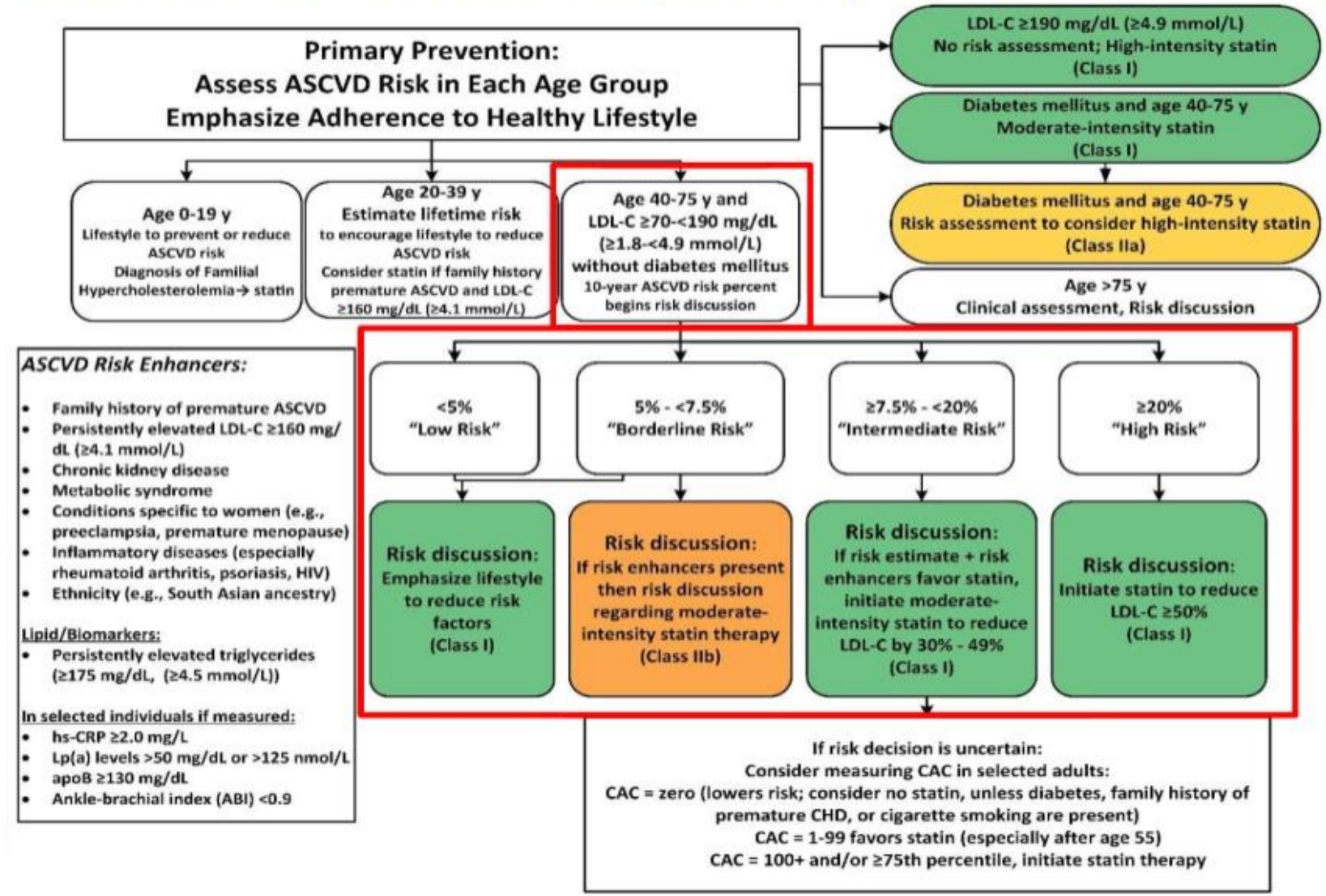
2018 AHA/ACC/Multi-Specialty Cholesterol Guidelines



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C= Calculate: Use Pooled Cohort Equations for ASCVD Risk Estimation

- Recommended for use based on:
  - Broad utilization and desired endpoint of hard ASCVD
  - Most widely validated score in contemporary US populations
    - SR identified 23 manuscripts evaluating PCE in diverse populations
  - PCE are well calibrated near decision thresholds (e.g., 7.5% 10-year risk) in broad US clinical population
  - As with all risk scores, PCE can under- and over-estimate true risk in some subgroups
  - Reclassification by CAC well understood
- New recommendations - Deploy PCE with:
  - Expanded clinician-patient discussion with consideration of risk-enhancing factors
  - Judicious use of CAC measurement in intermediate risk and selected borderline risk patients to reclassify risk

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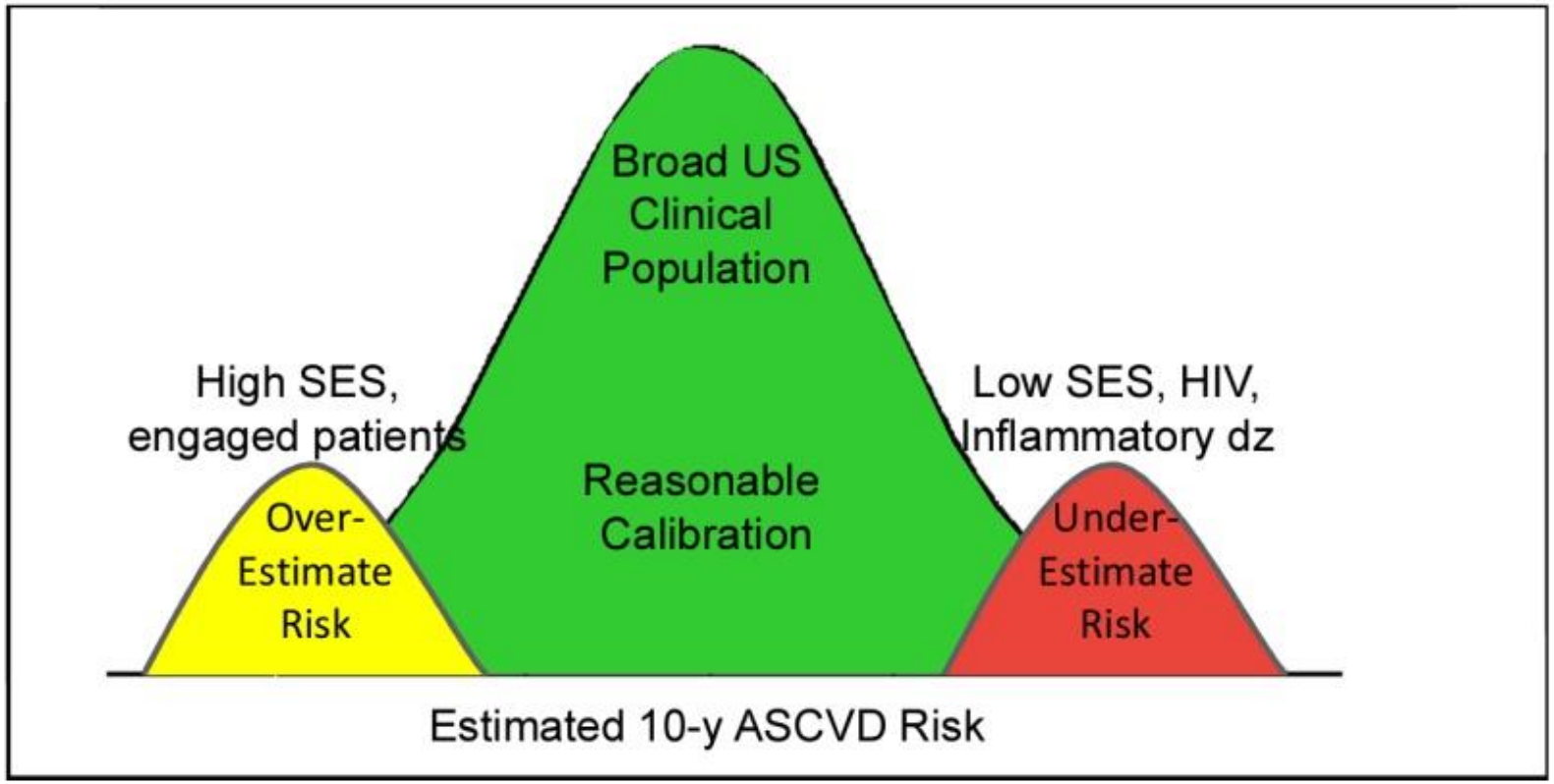
Performance of Pooled Cohort Equations in Diverse Population Samples: Predictable



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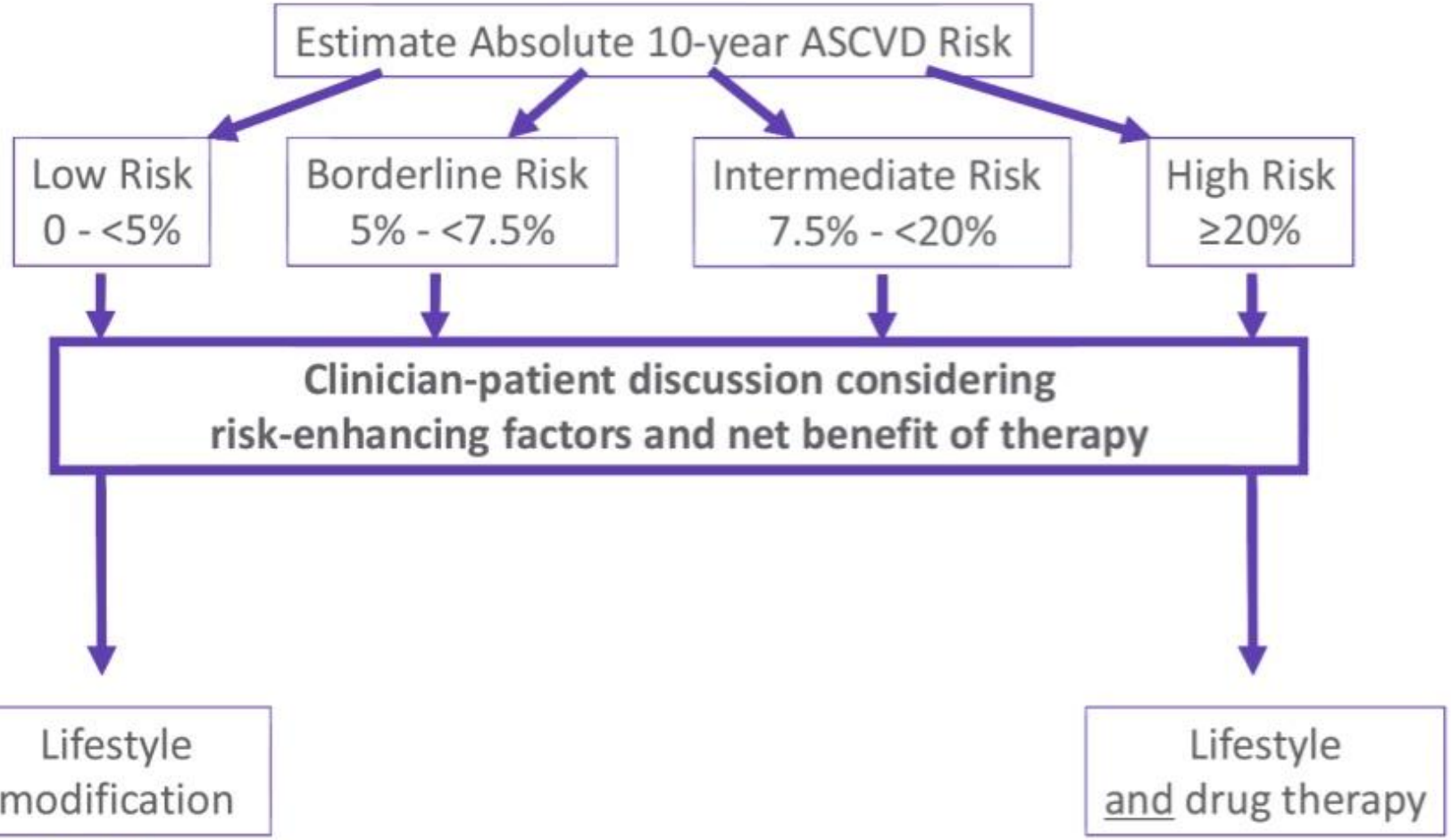
P = Personalize: Refine Risk for Individual Patients



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Risk-Enhancing Factors
• **Family history of premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS • **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia** • **High-risk race/ethnicities** (e.g., South Asian ancestry)

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Risk-Enhancing Factors

- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    - **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
    - **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
    - **ABI** <0.9

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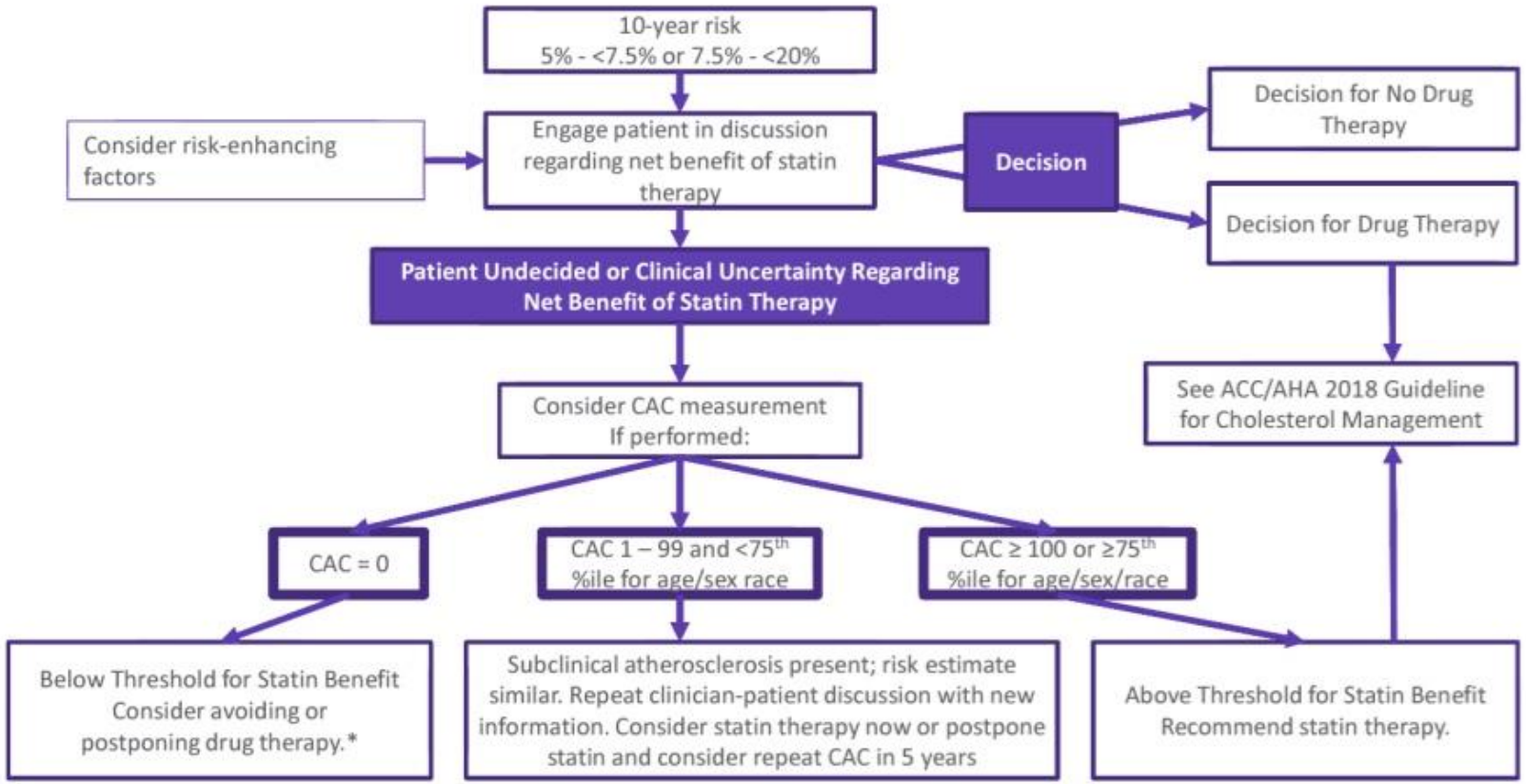
R = Reclassify Risk in Selected Patients



*Clinicians and patients may not wish to postpone therapy in patients with a CAC score of 0 and diabetes mellitus, heavy current cigarette smoking, or strong family history of premature ASCVD.

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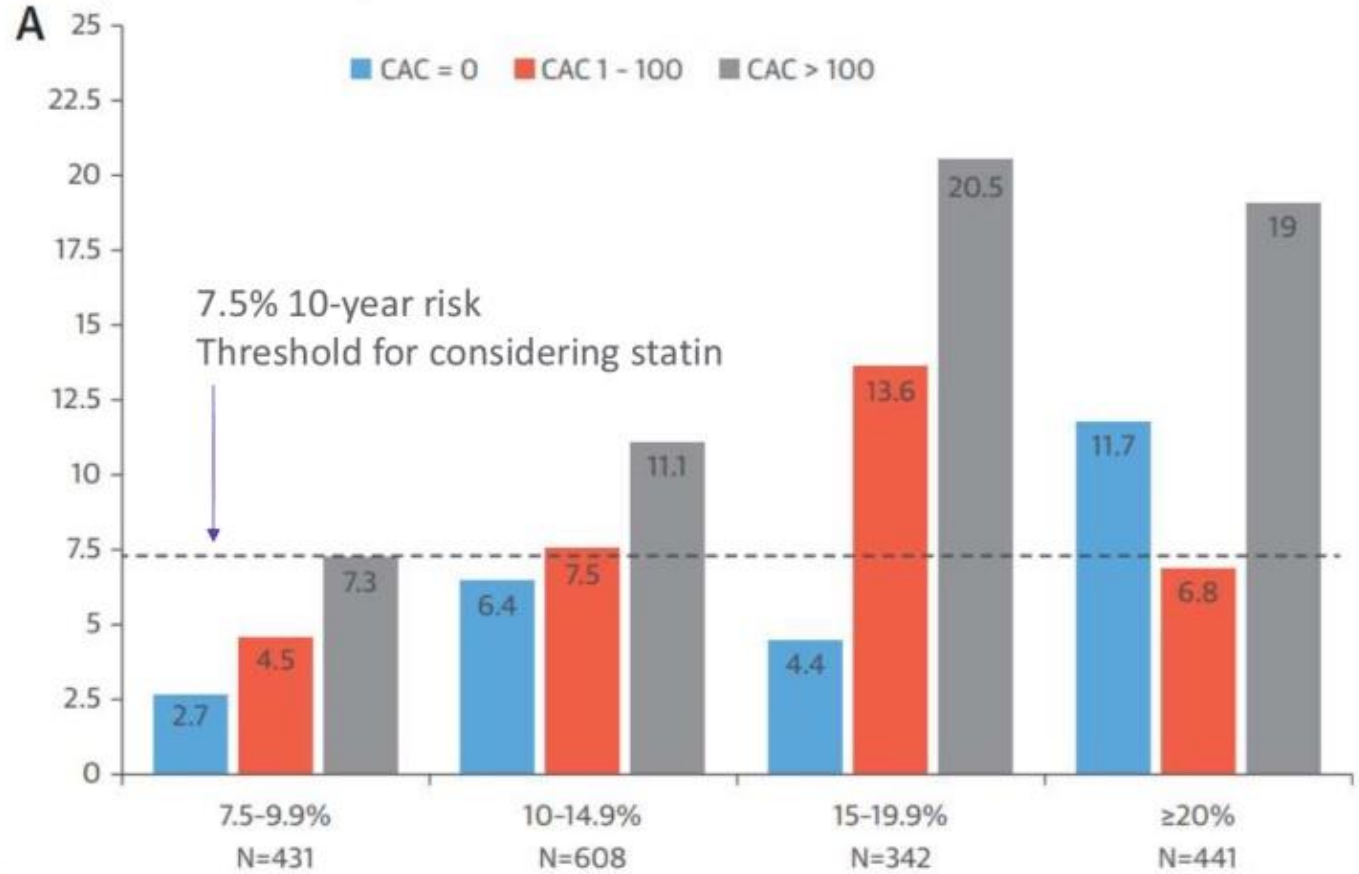
Reclassification of Risk by CAC

Example: MESA Study



Dotted line represent reference line for 10-year ASCVD risk estimate of 7.5%

Nasir et al., MESA Study, JACC 2015

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Perform CPR …Then Treat Accordingly

- Risk-based and risk-enhanced algorithm for selecting patients considered for treatment with statins in primary prevention likely to lead to better decisions and greater patient satisfaction/adherence
- This CPR now or that CPR later

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Joseph Yeboah, MD, MS, FACC, FAHA*
Boback Ziaeian, MD, PhD, FACC, FAHA§

*ACC/AHA Representative, †Lay Representative, § Task Force Performance Measures Representative

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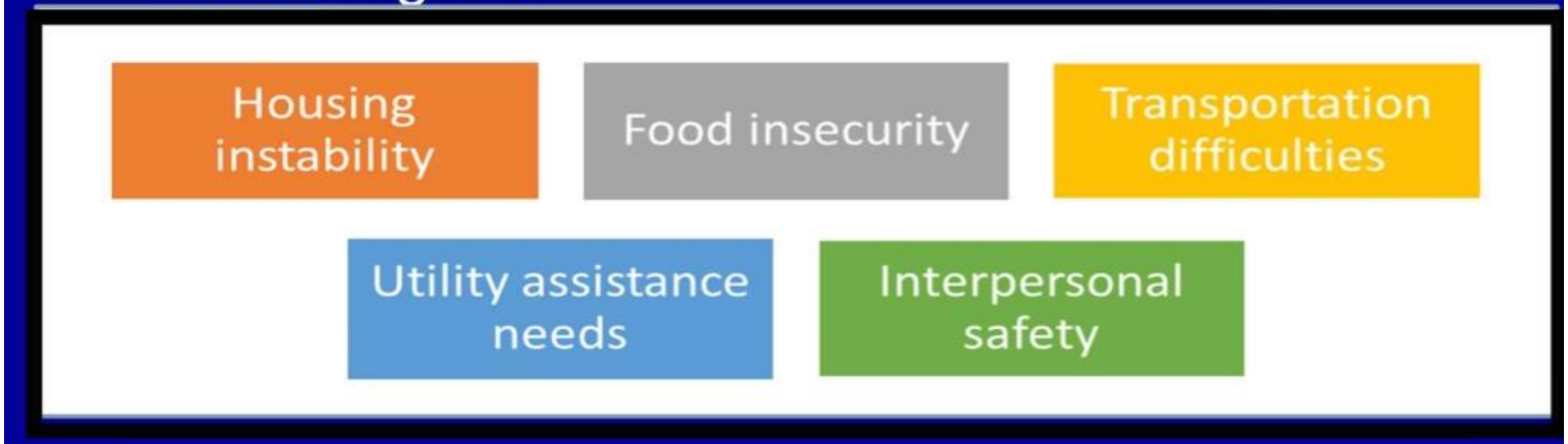
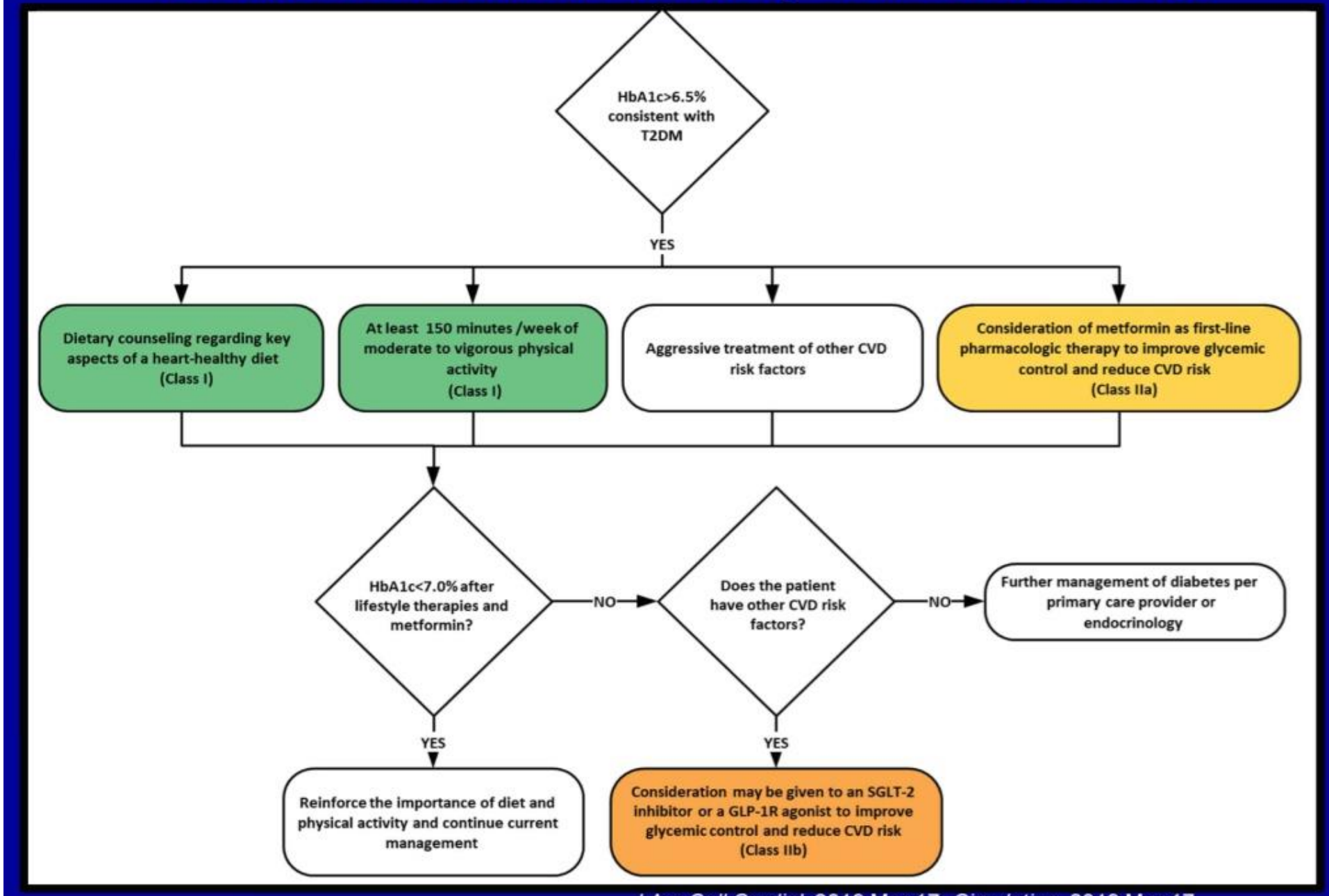
Social Determinants of Health

- Socioeconomic factors may limit the effectiveness of prevention recommendations
- Socioeconomic disadvantages are not captured by existing CVD risk equations.
- Medicare/Medicaid developed a 5 domain screening tool



https://nam.edu/standardized-screening-for-health-related-social-needs-in-clinical-settings-the-accountable-health-communities-screening-tool/

Treatment of T2DM for Primary Prevention of CVD



J Am Coll Cardiol. 2019 Mar 17; *Circulation*. 2019 Mar 17

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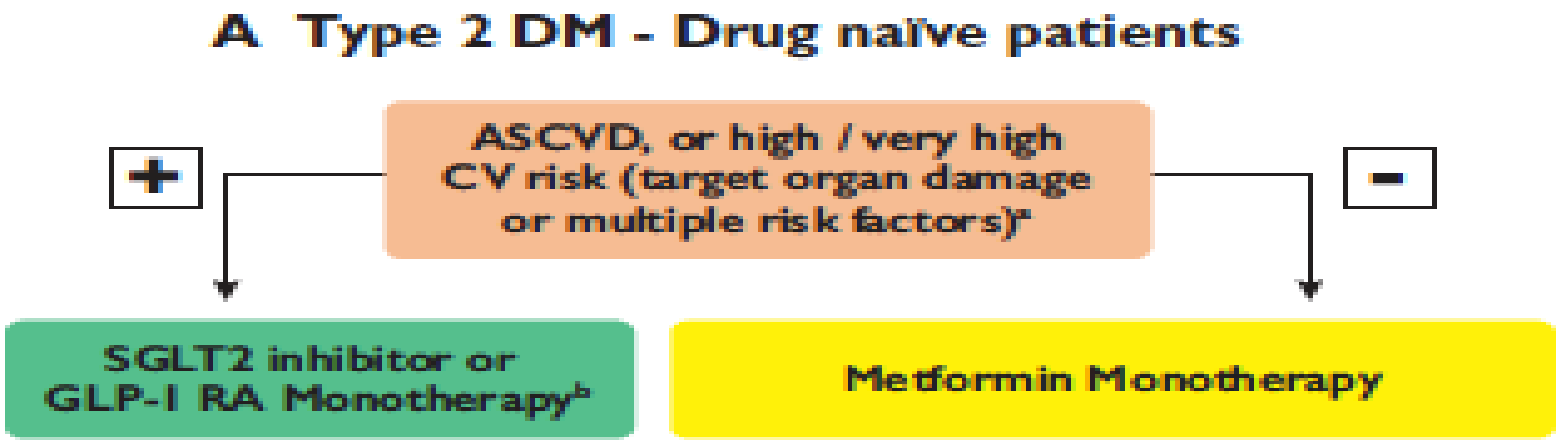
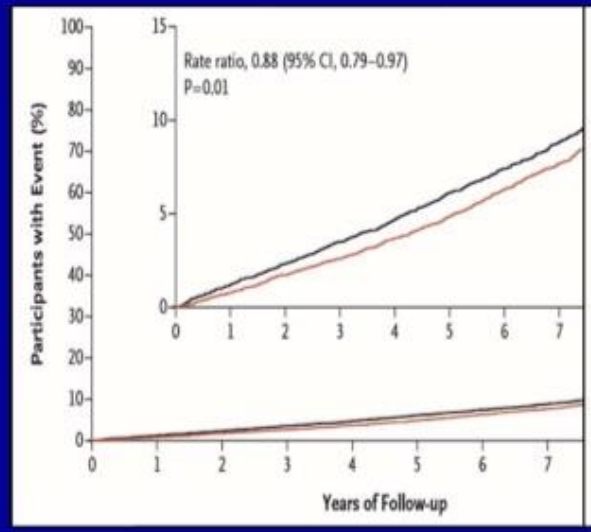
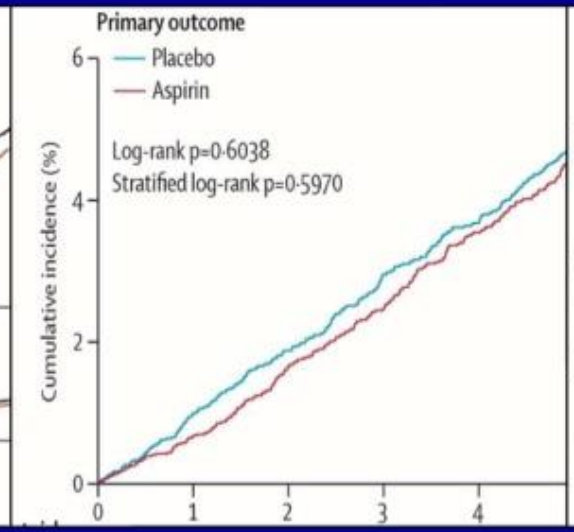
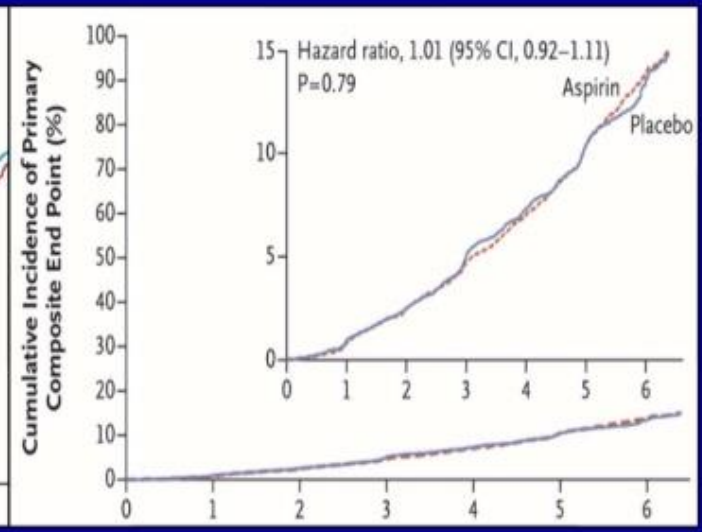

A Type 2 DM - Drug naïve patients
+
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)a
-
SGLT2 inhibitor or GLP-1 RA Monotherapyb
Metformin Monotherapy

New Trials: Aspirin for Primary Prevention







ASCEND	ARRIVE	ASPREE, 2018
15,480 with diabetes and no evident CVD.	12,546 with Moderate CVD risk w/o DM or high risk of GI bleeding	19,114 adults > 70 yr with no cardiovascular disease.
100 mg of aspirin vs. placebo	100 mg aspirin vs. placebo	100 mg aspirin vs. placebo
Reduction in vascular events was counterbalanced by bleeding	No difference in a composite of CV death, MI, UA, CVA, or TIA. With increased risk of bleeding	Aspirin did not prolong disability free survival but increased major hemorrhage
N Engl J Med. 2018;379:1529-39	Lancet. 2018;392:1036-46	N Engl J Med 2018; 379:1509-1518

Slide Courtesy: Dr. Abdulhamied Al Faddagh

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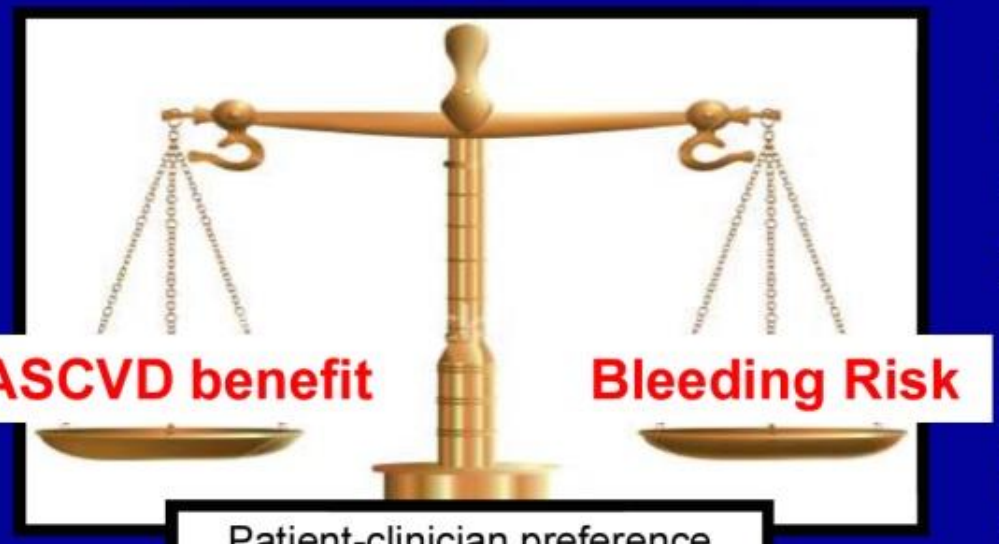
Prescribing based on totality of evidence

Elevated PCE
+ CAC
+ risk enhancing factors
Inability to achieve lipid or BP targets



Previous GIB or PUD
Bleeding from other sites
Age >70 years
Thrombocytopenia
Coagulopathy
CKD
Use of NSAIDs, steroids,
DOAC, and warfarin

Low dose ASA
(Class IIb)

Avoid ASA (Class III)
Focus on other risk factors

Slide Courtesy: Dr. Abdulhamied Al Faddagh

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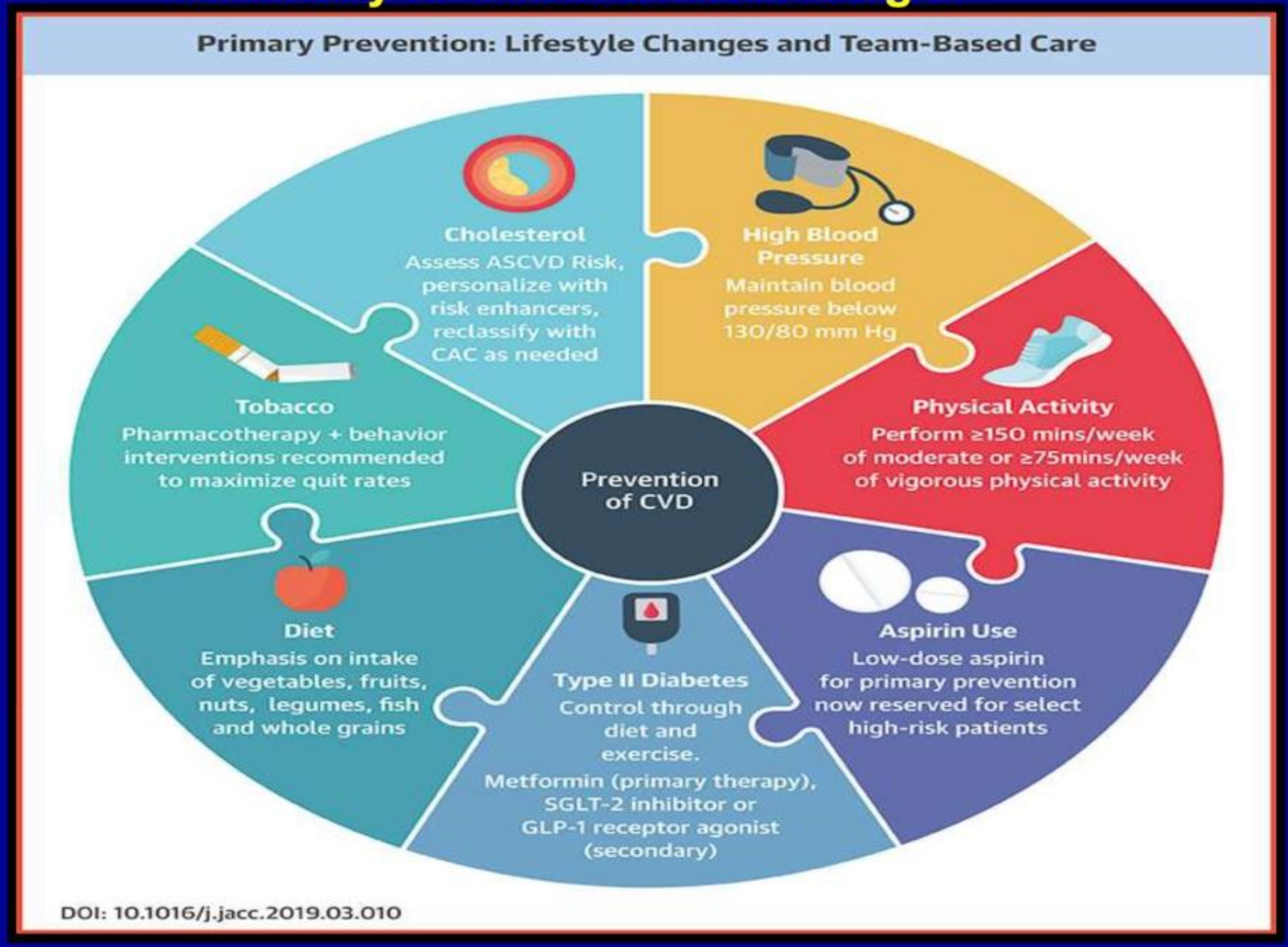
Primary Prevention of Cardiovascular Disease- A Team Sport
Summary of Take Home Messages



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Early Screening & Prevention Strategies

Dinesh Kalra, MD, FACC, FSCCT, FSCMR

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Our Risk Prediction models FAIL sometimes

Winston Churchill

- Obese
- Heavy smoker
- "Stressful" job
- Sedentary
- Died age 91

Jim Fixx

- Marathon Runner
- Author of "The complete Book of Running"
- Non smoker
- Died age 52

Tim Russert

- News anchor for Meet the Press
- In June 2008 at age 58, died suddenly of MI and SCD while at work
- Had "normal" stress test April 2008
- But, had CACS of 210 - 10 years prior
- Autopsy: extensive atherosclerosis

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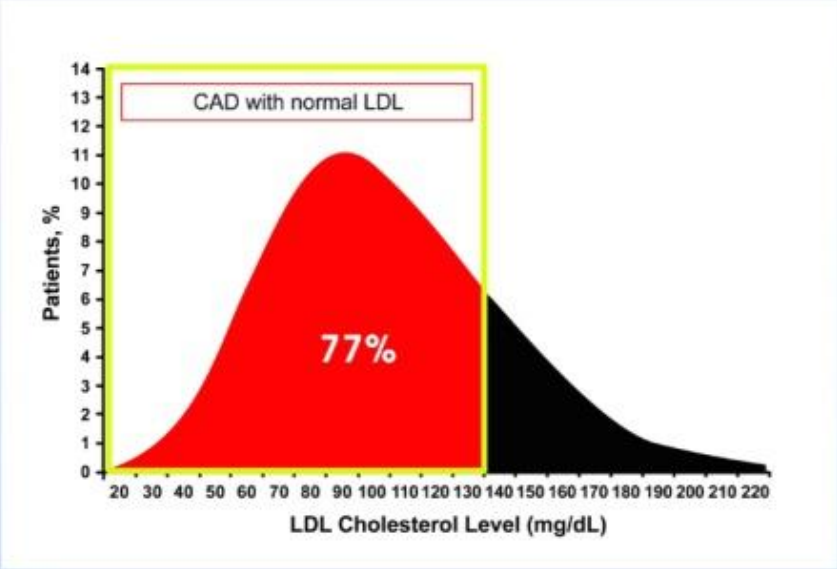
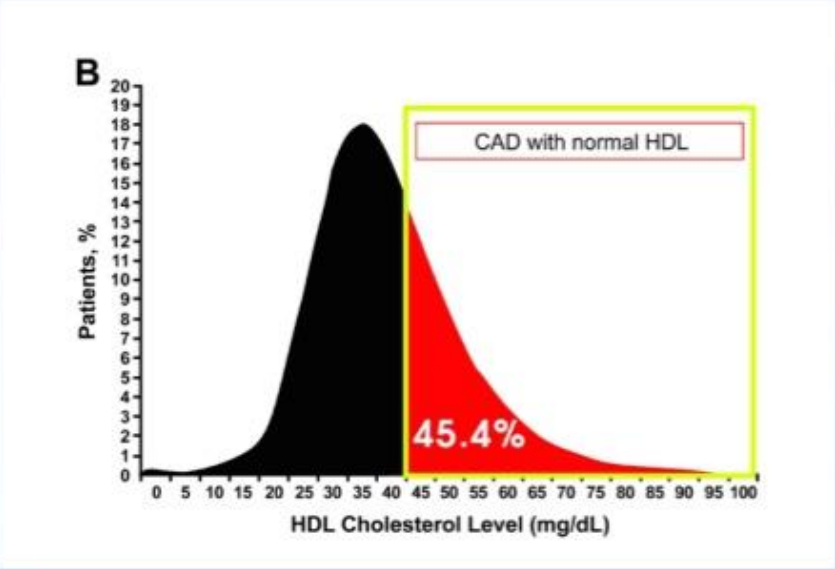
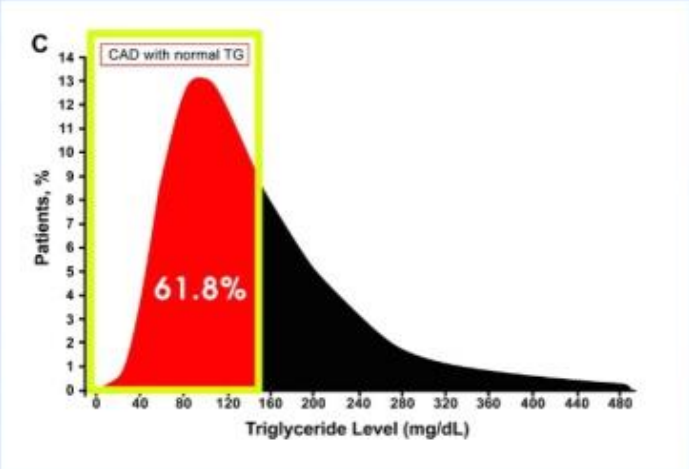
Of 136,905 patients hospitalized with CAD, most patients had “normal” lipid values







Sachdeva et al. AHJ, 2009

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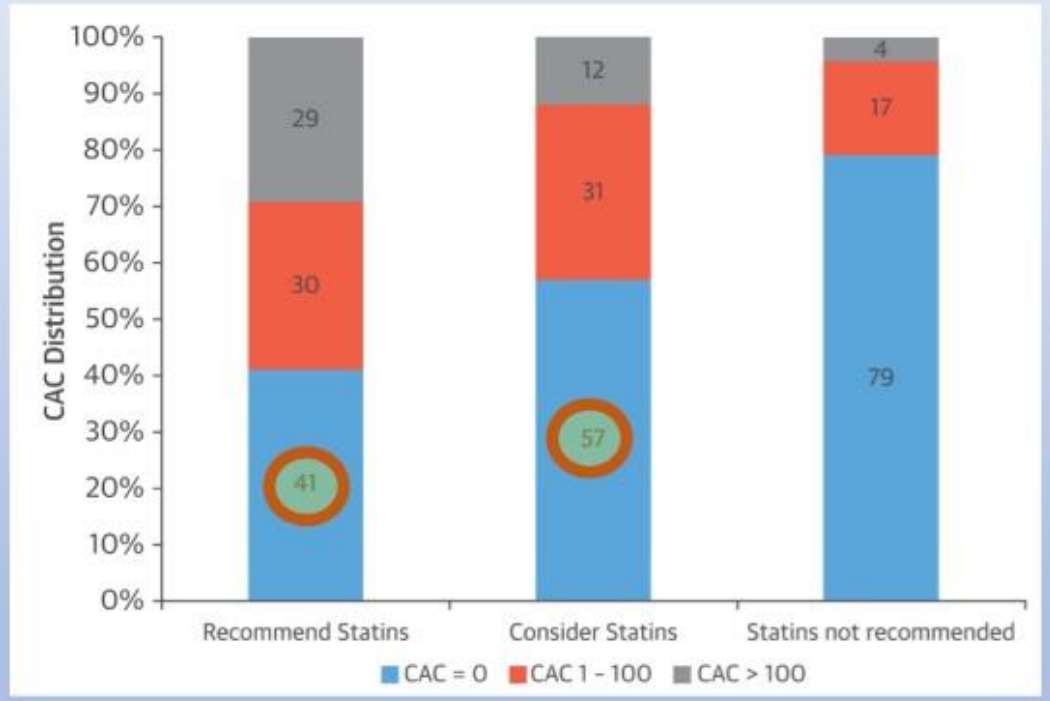
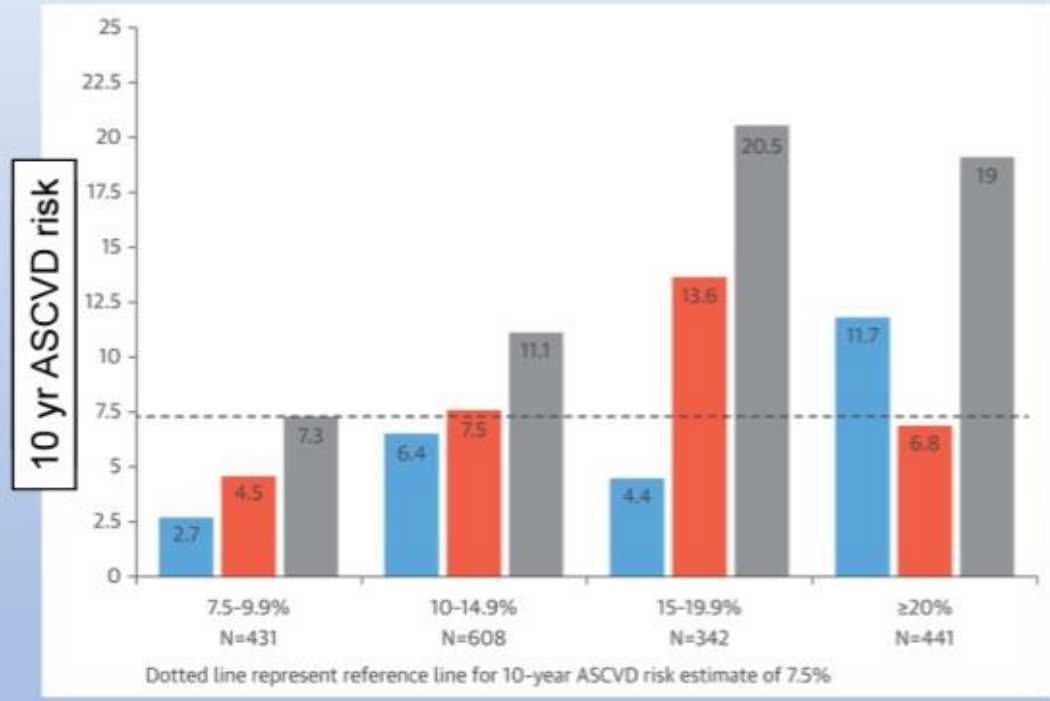
CACS of 0: can de-risk patients not needing statin (MESA)

MESA Study: n=4758 pts, median age 59, f/u 10.3 yrs





44% of pts where PCE-calculator indicated a statin (10 yr predicted risk >7.5%) had a CACS=0 and a much lower ACTUAL 10 year risk (<4.2%) and thus didn't need a statin

Nasir, J Am Coll Cardiol 2015;66:1657–68

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ACC/AHA cholesterol 2018 Guidelines - CACS

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

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Incorporating Other Lab Testing in Clinical Practice

Genetic Testing and Lp(a)

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THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Clinical Genetic Testing for Familial Hypercholesterolemia

JACC Scientific Expert Panel

Amy C. Sturm, MS,[a,*] Joshua W. Knowles, MD, PhD,[b,c,*] Samuel S. Gidding, MD,[d,*] Zahid S. Ahmad, MD,[e] Catherine D. Ahmed, MBA,[c] Christie M. Ballantyne, MD,[f] Seth J. Baum, MD,[c,g] Mafalda Bourbon, PhD,[h,i] Alain Carrié, MD, PhD,[j] Marina Cuchel, MD, PhD,[k] Sarah D. de Ferranti, MD, MPH,[l] Joep C. Defesche, PhD,[m] Tomas Freiberger, MD, PhD,[n,o] Ray E. Hershberger, MD,[p] G. Kees Hovingh, MD, PhD,[q] Lala Karayan, MPH,[c] Johannes Jacob Pieter Kastelein, MD, PhD,[q] Iris Kindt, MD, MPH,[c] Stacey R. Lane, JD, MBE,[c] Sarah E. Leigh, MSc, PhD,[r] MacRae F. Linton, MD,[s] Pedro Mata, MD, PhD,[t] William A. Neal, MD,[c,u] Børge G. Nordestgaard, MD, DMSc,[v,w] Raul D. Santos, MD, PhD,[x] Mariko Harada-Shiba, MD, PhD,[y] Eric J. Sijbrands, MD, PhD,[z] Nathan O. Stitziel, MD, PhD,[aa] Shizuya Yamashita, MD, PhD,[bb,cc] Katherine A. Wilemon, BS,[c,†] David H. Ledbetter, PhD,[a,†] Daniel J. Rader, MD,[c,dd,†]
Convened by the Familial Hypercholesterolemia Foundation

EBAC

ABIM CME MOC ACCREDITED

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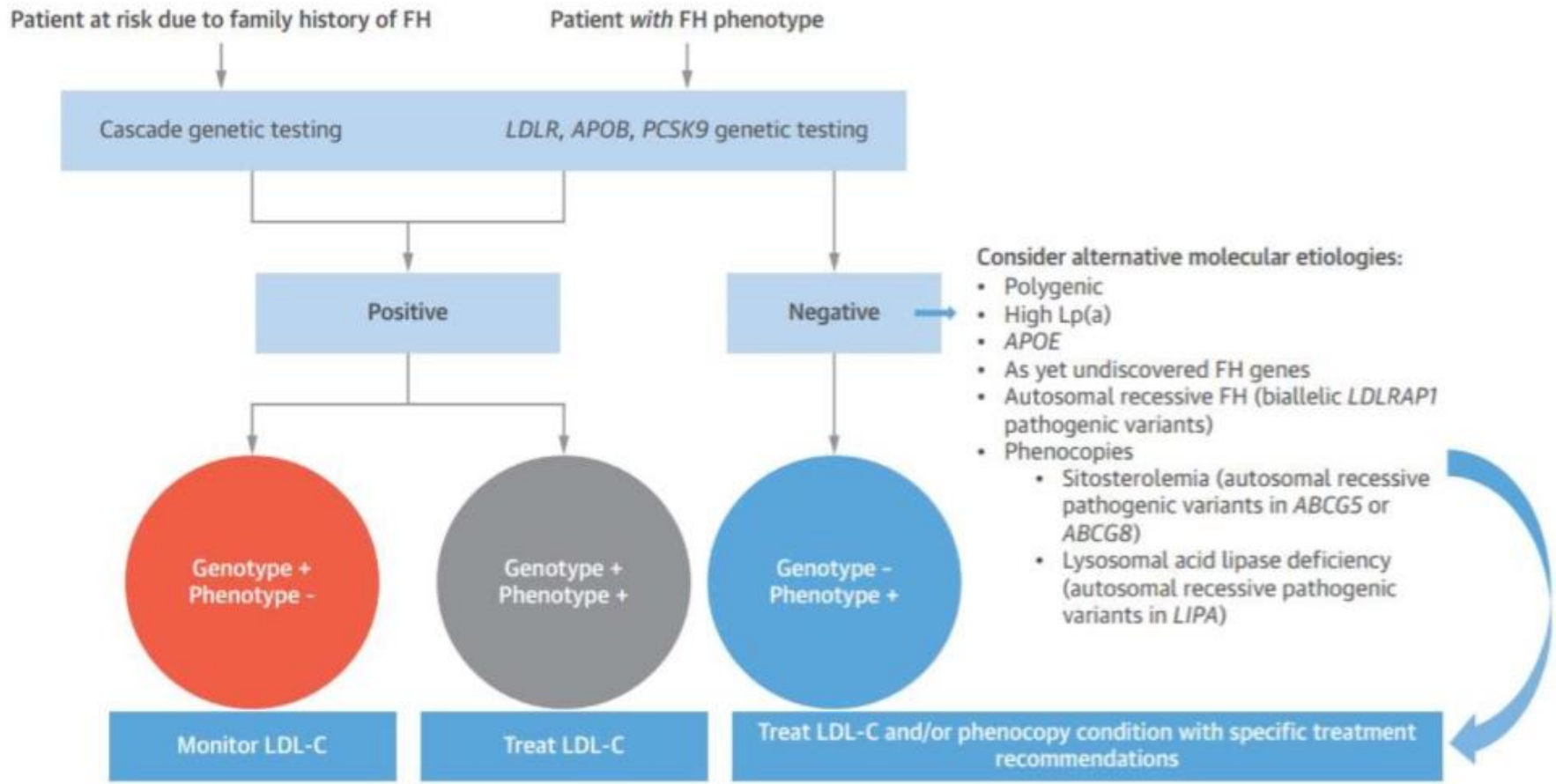
FIGURE 2 **Different Categories of Patients May Undergo FH Genetic Testing**



Individuals at risk due to family history as well as individuals with an FH phenotype may undergo FH genetic testing. The results of this testing can result in 3 categories of individuals: 1) genotype positive, phenotype negative; 2) genotype positive, phenotype positive; and 3) genotype negative, phenotype positive. In some cases, alternative molecular etiologies should be explored. Abbreviations as in Figure 1.

Sturm AC et al. J Am Coll Cardiol. 2018;72:662-680

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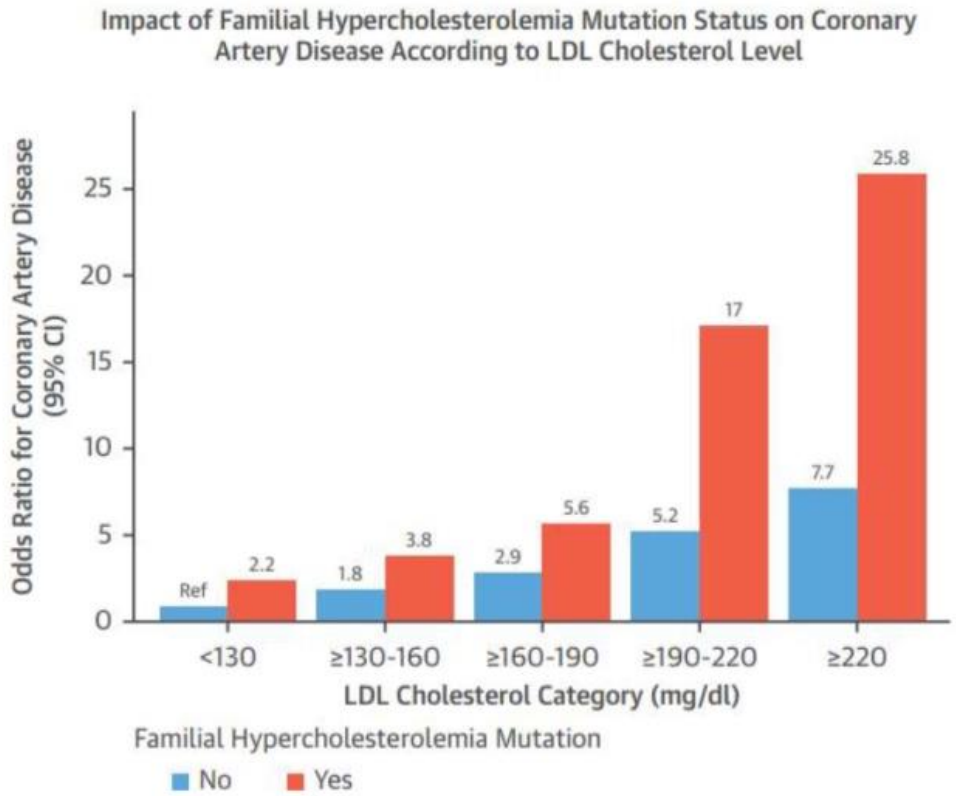
FIGURE 3 **FH Genetic Testing Provides Prognostic Information and the Ability to Perform Refined Risk Stratification**



The risk for CAD is higher in FH pathogenic variant carriers compared to noncarriers at any LDL-C value. Reproduced with permission from Khera et al. (36). Abbreviations as in Figure 1.

Sturm AC et al. J Am Coll Cardiol. 2018;72:662-680

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TABLE 2 Recommendations and Considerations for Genetic Testing for FH

A. Proband (index case)

Genetic testing for FH **should be offered** to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient's clinical and/or family histories. This index of suspicion includes the following:

1. Children with persistent* LDL-C levels ≥160 mg/dl or adults with persistent* LDL-C levels ≥190 mg/dl without an apparent secondary cause of hypercholesterolemia† and with at least 1 first-degree relative similarly affected or with premature CAD‡ or where family history is not available (e.g., adoption)
2. Children with persistent* LDL-C levels ≥190 mg/dl or adults with persistent* LDL-C levels ≥250 mg/dl without an apparent secondary cause of hypercholesterolemia,† even in the absence of a positive family history

Evidence Grade: Class of Recommendation IIa, Strength of Evidence B-NR

Genetic testing for FH **may be considered** in the following clinical scenarios:

1. Children with persistent* LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia†) with an LDL-C level ≥190 mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD‡
2. Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD‡ and family history of both hypercholesterolemia and premature CAD‡
3. Adults with persistent* LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia†) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD‡

Evidence Grade: Class of Recommendation IIb, Strength of Evidence C-EO

B. At-risk relatives

1. Cascade genetic testing for the specific variant(s) identified in the FH proband (known familial variant testing) should be offered to all first-degree relatives. If first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to second-degree relatives. Cascade genetic testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified

Evidence Grade: Class of Recommendation I, Strength of Evidence B-R

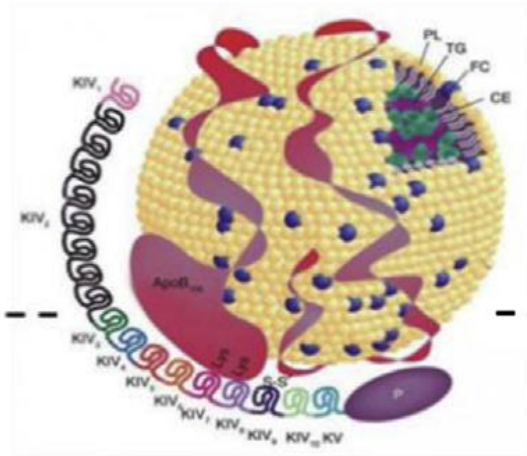
Sturm AC et al. J Am Coll Cardiol. 2018;72:662-680

Clinical Utility of Lp(a) from NLA

Lipoprotein(a)

Effect

Thrombosis **Atherosclerosis**



Lp(a) Component

Apolipoprotein (a) ← LDL-like particle

Mechanism

Indirectly through fibrinolysis inhibition.

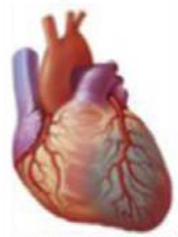
Intimal cholesterol deposition, inflammation & OxPL.

Site

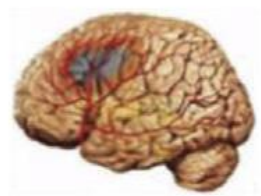
At plaque rupture

At turbulent blood flow

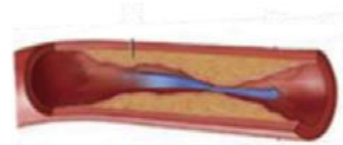
Clinical Event



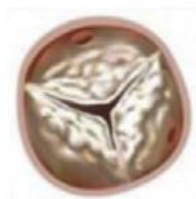
Myocardial Infarction



Ischemic Stroke

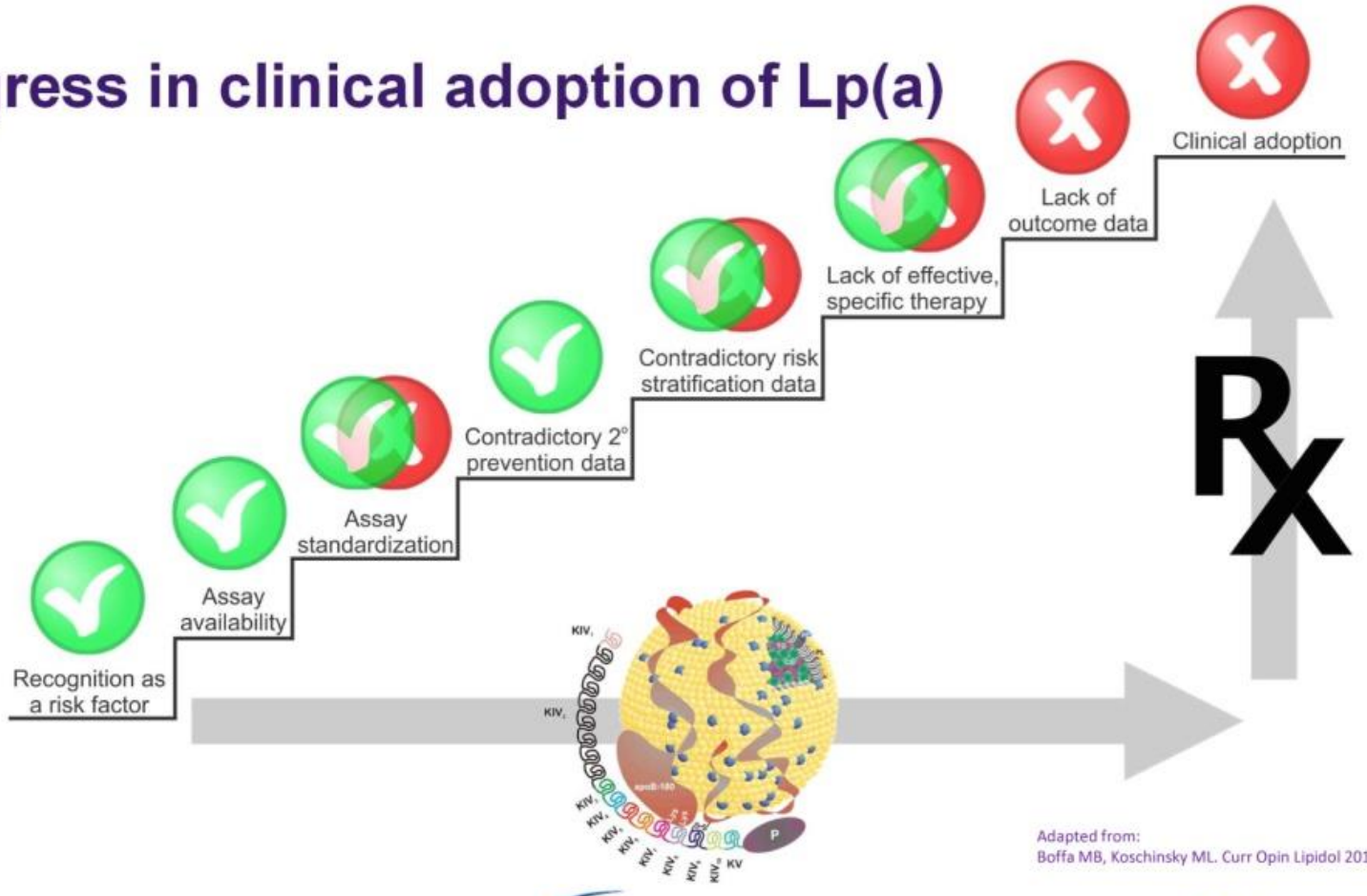


Atherosclerotic Stenosis



Aortic Valve Stenosis

Progress in clinical adoption of Lp(a)



Adapted from:
Boffa MB, Koschinsky ML. Curr Opin Lipidol 2018;29:259

Schulich MEDICINE & DENTISTRY

robarts RESEARCH

Western

Use of Lipoprotein(a) in Clinical Practice: A Biomarker Whose Time Has Come.

A Scientific Statement from the National Lipid Association

Lipoprotein (a)
… an independent risk marker for ASCVD.

- What are the causal links between increased circulating concentrations of Lp(a) and 1) ASCVD and 2) valvular aortic stenosis?
- How should we measure and report Lp(a)?
- Who should have Lp(a) measured and when?
- How does the level of Lp(a) affect treatment?

Choice of Lp(a) Assay

- Recommendation is to select assay with all of the following characteristics, where possible:
  - Reports results in nmol/L
  - Utilizes a 5-point calibrator (or similar)
  - Calibrated against WHO/IFCCLM secondary reference material

II. Lipoprotein(a) Testing in Clinical Practice

1. Adults (> 20 years of age)

Measurement of Lp(a) is reasonable to refine risk assessment for ASCVD events in:

1)	Individuals with a family history of 1st degree relatives with premature ASCVD (<55 years of age in men; <65 years of age in women)	IIa	C-LD	Rallidis, 2018
2)	Individuals with premature ASCVD (<55 years of age in men and <65 years of age in women), particularly in the absence of traditional risk factors.	IIa	B NR	Erqou, 2009; Kamstrup, 2013 ; Clarke 2009; CARDIoGRAMplus C4D Consortium, 2013; Genest,1992
3)	Individuals with primary severe hypercholesterolemia (LDL ≥190mg/dL) or suspected familial hypercholesterolemia.	IIa	B-NR	Pérez de Isla, 2017; Ellis, 2016; Langsted 2016; Ellis, 2019
4)	Individuals at very high** ASCVD risk to better define those who are more likely to benefit from PCSK9 inhibitor therapy	IIa	B-NR	O'Donoghue,2018; Bittner, 2018

II. Lipoprotein(a) Testing in Clinical Practice

1. **Adults (> 20 years of age)**
   Measurement of Lp(a) may be reasonable with:

1) Intermediate (7.5-19.9%) 10-year ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIa	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
2) Borderline (5-7.4%) 10-year ASCVD risk when the decision to use a statin is uncertain, to improve risk stratification in primary prevention.	IIb	B-NR	Nave, 2015; Willeit 2014; Grundy 2018; Wei, 2018; Kamstrup, 2013
3) Less-than-anticipated LDL-C lowering, despite good adherence to therapy.	IIb	C-LD	Yeang 2016; CARDIoGRAMplus C4D Consortium 2013; Langstead 2016
4) A family history of elevated Lp(a).	IIb	C-LD	Clarke 2009; CARDIoGRAMplus C4D Consortium 2013; Langsted 2016
5) Calcific valvular aortic stenosis.	IIb	C-LD	Thanassoulis 2013; Kamstrup 2014; Arsenault 2014; Vongpromek 2015; Capoulade 2015
6) Recurrent or progressive ASCVD, despite optimal lipid-lowering therapy.	IIb	C-LD	Albers 2013; Khera 2014; Nestel 2013;

New AHA/ACC Guidelines for Lp(a)

- E78.41 Elevated Lp(a)
- Z83.430 Family History of Elevated Lp(a)
- The ICD Codes should improve insurance coverage of the test

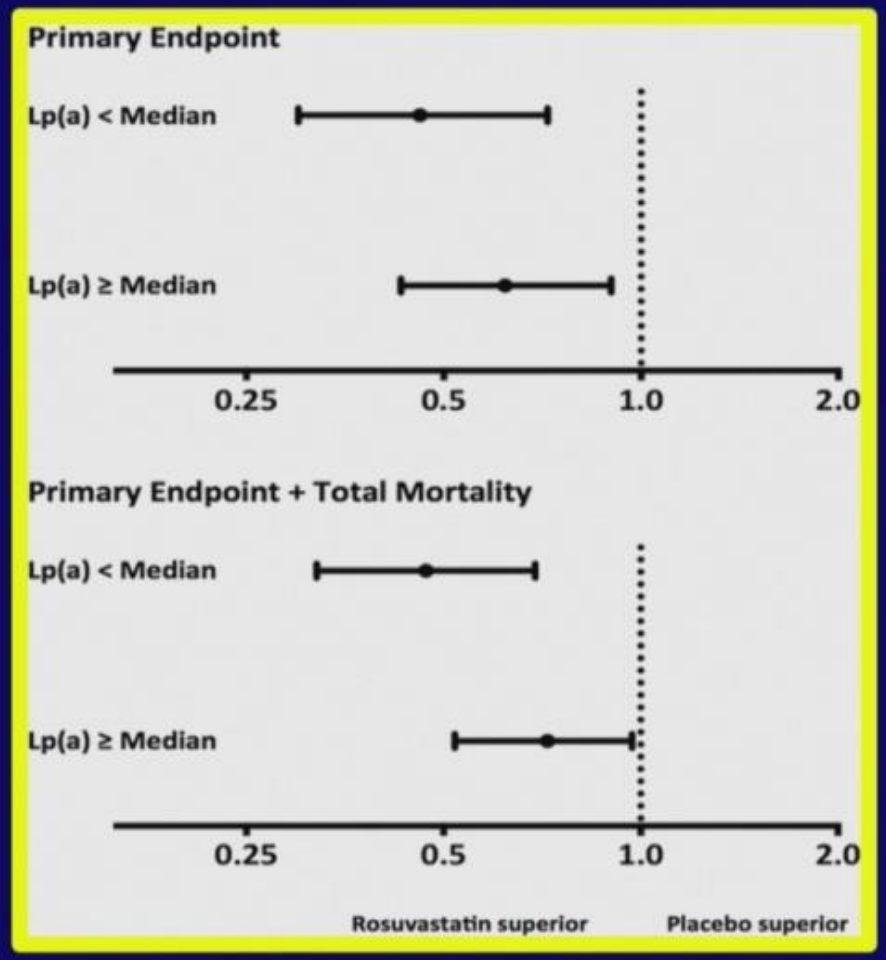
- More providers are currently covering Lp(a), resulting in reasonable patient copays
    - Quest & Cleveland Heart Lab
        - Cost to Patients (average) $25.00
        - Cost to Providers (Client Pricing) $15.00

Lp(a) as a Risk Marker for MACE in Statin-Treated Patients

- Patient-level data from 7 placebo controlled statin RCT's (N=29,069) was examined for fatal or non fatal CHD, stroke or revascularization across Lp(a) tertiles compared to Lp(a) <15 mg/dL, with multivariate adjustment
- MACE risk more strongly associated with on-statin Lp(a) than on-placebo Lp(a), especially at younger ages
- **Elevated Lp(a) in statin-treated patients signifies increased risk**

Willeit P et al. Lancet 2018;392:1311-20.

Efficacy of Rosuvastatin* According to Baseline Lp(a)



*On-statin Lp(a) concentrations were associated with residual risk of CVD (adjusted hazard ratio, 1.27; 95% CI, 1.01-1.59; P=0.04), which was independent of LDL-c and other factors.

Khera A V et al. *Circulation*. 2014;129:635-642

Does Drug Therapy Affect Risk in ASCVD patients with ↑Lp(a)?

	Impact on Lp(a)	Effect on ASCVD Outcomes
Statins	Minimal or mild ↑	Rosuvastatin 20 mg daily reduced ASCVD risk equally in all ethnicities, whether Lp(a) above or below median[1]
Ezetimibe	Minimal ↓ as monotherapy[2]	Unknown
PCSK9 inhibitors	Evolocumab ↓ by median 27%	Reduces RR of CHD death, MI or urgent revascularization 23% if Lp(a) >37 nmol/L (NNT_{3y} 40) vs. those with Lp(a) ≤37 (NNT_{3y} 105)[4]
	Alircomab ↓ by median 29%[3]	Proportion of MACE reduction attributable to changes in Lp(a) greatest in those with Lp(a) >59.6 mg/dL[5]

1. Khera AV et al. Circulation. 2014 Feb 11;129(6):635-42. 2. Awad K et al. Drugs 2018;78:453-62.
3. Gaudet D et al. Am J Cardiol 2017;119: 40-64. 4. O'Donoghue M et al. Circulation. 2019;139:1483–1492
5. Presented by V. Bittner ACC19

What Does the NLA Lp(a) Expert Panel Advise?

6. Niacin, which lowers Lp(a) concentration, ***is not recommended*** to reduce ASCVD risk in patients receiving moderate-to-high intensity statins +/- ezetimibe and an on-treatment LDL-C <80 mg/dL	III (harm)	A	Albers, 2013 ; Parish, 2018

2. In high* or very high** risk patients, with Lp(a) ≥50 mg/dL or ≥100 nmol/L[§], it ***is reasonable*** to consider more intensive LDL-C lowering to achieve greater ASCVD risk reduction.	IIa	A	Willeit, 2018); Khera, 2014; Baigent, 2000

What Does the NLA Lp(a) Expert Panel Advise?

3. In very high** risk patients, taking a maximally tolerated statin with Lp(a) ≥50 mg/dL or ≥100 nmol/L§, the addition of ezetimibe ***is reasonable*** in those with on-treatment LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL).	IIa	B-R	Cannon, 2015
5. In very high risk** patients taking a maximally tolerated statin and ezetimibe, with an LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL) and an Lp(a) of ≥50 mg/dL or ≥100 nmol/L§, the addition of a PCSK9 inhibitor ***is reasonable***.	IIa	B-R	O'Donoghue,2018; Bittner, 2018; Sabatine, 2017; Schwartz, 2018
4. In high* risk patients taking a maximally tolerated statin, with Lp(a) ≥50 mg/dL or ≥100 nmol/L§, the addition of ezetimibe ***may be reasonable*** in those with on-treatment LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL).	IIb	B-R	Cannon, 2015

Lipid Levels Pre and Post Lipid-Apheresis

Pre

Total Cholesterol	611 mg/dL
Triglycerides	128 mg/dL
HDL	78 mg/dL
LDL	507 mg/dL
Lp(a)	105 mg/dL

Post

Total Cholesterol	216 mg/dL
Triglycerides	49 mg/dL
HDL	72 mg/dL
LDL	134 mg/dL
Lp(a)	28mg/dL

International Guidelines for Initiating Lipid-Apheresis

North America	LDL-C ≥ 160 mg/dL (with CHD) -or - LDL-C ≥ 300 mg/dL (without CHD)
Japan	TC ≥ 250 mg/dL (with CHD)
Germany	LDL-C ≥ 130 mg/dL (with CHD) Lp(a) ≥ 60mg/dL (with progressive CHD)

Lp(a) and Secondary Prevention: Summary

- Be aware of Lp(a)-associated increased risk for recurrent events
- Continue to follow Guideline based therapies, as most lipid-related risk is still attributable to LDL-C
- Consider more aggressive LDL-C lowering for ASCVD patients with increased Lp(a)
- Consider earlier use of PCSK9 inhibitors in ASCVD patients with elevated Lp(a)

ESC
European Society of Cardiology
European Heart Journal (2019) **00**, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

2019 ESC/EAS Guidelines for themanagement of dyslipidaemias

- Measurement of Lp(a) should be considered at least once in each person's lifetime to identify people who have inherited an extremely elevated level of Lp(a) >_180 mg/dL (>_430 nmol/L) and therefore have a very high lifetime risk of ASCVD that is approximately equivalent to the risk associated with HeFH.
- To identify people with less-extreme Lp(a) elevations who may be at a higher risk of ASCVD, which is not reflected by the SCORE system, or by other lipid or lipoprotein measurements.
- Measurement of Lp(a) has been shown to provide clinically significant improved risk reclassification under certain conditions, and therefore should be considered in patients who have an estimated 10-year risk of ASCVD that is close to the threshold between high and moderate risk.

Lipoprotein™ a FOUNDATION

Educating, empowering and saving lives

nla NATIONAL LIPID ASSOCIATION

Clinical Trials

Lower LDL, PCSK9i event reduction, REDUCE IT

NATIONAL LIPID ASSOCIATION

Low LDL-C is Unsafe

- Early epidemiologic studies showed an association between low cholesterol level and increased risk for cancer, intracranial hemorrhage, and death[1-3]
- Furthermore, studies in canine models raised concerns that supratherapeutic doses of statins may cause brain and optic pathology[4]

1. Kritchevsky SB. *Am J Epidemiol*. 1992;135(5):509-520.
2. Neaton JD. *Arch Intern Med*. 1992;152(7):1490-1500.
3. Tirschwell DL. *Neurology*. 2004;63(10):1868-1875.
4. Berry PH. *Am J Pathol*. 1988;132(3):427-443.

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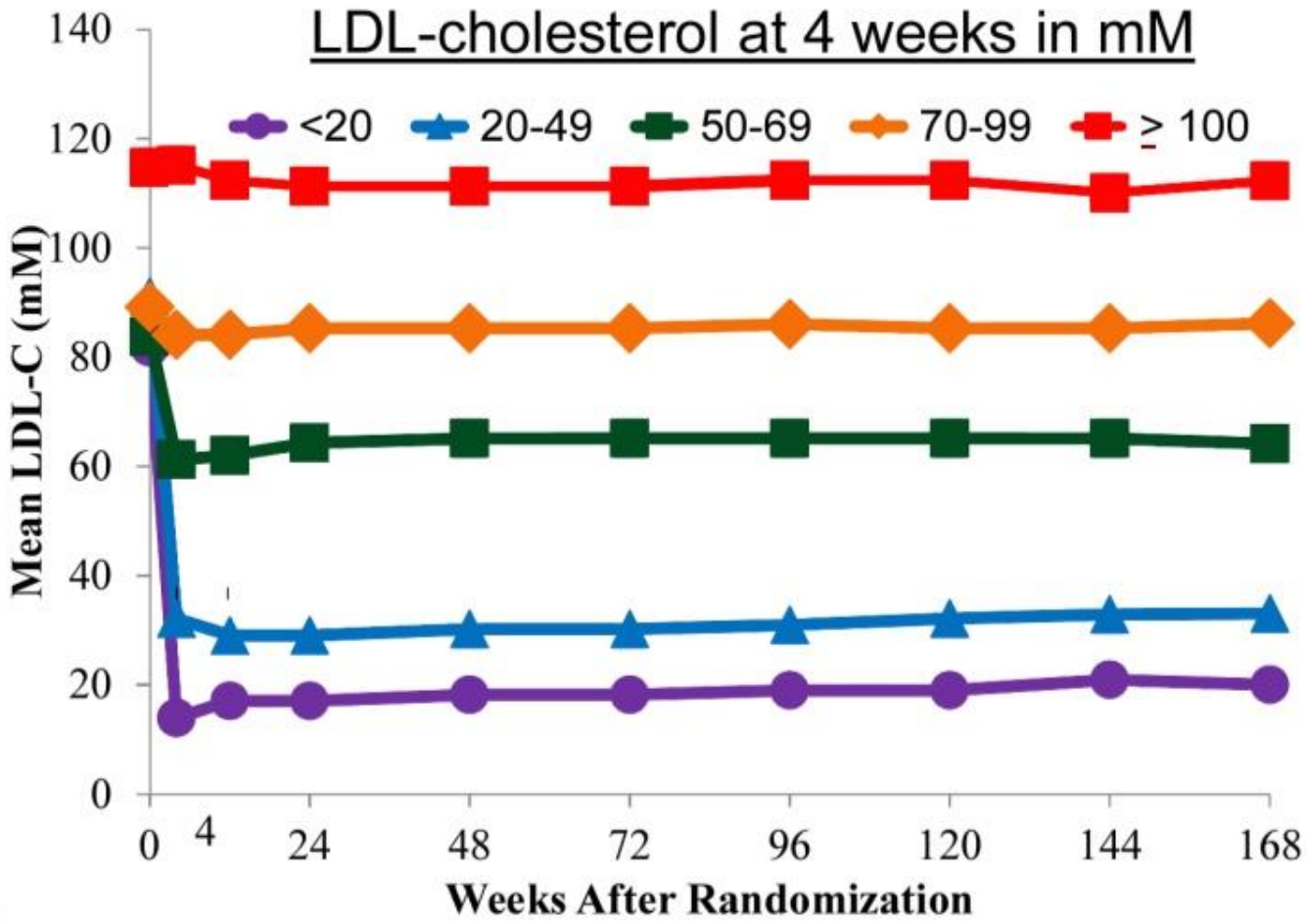
LDL-C Over Time



An Academic Research Organization of
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. Giugliano RP, Lancet. 2017;390(10106):1962-71

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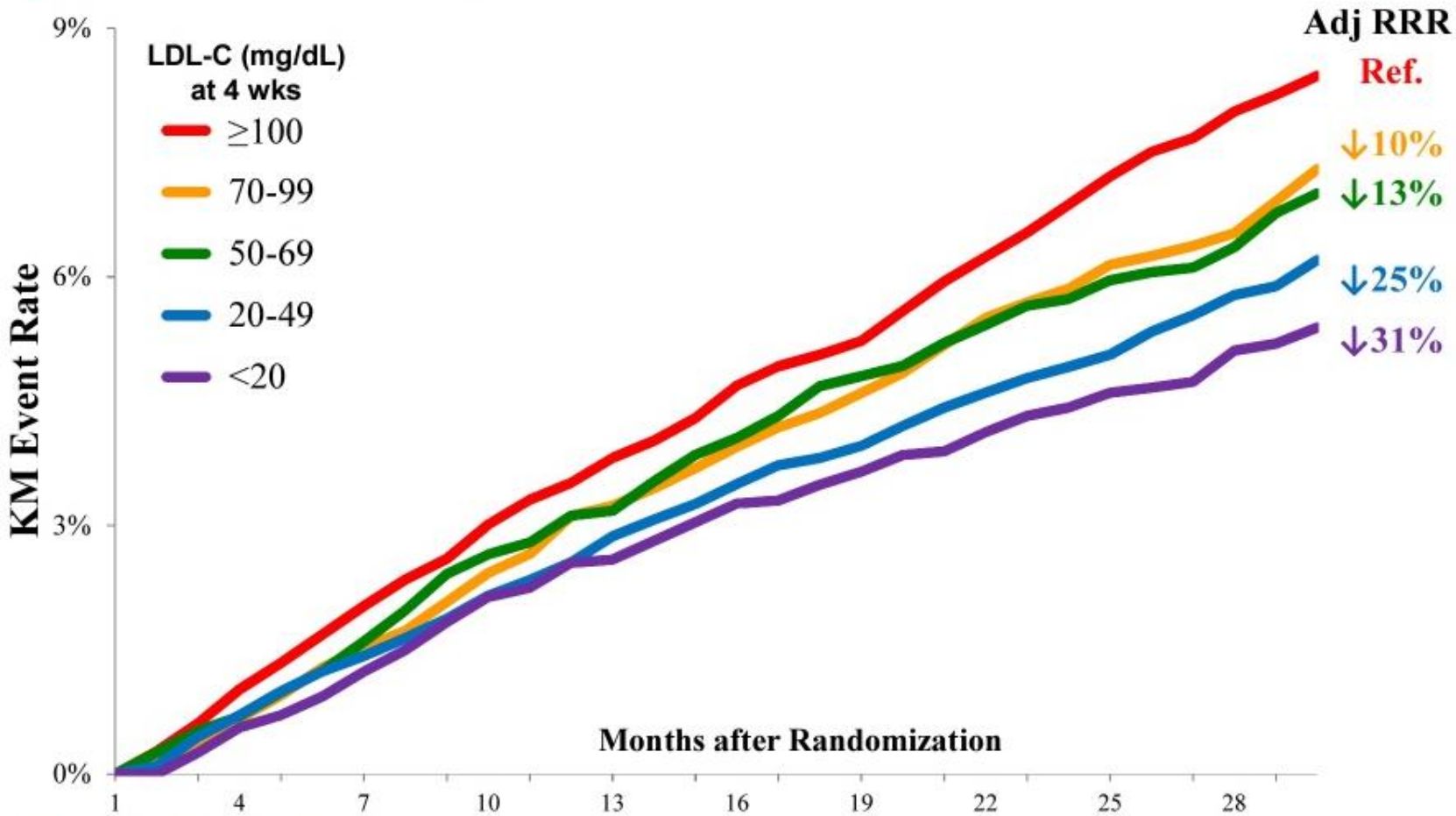
CV Death, MI or Stroke by Achieved LDL-C at Month 1

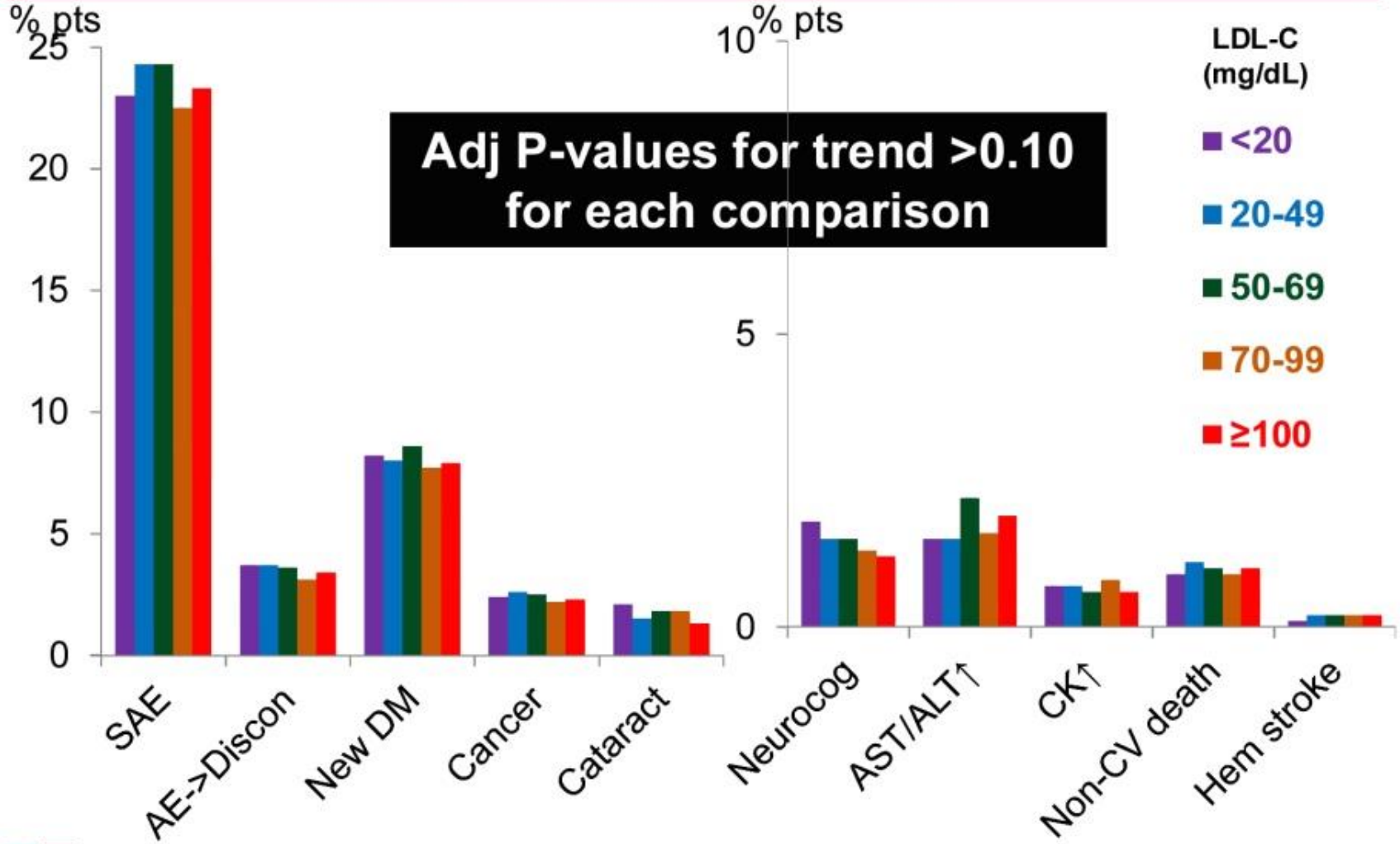


An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School

Giugliano RP et al, Lancet 2017;390:1962-71)

NATIONAL LIPID ASSOCIATION

Safety Events by Achieved LDL-C



An Academic Research Organization of
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Giugliano RP et al, *Lancet* 2017;309:1962–71

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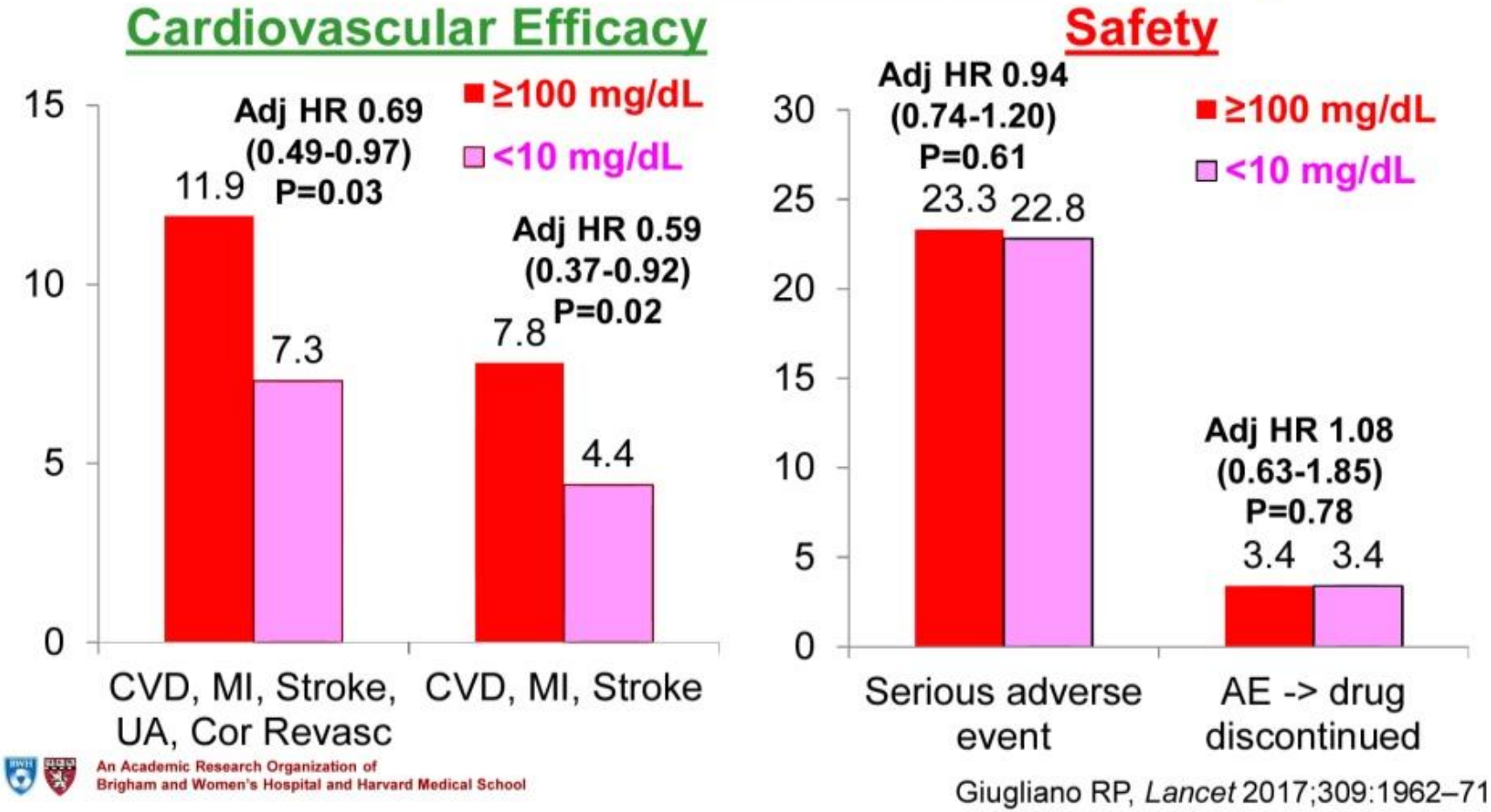
Efficacy and Safety in Pts with *Ultra-Low LDL-C* at 4 wks

N=504: Median LDL-C = 7 mg/dL



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Giugliano RP, *Lancet* 2017;309:1962–71

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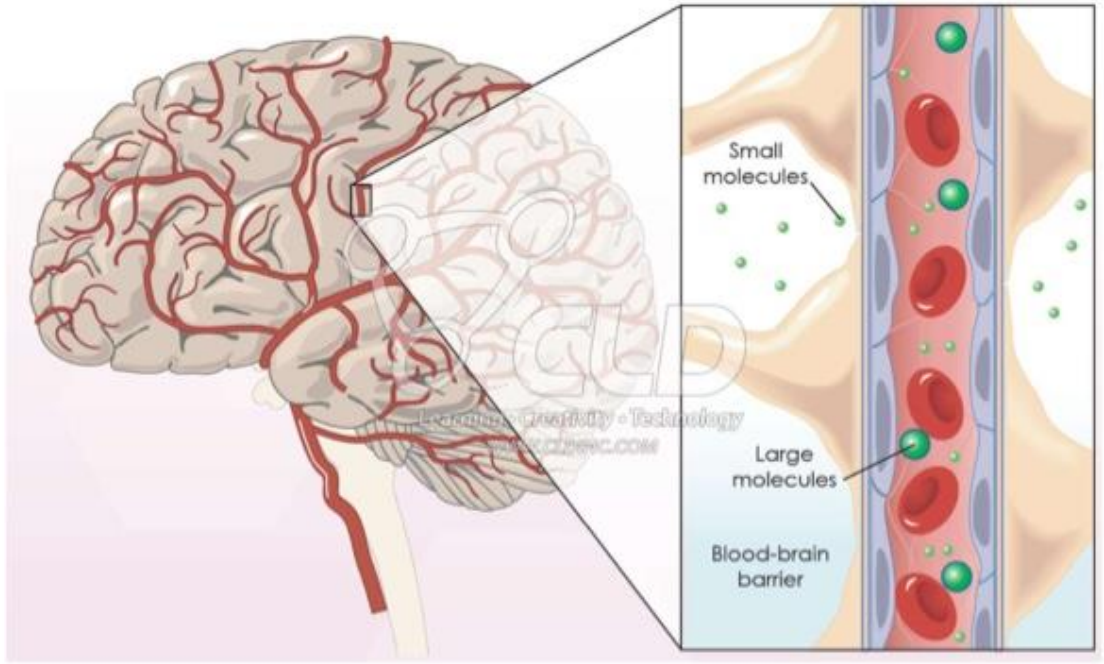
Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally



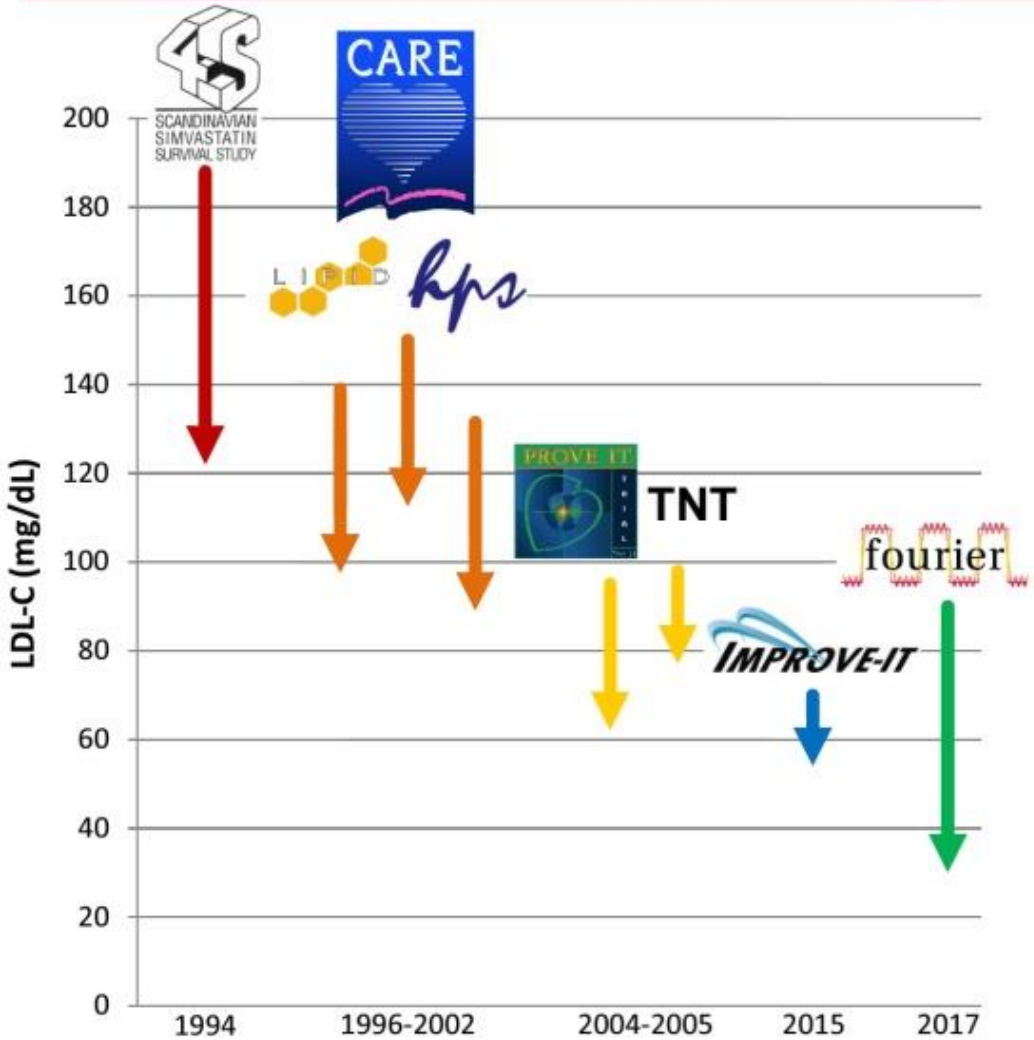
mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

*Lipinski MJ, et al. *Eur Heart J.* 2016;37(6):536-545.

A Quarter of a Century of Treating LDL-C



High is bad

Average is not good

Lower is better

Even lower is even better

Lowest is best

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LDL-C Treatment Goals Per Total ASCVD Risk Categories

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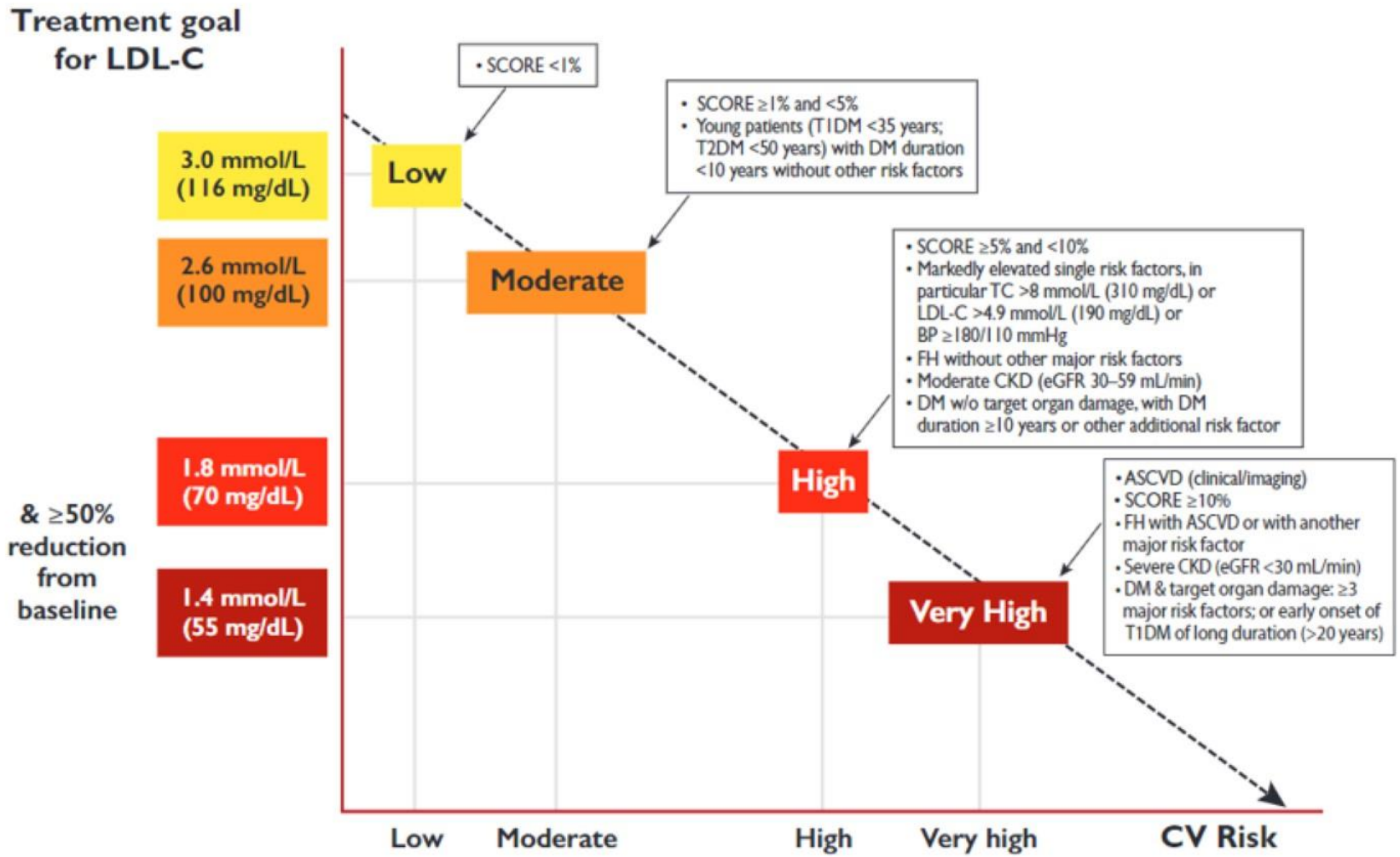


Mach F, et al. *Eur Heart J*. 2019;00:178. By permission of Oxford University Press.

2019 ESC/EAS Guidelines
New Lipid Targets and Goals

ESC
European Society of Cardiology

Patients with established ASCVD with recurrent event(s) (can be different from first event), while taking maximally tolerated statin therapy:

LDL-C Goal: < 1 mmol/L (< 40 mg/dL); Class IIb, Level B

Lower LDL-C is better for patients at very high-risk of recurrent ASCVD events

Mach F, et al. *Eur Heart J*. 2019;00:1-78.

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

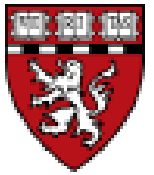
Deepak L Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD,

Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD,

Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD,

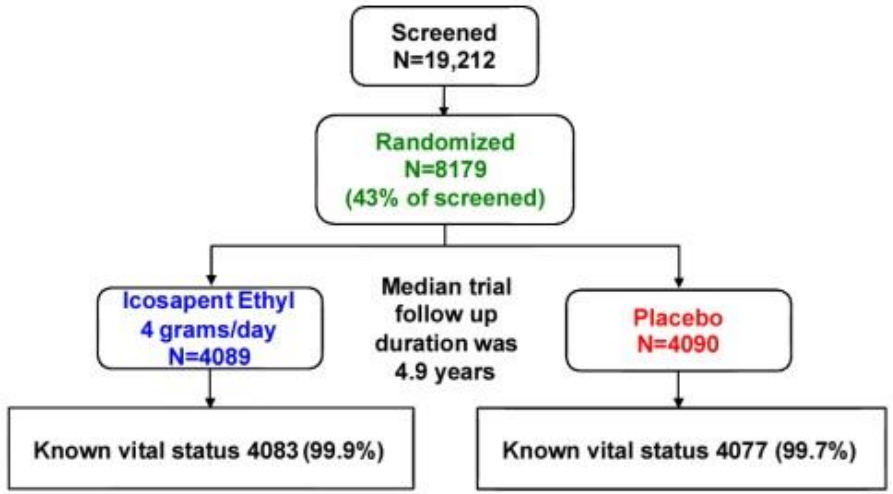
Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, Christie M. Ballantyne, MD,

on Behalf of the REDUCE-IT Investigators



REDUCE-IT In Context

REDUCE-IT Design



1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)
2. Fasting TG levels ≥135 mg/dL and <500 mg/dL
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

Primary Endpoint Events: CV death, nonfatal MI, nonfatal stroke, coronary revasc, hospitalization for unstable angina

Key Secondary Endpoint Events: CV death, nonfatal MI, nonfatal stroke

Double-blind study; Events adjudicated by CEC that was blinded to treatment during adjudication

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

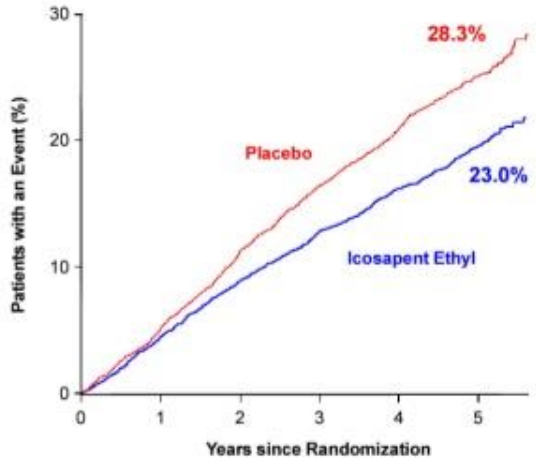
Key Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

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

REDUCE-IT In Context

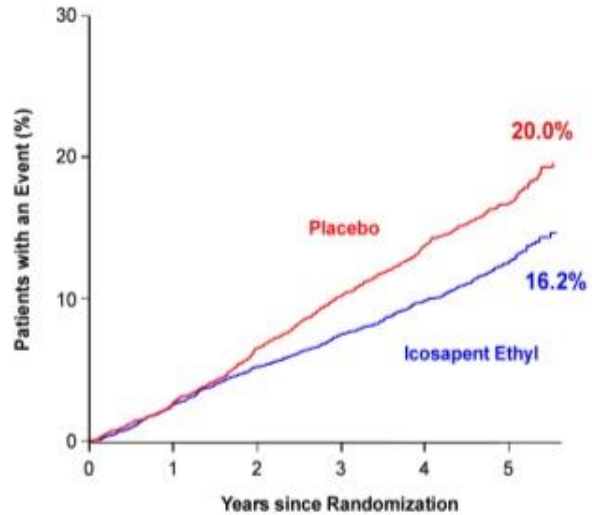
Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

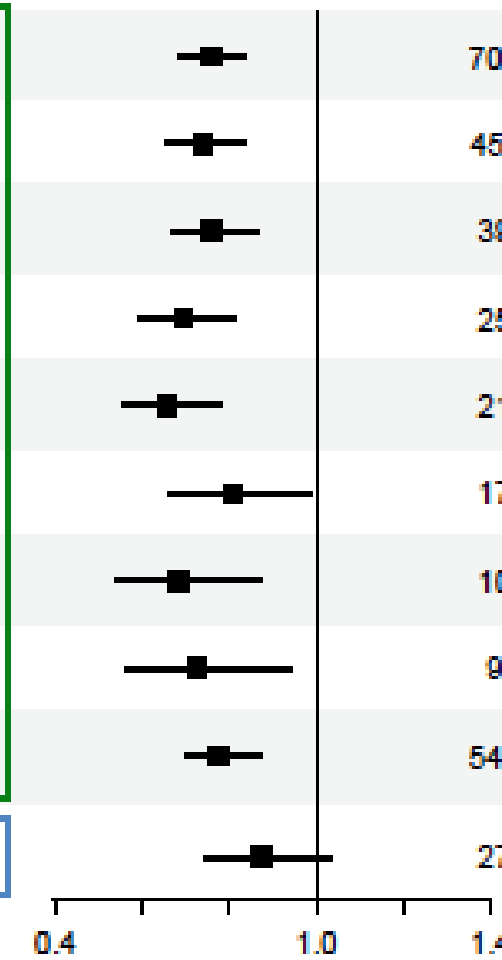
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

Prespecified Hierarchical Testing



Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

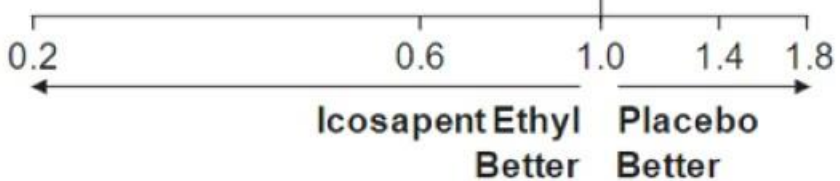
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

Roadmap

- There is a compelling body of evidence to support the association of triglycerides with cardiovascular risk, in both epidemiologic and Mendelian randomization studies.
- While clinical trials have been mixed, there certainly are data to support the role of triglyceride lowering to reduce adverse CV events.
- Against this backdrop, one can properly put into context the benefits seen in the REDUCE-IT trial with the achieved triglyceride lowering with EPA.

Primary Composite Endpoint
Total Endpoint Events by Baseline TG Tertiles

TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001



***P (interaction) = 0.17**

Bhatt DL, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.

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REDUCE-IT to Practice: Is it the Dose?

Donald M. Lloyd-Jones, MD ScM FACC FAHA
Eileen M. Foell Professor
Chair, Dept. of Preventive Medicine
Senior Associate Dean
Director, NUCATS Institute
Northwestern Feinberg School of Medicine

Meta-Analysis 2018

- Median dose of omega-3 supplement ~1 g/day of combination EPA/DHA*

*JELIS had 1.8 g/day EPA only

Table. Characteristics of Included Trials

Study (Year)	Patients, No.	Dose of EPA/DHA (mg/d)	Male, No. (%)	Mean Trial Duration, y	Mean (SD) Age, y	No. (%)			
						Prior CHD	Prior Stroke	Prior Diabetes	Statin Use
DOIT (2010)	563	1150/800	563 (100)	3	70 (3)	133 (23.6)	37 (6.6)	46 (8.2)	NA
AREDS-2 (2014)	4203	650/350	1816 (43.2)	4.5	74 (NA)	405 (9.7)	211 (5.0)	546 (13.0)	1866 (44.4)
SU.FOL.OM3 (2010)	2501	400/200	1987 (79.4)	4.7	61 (NA)	1863 (74.5)	638 (25.5)	440 (17.9)	2079 (83.1)
JELIS (2007)[a,b]	18 645	1800/NA	5859 (31.4)	4.6	61 (8)	NA	NA	3040 (16.3)	18 645 (100.0)
Alpha Omega (2010)	4837	226/150	3783 (78.2)	3.3	69 (6)	4837 (100.0)	345 (7.2)	1014 (21.0)	4122 (85.2)
OMEGA (2010)	3818	460/380	2841 (74.4)	1	64 (NA)	796 (22.5)	192 (5.5)	948 (27.0)	3566 (94.2)
R&P (2013)	12 505	500/500	7687 (61.5)	5	64 (NA)	Not stated (30)	594 (4.8)	7494 (59.9)	12 505 (100.0)
GISSI-HF (2008)	6975	850/950	5459 (78.3)	3.9	67 (11)	3614 (51.8)	346 (5.0)	1974 (28.3)	NA
ORIGIN (2012)	12 536	465/375	8150 (65.0)	6.2	64 (8)	8094 (64.6)	10 877 (86.8)	11 081 (88.4)	6739 (53.8)
GISSI-P[b] (1999)	11 334	850/1700	9658 (85.2)	3.5	59 (11)	11 334 (100.0)	NA	2139 (18.9)	NA
Total	77 917	NA	47 803 (61.4)	4.4	64	31 076/46 767 (66.4)	13 240/47 938 (27.6)	28 722 (36.9)	49 522 (83.4)

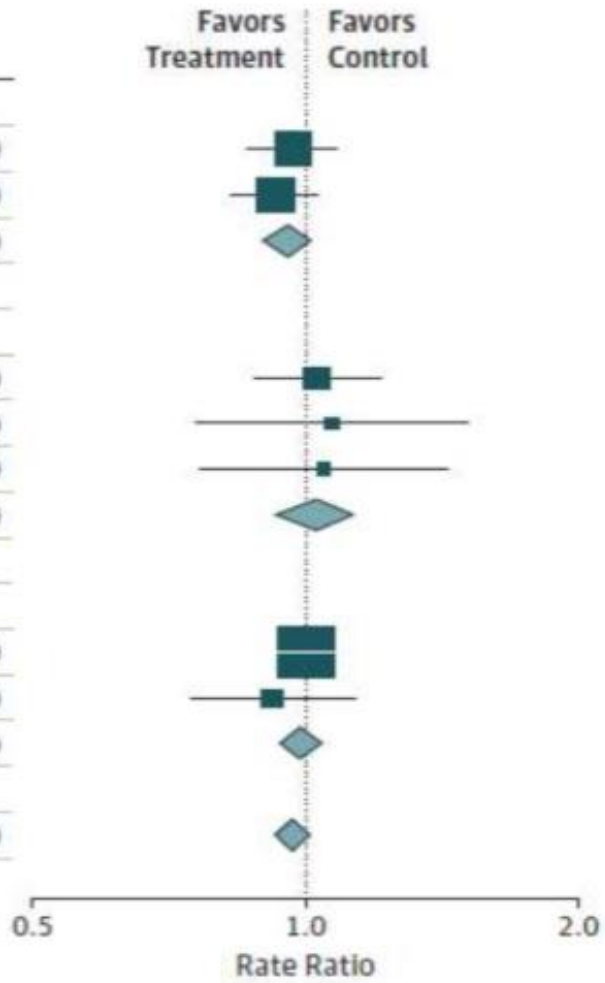
Northwestern Medicine

Aung, *JAMA Cardiol*, 2018

Meta-Analysis 2018

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

Source	No. of Events (%)		Rate Ratios (CI)
	Treatment	Control	
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	3040 (9.3)	3044 (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

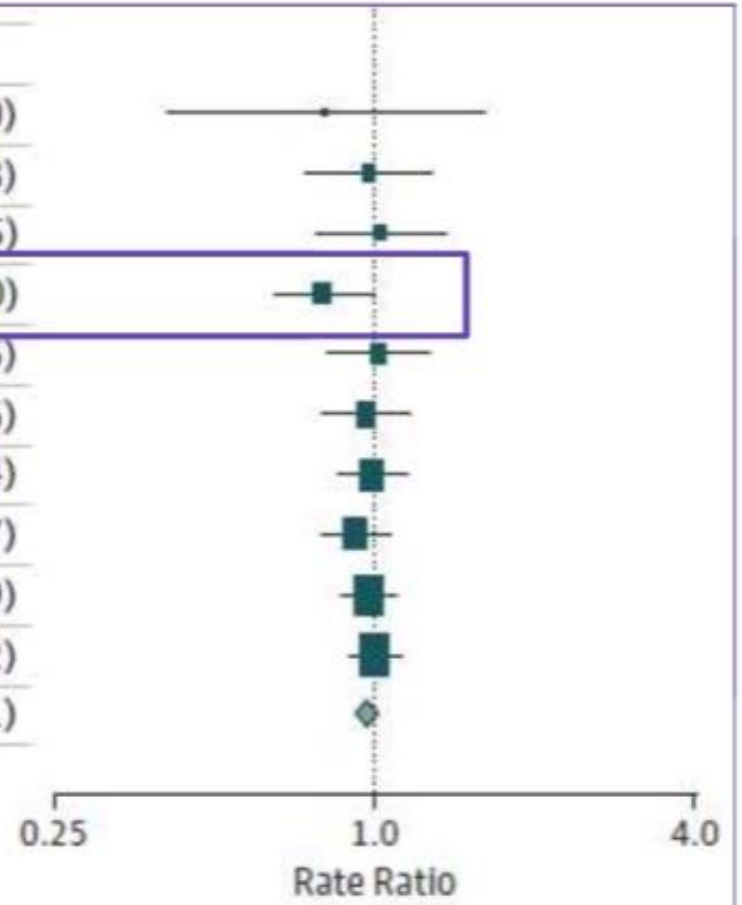


Aung, *JAMA Cardiol*, 2018

Meta-Analysis 2018

JELIS as an outlier

Major vascular events			
DOIT	29 (10.3)	35 (12.5)	0.81 (0.41-1.60)
AREDS-2	213 (9.9)	208 (10.1)	0.98 (0.75-1.28)
SU.FOL.OM3	216 (17.2)	211 (16.9)	1.02 (0.78-1.35)
JELIS	262 (2.8)	324 (3.5)	0.80 (0.65-1.00)
Alpha Omega	332 (13.8)	331 (13.6)	1.02 (0.82-1.26)
OMEGA	534 (27.7)	541 (28.6)	0.96 (0.80-1.16)
R&P	733 (11.7)	745 (11.9)	0.99 (0.86-1.14)
GISSI-HF	783 (22.4)	831 (23.9)	0.92 (0.80-1.07)
ORIGIN	1276 (20.3)	1295 (20.7)	0.98 (0.87-1.09)
GISSI-P	1552 (27.4)	1550 (27.3)	1.00 (0.90-1.12)
All	5930 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P=.10



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Aung, *JAMA Cardiol*, 2018

Dose Response of Plasma EPA Levels and Clinical Outcomes

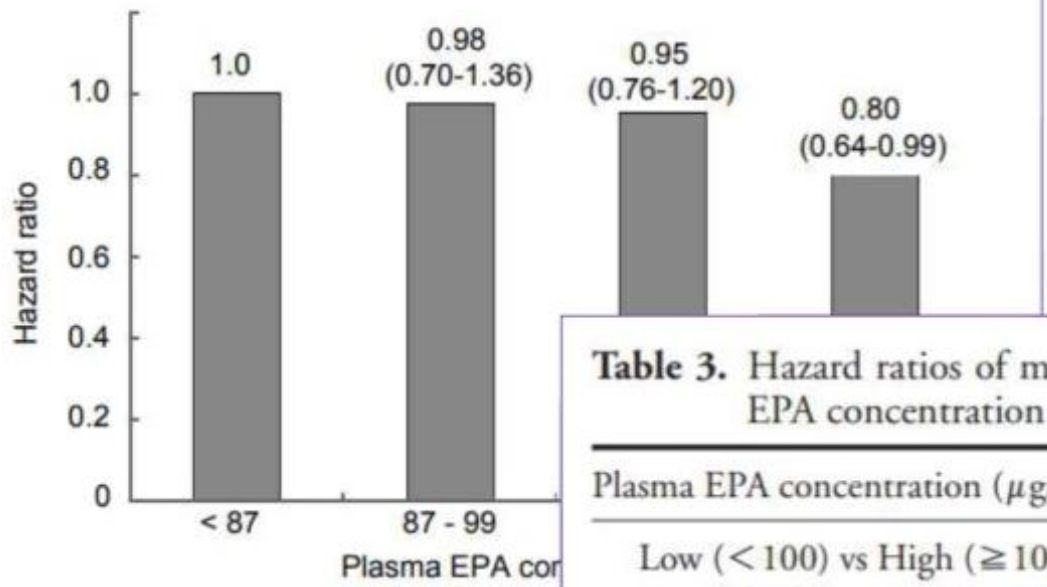

Fig. 3. Relationship between on-t
tion and adjusted risk of m

Table 3. Hazard ratios of major coronary events by cut-off point of on-treatment plasma EPA concentration and EPA/AA ratio

Plasma EPA concentration (μg/mL)	Hazard ratio	95% CI	*p* value
Low (<100) vs High (≧100)	0.87	0.72-1.03	0.110
Low (<150) vs High (≧150)	0.82	0.68-0.98	0.032
Low (<200) vs High (≧200)	0.78	0.62-0.99	0.043
Plasma EPA/AA ratio	**Hazard ratio**	**95% CI**	***p* value**
Low (<0.50) vs High (≧0.50)	0.94	0.77-1.14	0.519
Low (<0.75) vs High (≧0.75)	0.83	0.69-0.98	0.031
Low (<1) vs High (≧1)	0.80	0.67-0.97	0.021

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Itakura, *J Athero Thromb* 2011

Dose Response of Plasma EPA Levels and Clinical Outcomes

- Plasma EPA levels in JELIS
  - 170 ug/mL vs 93 ug/mL
- Plasma EPA levels in REDUCE-IT
  - 144 ug/mL vs. 23 ug/mL
- VITAL and ASCEND used lower doses (840 mg/day of EPA + DHA) and appear to have achieved lower levels, and had no significant outcome reductions

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Itakura, *J Athero Thromb* 2011

Ongoing Studies that May Shed Light on Mechanisms and Dose Effects – Expected 2020-2022

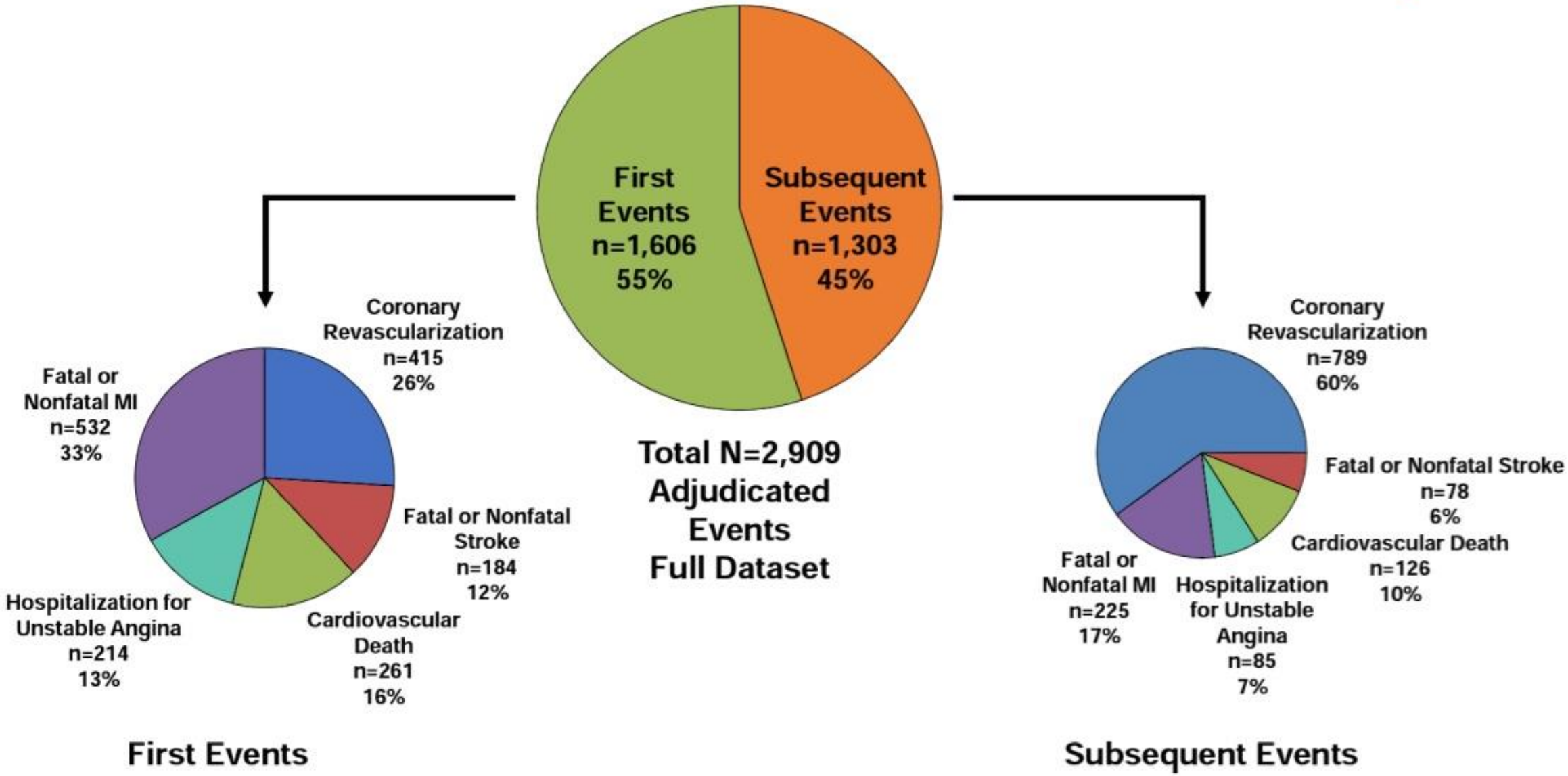
- STRENGTH
  - 2º prevention or 1º with DM, EPA + DHA 4 g/day, similar to REDUCE-IT
- EVAPORATE
  - Icosapent ethyl and changes in coronary plaque over 9-18 months
- RESPECT-EPA
  - Japan, 2º prevention, 1.8 g/day EPA
- OMEMI
  - Norway, 2º prevention, 1.8 g/day EPA + DHA

Journal of the American College of Cardiology

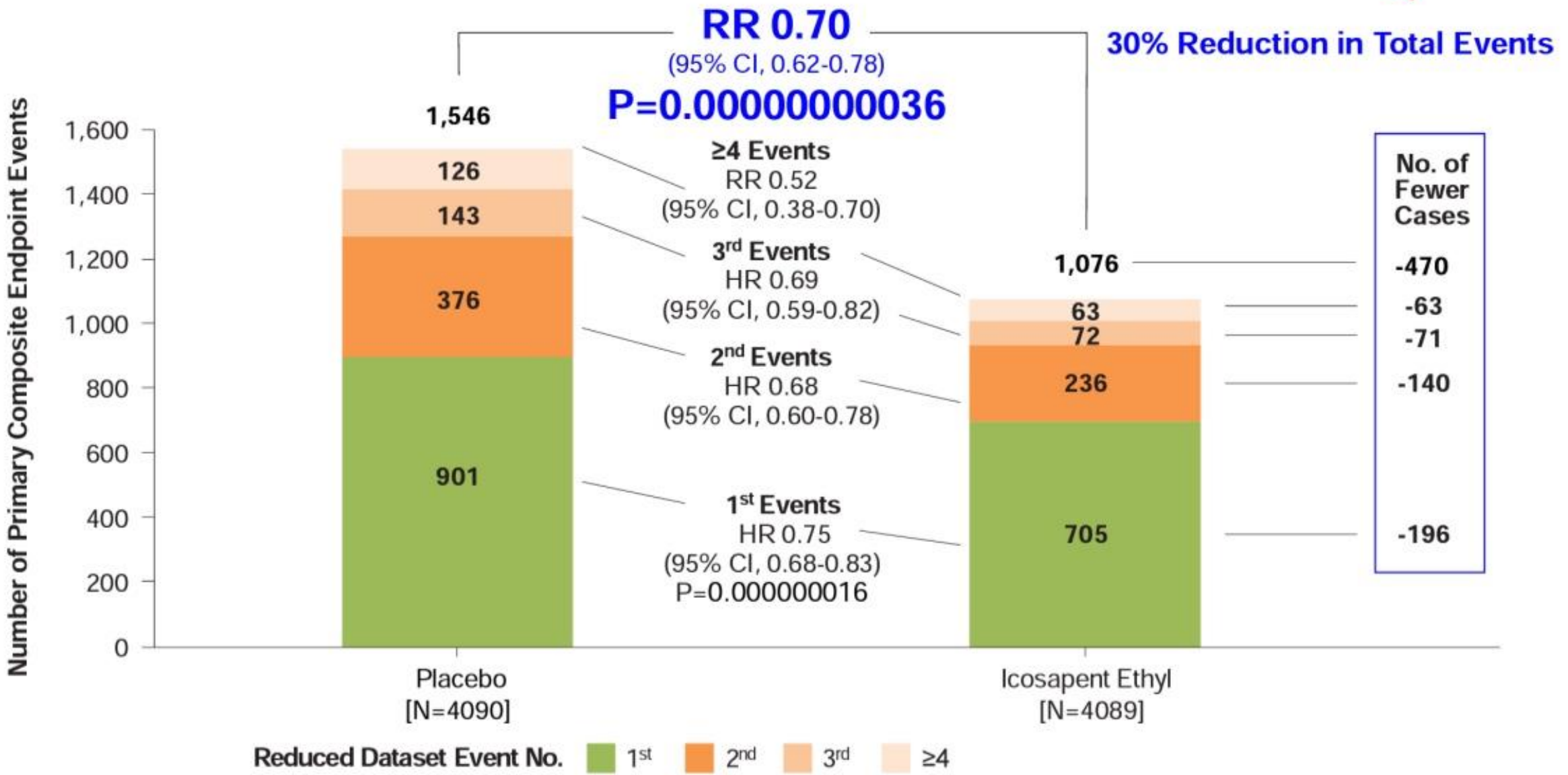
Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT

Deepak L. Bhatt, MD, MPH; Ph. Gabriel Steg, MD; Michael Miller, MD; Eliot A. Brinton, MD; Terry A. Jacobson, MD; Steven B. Ketchum, PhD; Ralph T. Doyle, Jr, BA; Rebecca A. Juliano, PhD; Lixia Jiao, PhD; Craig Granowitz, MD, PhD; Jean-Claude Tardif, MD; John Gregson, PhD; Stuart J. Pocock, PhD; Christie M. Ballantyne, MD; on Behalf of the REDUCE-IT Investigators

Proportions of First and Subsequent Events



First and Subsequent Events

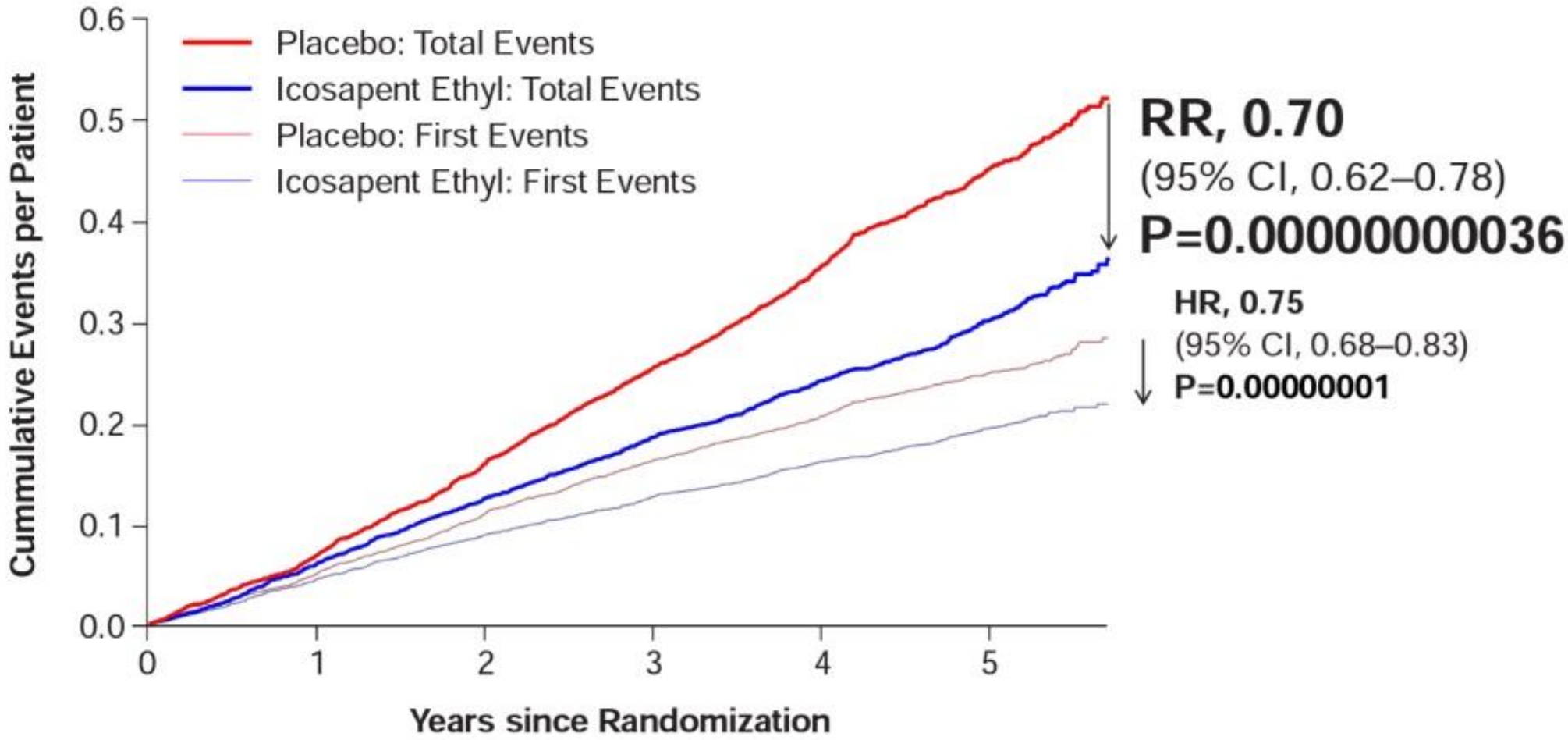


Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

Total (First and Subsequent) Events

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

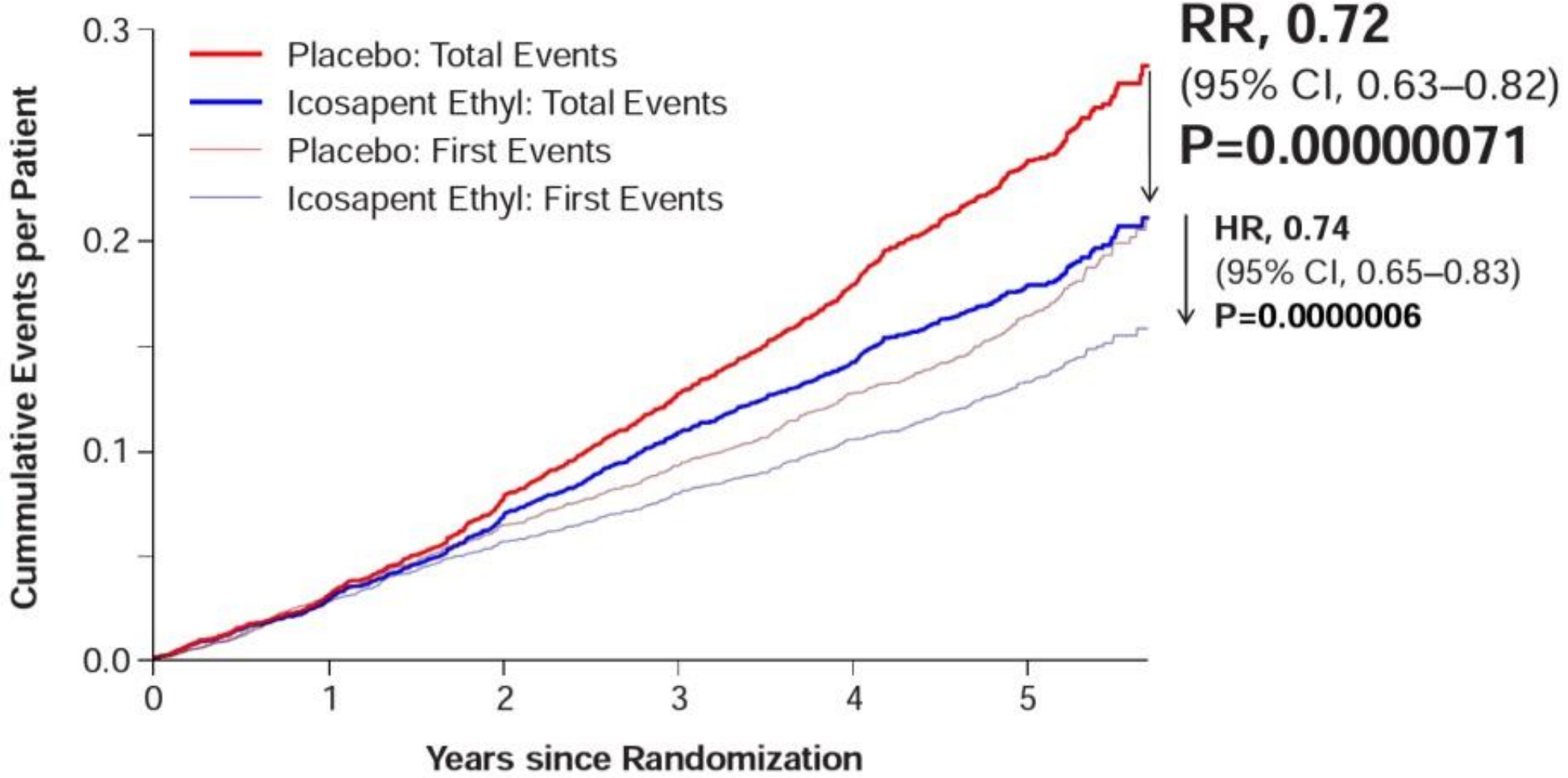
Primary Composite Endpoint



Total (First and Subsequent) Events

Key Secondary: CV Death, MI, Stroke

Key Secondary Composite Endpoint



Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events
- **48%** reduction in fourth or more cardiovascular events

Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides > ~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

NATIONAL LIPID ASSOCIATION

NLA Position on the Use of Icosapent Ethyl in High and Very-high-risk Patients

- For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with type 2 diabetes requiring medication and ≥1 additional risk factor*, and fasting triglycerides 135-499 mg/dL on maximally tolerated statin, with or without ezetimibe, treatment with icosapent ethyl is recommended for ASCVD risk reduction. (I B-R)

CLASS I (STRONG) Benefit >>> Risk
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial

LEVEL B-R (Randomized)
• Moderate-quality evidence from 1 or more RCTs • Meta-analysis of moderate-quality RCTS

*
- Age: men ≥55 years and women ≥65 years
- Cigarette smoker or stopped smoking within 3 months
- Hypertension (≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication
- HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women
- hs-CRP >3.0 mg/L
- Renal dysfunction: Creatinine clearance >30 and <60 mL/min
- Retinopathy
- Micro- or macro-albuminuria
- ABI <0.9 without symptoms of intermittent claudication

2019 American Heart Association (AHA) Science Advisory
Omega-3 Fatty Acids for the Management of Hypertriglyceridemia

- An advisory panel review of evidence from 17 randomized, controlled clinical trials evaluating n-3 FAs in patients with high TG levels found:

Advisory Highlights	
High TGs (200 – 499 mg/dL)	• ≈ 20-30% reduction in TGs and no LDL-C increase with prescription n-3 FAs (EPA+DHA or EPA-only) at a dose of 4g/day
Very High TGs (≥ 500 mg/dL)	• ≥ 30% reduction in TGs with prescription n-3 FAs at a dose of 4g/day; • Concurrent increase in LDL-C with EPA+DHA containing agents, whereas EPA-only did not increase LDL-C
Use with other lipid therapy	• Prescription n-3 FAs are an effective and safe option for reducing TGs as monotherapy or as an adjunct to other lipid-lowering agents
Omega-3 Dietary Supplements	• Should not be used in place of prescription medication for the treatment of high TGs because they are not approved by the FDA for this purpose; • The potency, quality, and efficacy of dietary supplements are not reviewed or approved, nor monitored or assured by the FDA
ASCVD Risk	• 4 g/day of EPA-only demonstrated a 25% reduction in MACE in REDUCE-IT; • Results from the STRENGTH trial (4 g/day EPA+DHA in patients on statins with high TGs and low HDL-C) are anticipated in 2020

Skulas-Ray AC, et al. *Circulation*. 2019;140: e1-e19.

American Diabetes Association (ADA) Issues Updates to the 2019 Standards of Medical Care in Diabetes

Section 10 – Cardiovascular Disease and Risk Management: Lipid Management

Treatment of Other Lipoprotein Fractions or Targets

- In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk. A
- "It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products."

Other Combination Therapy

- Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended. A
- Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. A

American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2019 [web annotation]. *Diabetes Care* 2019;42(Suppl.1):S103–S123. https://hyp.is/JHhz_lCrEembFJ9LIVBZIw/care.diabetesjournals.org/content/42/Supplement_1/S103. Updated March 27, 2019. Accessed March 28, 2019.

2019 ESC/EAS Guidelines

Guidelines for the management of dyslipidemias[a]

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

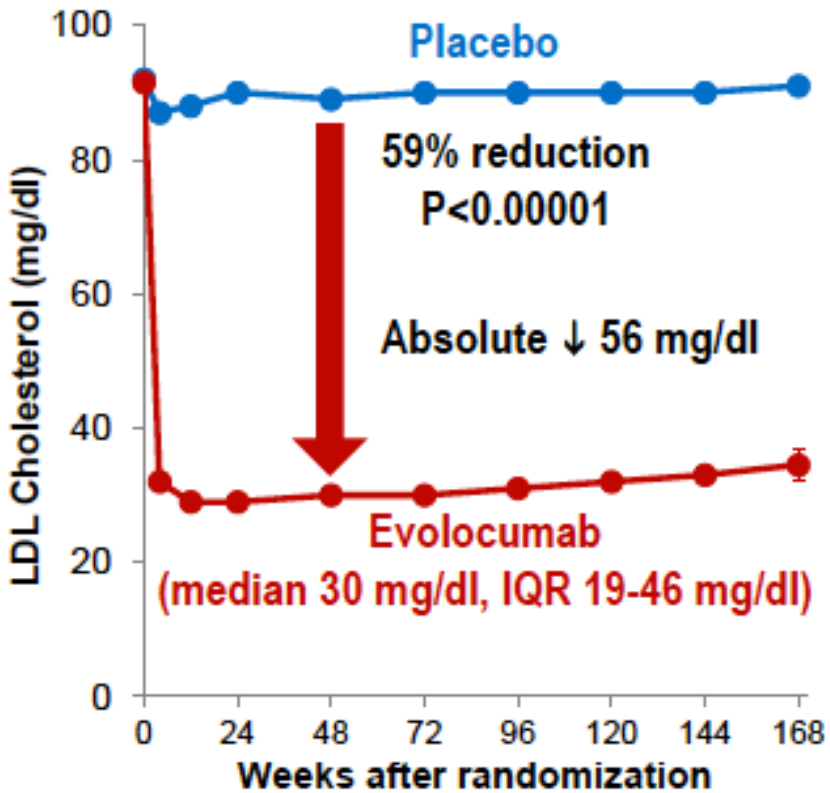
Guidelines on diabetes, pre-diabetes, and CVD[b]

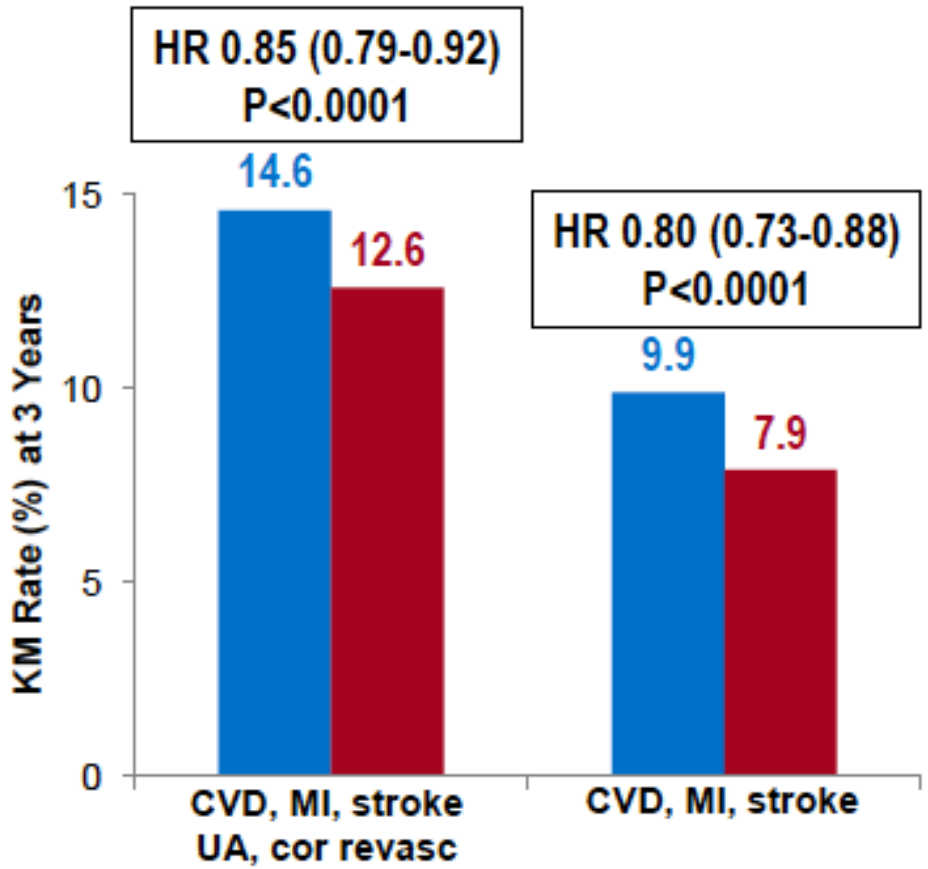
- In patients with high triglyceride levels [≥2.3 mmol/L (200 mg/dL)], lifestyle advice and improved glucose control are the main targets. Fibrates may be administered in patients with DM who are statin intolerant and have high TG levels. If TGs are not controlled by statins or fibrates, high-dose omega-3 fatty acids (4 g/day) of icosapent ethyl may be used.

a. Mach F, et al. *Eur Heart J.* 2019;00:178. By permission of Oxford University Press.; b. Cosentino F, et al. *European Heart Journal.* 2019; ehz486

Summary of Effects of PCSK9i Evolocumab

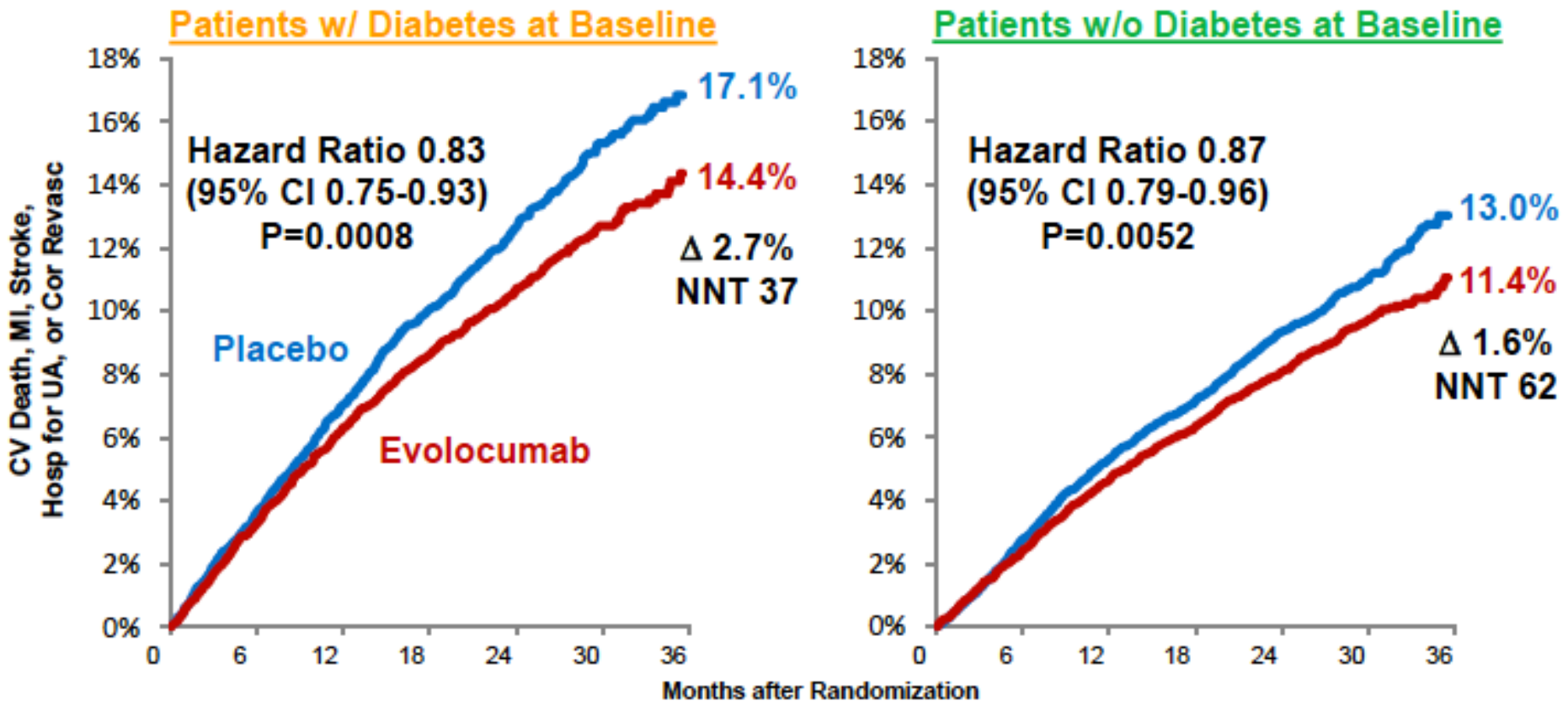
- 27,564 pts w/ stable ASCVD & LDL-C ≥70mg/dL on a statin
- ↓ LDL-C by 59% down to a median of 30 mg/dl
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated





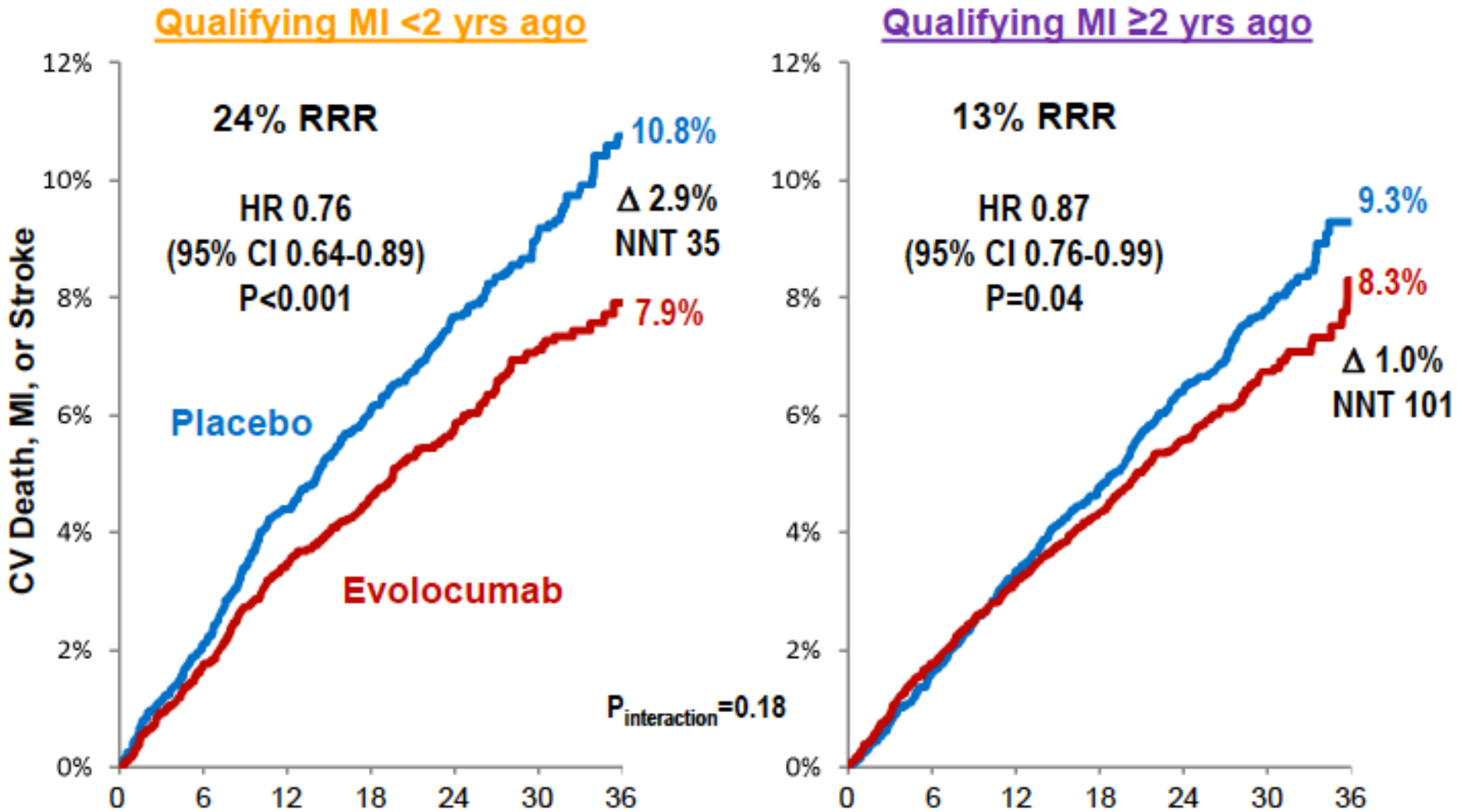
Sabatine MS et al. *NEJM* 2017;376:1713-22

Clinical Efficacy by Diabetes Status



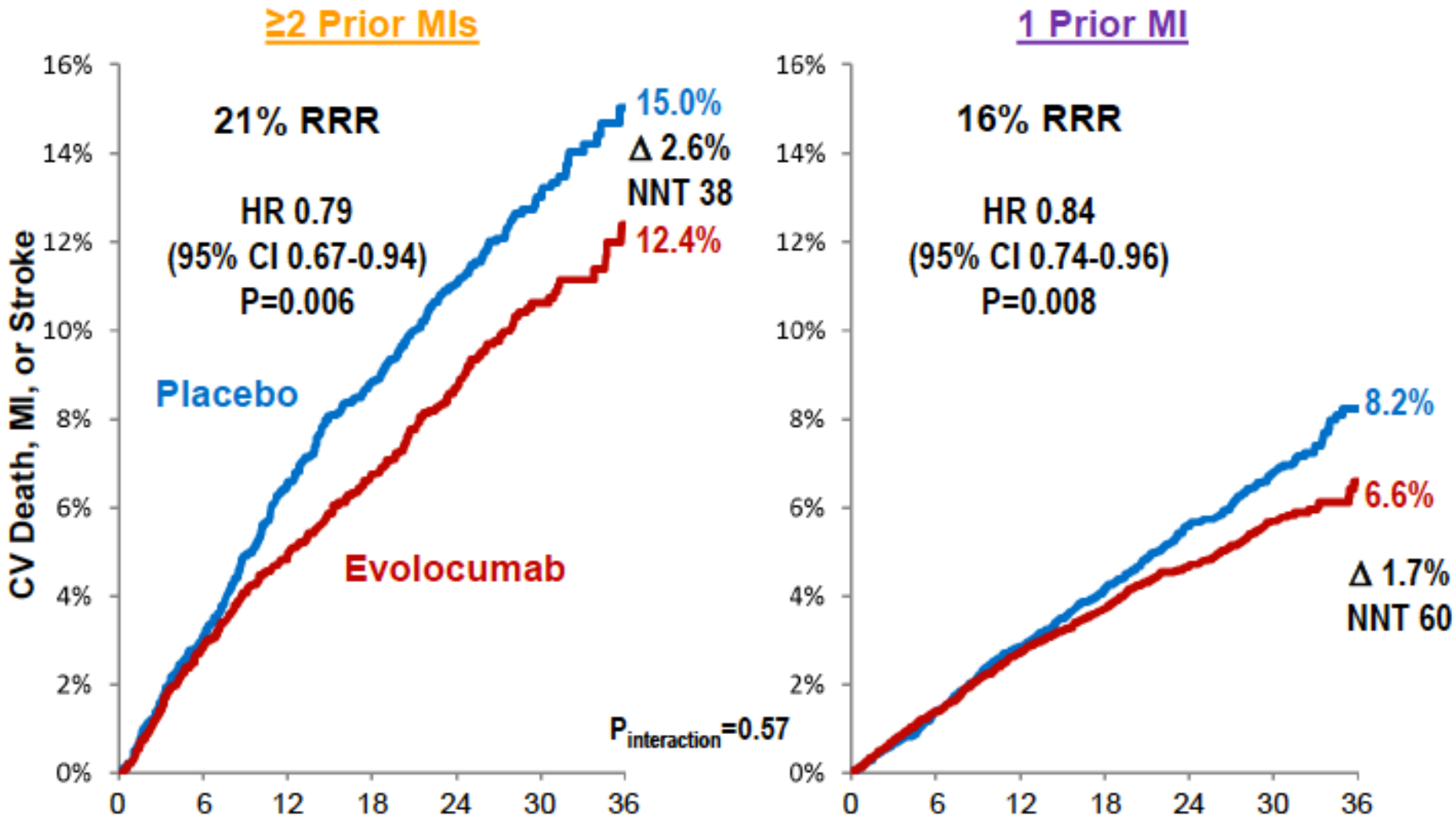
Sabatine MS, Leiter LA et al. *Lancet Diab & Endo* 2017;5;941-50

Benefit of EvoMab Based on Time from Qualifying MI



Sabatine MS et al. *Circulation* 2018;epub ahead of print

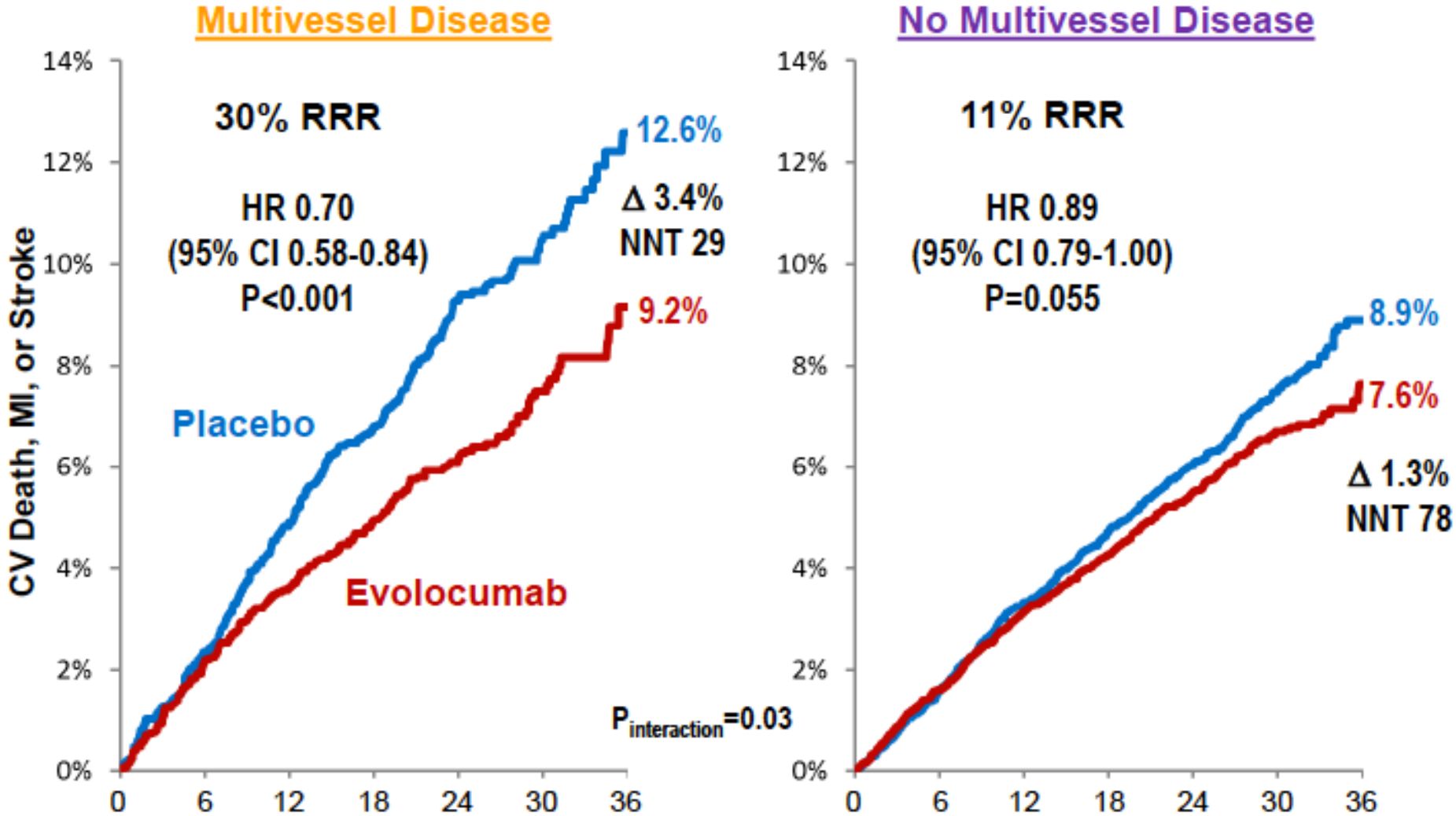
Benefit of EvoMab Based on # of Prior MIs



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

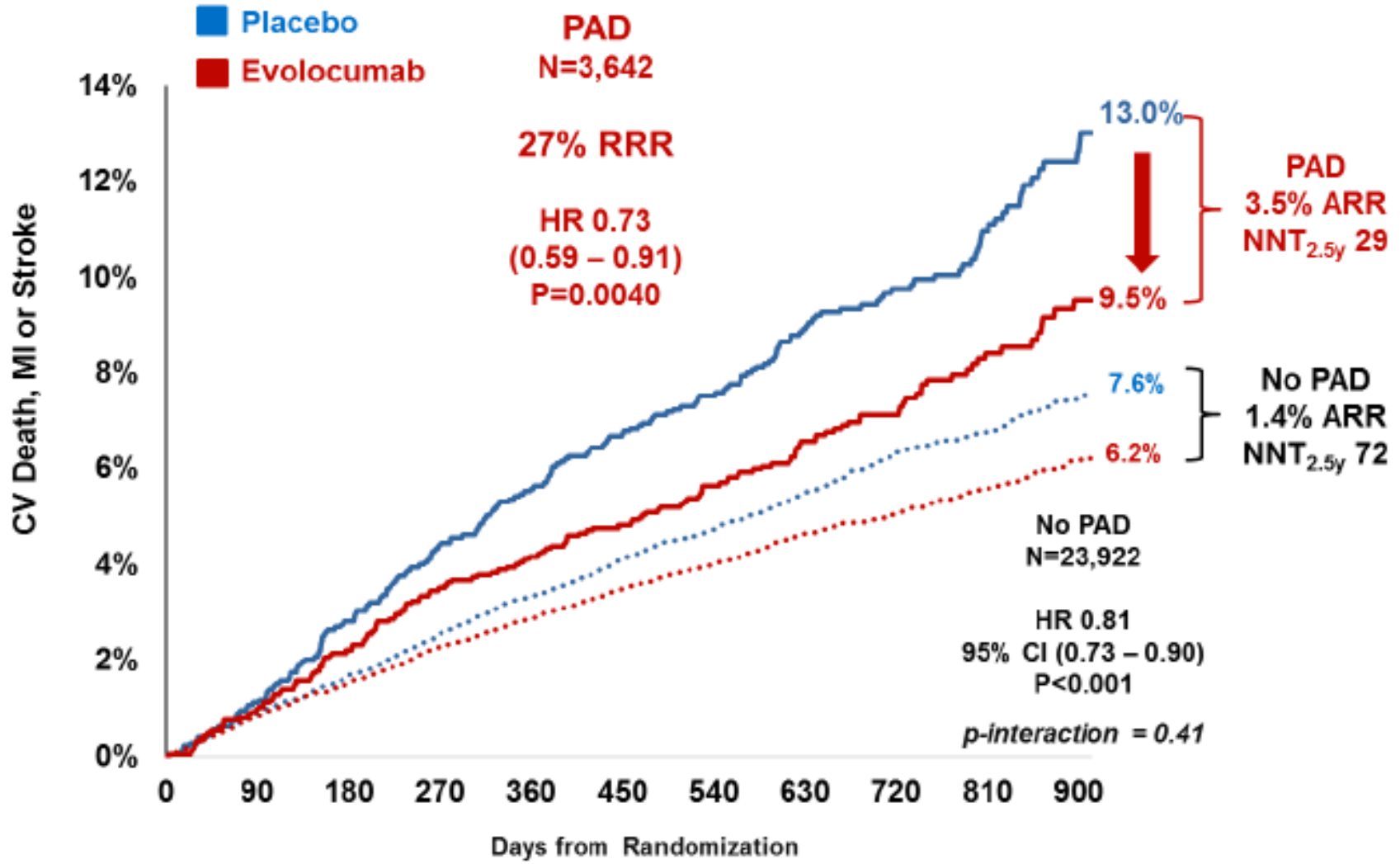
Sabatine MS et al. *Circulation* 2018;epub ahead of print

Benefit of EvoMab Based on Multivessel Disease



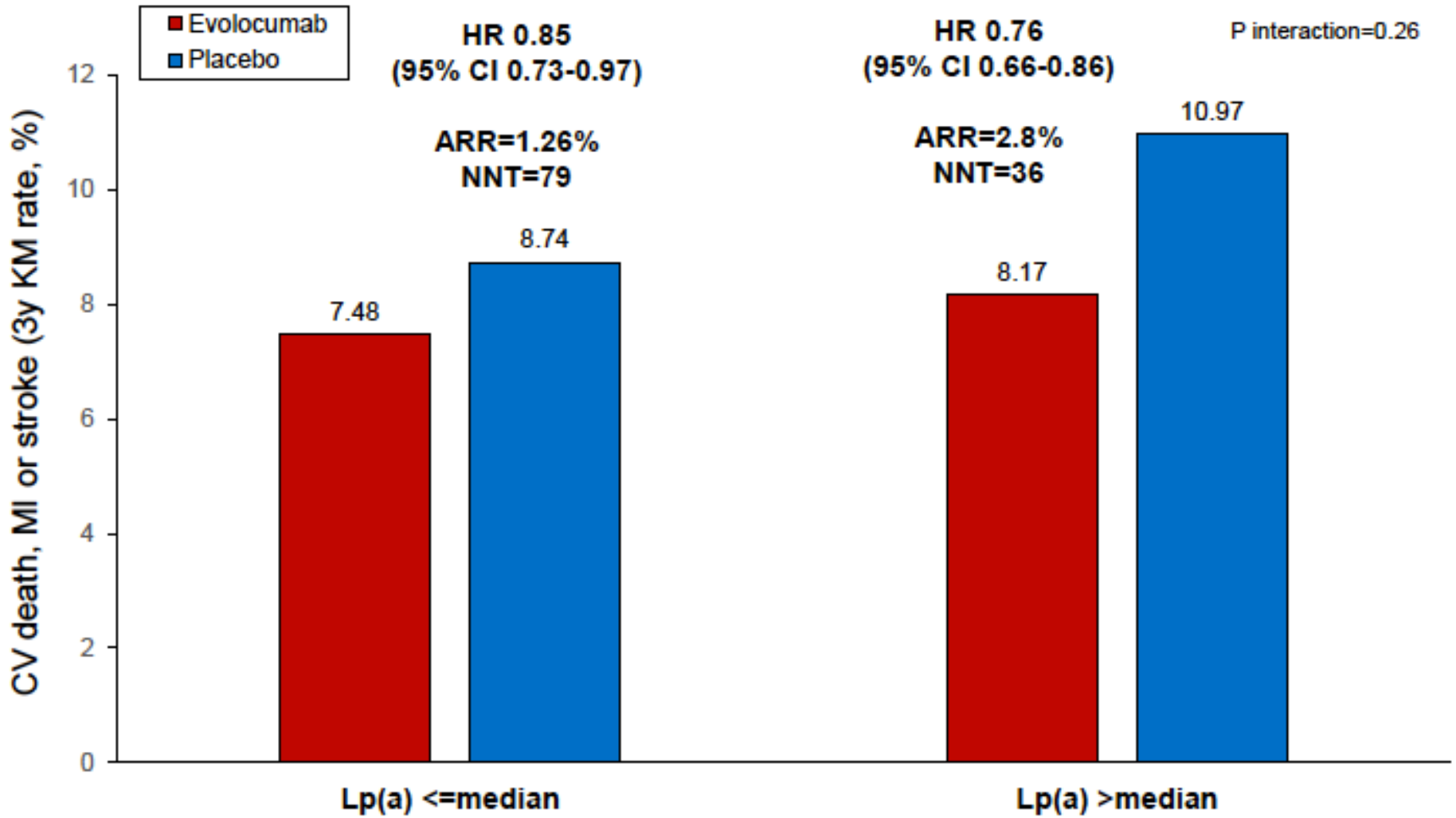
Sabatine. *Circulation* 2018; epub ahead of print

CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease



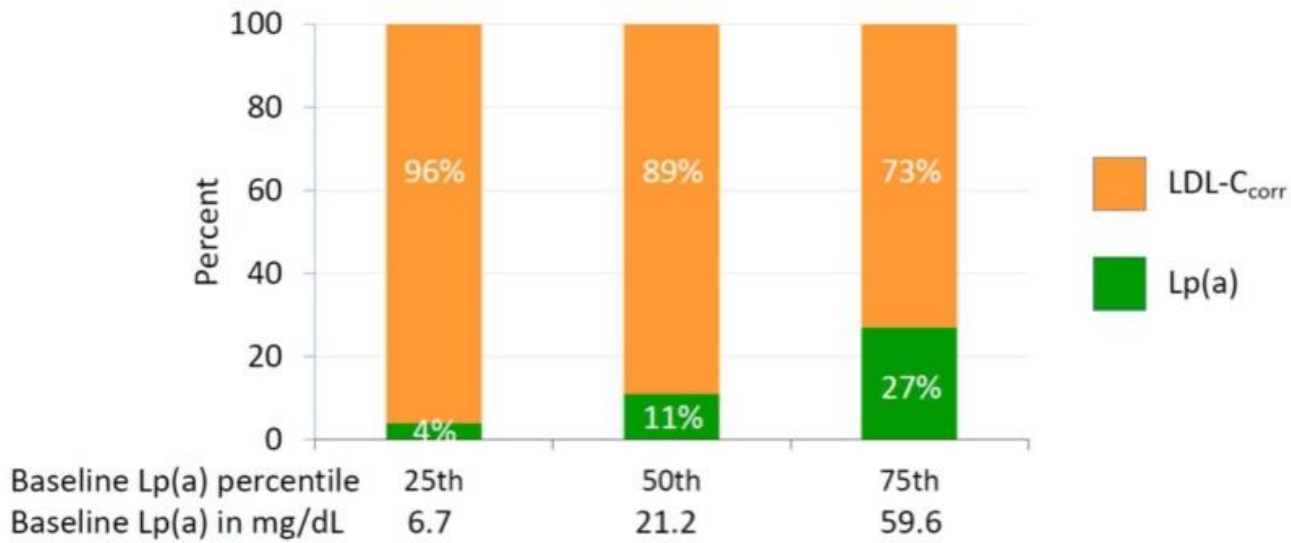
Bonaca MP et al. & Sabatine MS. *Circulation* 2018;137:338-50

Efficacy by Baseline Lp(a)



ODYSSEY OUTCOMES

Proportion of MACE Reduction Attributable to Changes in Lp(a) and Corrected LDL-C



From model with baseline and change in Lp(a), baseline and change in LDL-C_{corr} (Model 2)

Presented by Vera Bittner, ACC19

New Kids on the Block

Bempedoic Acid, O3CA, Inclisiran

NATIONAL LIPID ASSOCIATION

Bempedoic acid *properties and mechanism of action*

An oral, once-daily small molecule

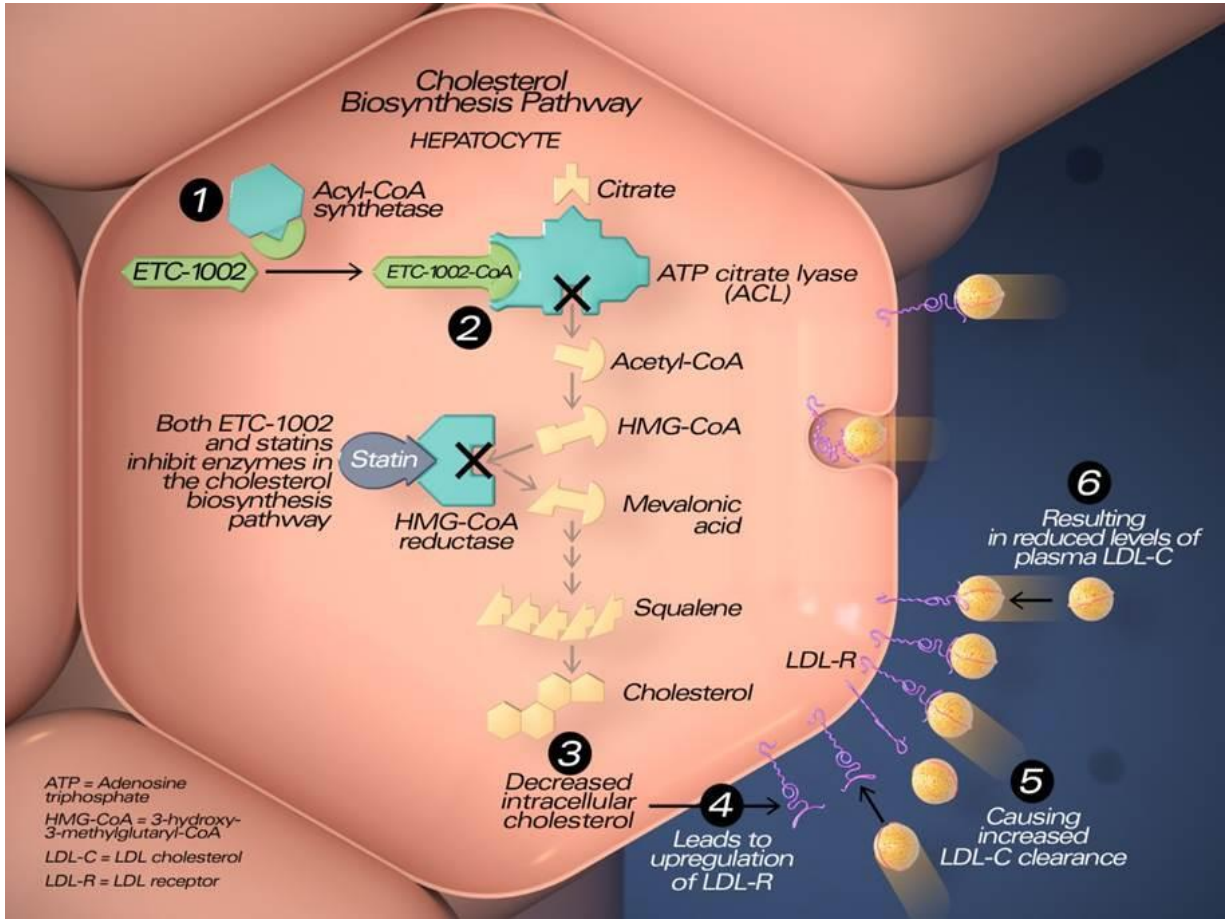
Inhibits ATP citrate lyase

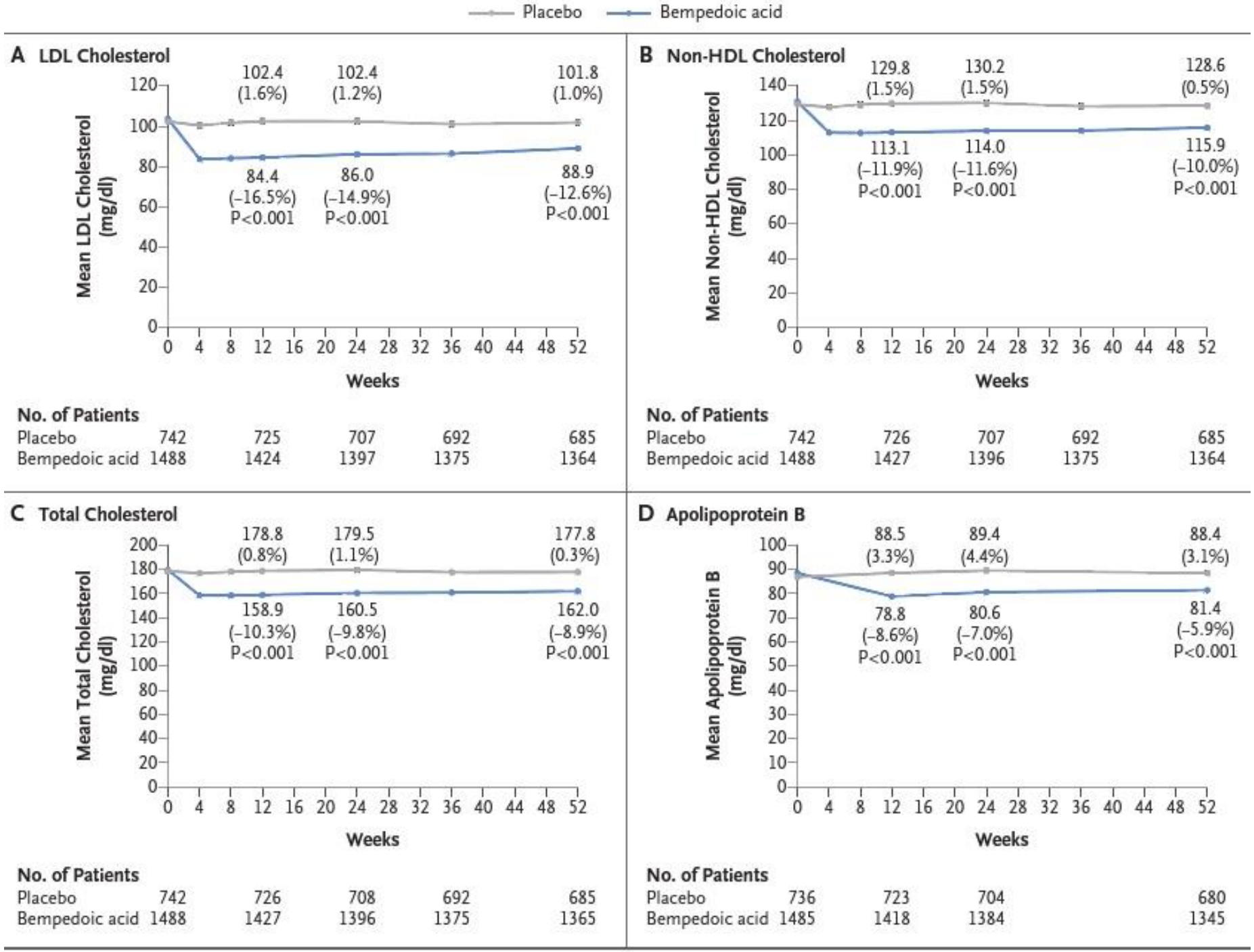
Half-life: 15-27 hr (ETC-1002)

T_{max}: <4 hours

Target organ: Liver

Elimination: Urinary excretion (primary route)




Placebo
Bempedoic acid
A LDL Cholesterol
Mean LDL Cholesterol (mg/dl)
102.4 (1.6%)
102.4 (1.2%)
101.8 (1.0%)
84.4 (–16.5%) P<0.001
86.0 (–14.9%) P<0.001
88.9 (–12.6%) P<0.001
Weeks
No. of Patients
Placebo 742 725 707 692 685
Bempedoic acid 1488 1424 1397 1375 1364
B Non-HDL Cholesterol
Mean Non-HDL Cholesterol (mg/dl)
129.8 (1.5%)
130.2 (1.5%)
128.6 (0.5%)
113.1 (–11.9%) P<0.001
114.0 (–11.6%) P<0.001
115.9 (–10.0%) P<0.001
Weeks
No. of Patients
Placebo 742 726 707 692 685
Bempedoic acid 1488 1427 1396 1375 1364
C Total Cholesterol
Mean Total Cholesterol (mg/dl)
178.8 (0.8%)
179.5 (1.1%)
177.8 (0.3%)
158.9 (–10.3%) P<0.001
160.5 (–9.8%) P<0.001
162.0 (–8.9%) P<0.001
Weeks
No. of Patients
Placebo 742 726 708 692 685
Bempedoic acid 1488 1427 1396 1375 1365
D Apolipoprotein B
Mean Apolipoprotein B (mg/dl)
88.5 (3.3%)
89.4 (4.4%)
88.4 (3.1%)
78.8 (–8.6%) P<0.001
80.6 (–7.0%) P<0.001
81.4 (–5.9%) P<0.001
Weeks
No. of Patients
Placebo 736 723 704 680
Bempedoic acid 1485 1418 1384 1345

Bempedoic Acid Global cardiovascular outcomes trial (CVOT)

- Assess the effects of bempedoic acid on the occurrence of major cardiovascular events in patients with—or at high risk for—cardiovascular disease (CVD), in patients with statin intolerance.

- CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-inhibiting Regimen) Outcomes is an event-driven, global, randomized, double-blind, placebo-controlled study, expected to enroll approximately 12,600 patients with hypercholesterolemia and high CVD risk at more than 600 sites in approximately 30 countries.

Esperion. Bempedoic Acid. https://www.esperion.com/development/bempedoic-acid/ (Accessed April 1 2019)

Available Prescription ω-3 FA Formulations

	EPA+DHA EE[1,2] (e.g. Lovaza)	EPA only EE[3] (e.g. Vascepa)	EPA+DHA FFA[4] (e.g. Epanova)
Generic available?	Yes	No	No
Indication	Indicated as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia		
Omega-3 Content	EPA: 0.465 g DHA: 0.375 g EPA/DHA: 55%/45%	EPA: 1 g EPA/DHA: 100%/0%	EPA: 0.55 g DHA: 0.2 g EPA/DHA: 73%/27%
Regimen, capsules	2 BID with meals or 4 QD with meals[2]	2 BID with meals	2 or 4 QD, with or without meals

1. Lovaza prescribing information 2. Omtryg prescribing information. 3. Vascepa prescribing information. 4. Epanova prescribing information.
EE=ethyl ester; FA=fatty acid(s); FFA=free FA; EPA = Eicosapentaenoic Acid; DHA = Docosahexaenoic acid
Sperling LS, Nelson JR. *Curr Med Res Opin*. 2016;32:301-11.

STRENGTH TRIAL

A Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia

- Randomized, double-blind, placebo-controlled, event-driven trial.
- Epanova 4 g or matching corn oil placebo capsules once daily.
- The trial will continue until 1600 primary endpoints are positively adjudicated.
- Expected median duration of the trial is 3 years with a maximum duration of 5 years.

Nicholls SJ, Lincoff AM, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, Mozaffarian D, Pedersen TR, Ridker PM, Ray K, Karlson BW, Lundström T, Wolski K, Nissen SE. Assessment of omega-3 carboxylic acids in statin-treated patients with high levels of triglycerides and low levels of high-density lipoprotein cholesterol: Rationale and design of the STRENGTH trial. Clin Cardiol. 2018 Oct;41(10):1281-1288.

Inclisiran

- PCSK9 production is inhibited by RNA interference
- Mean low density lipoprotein cholesterol (LDL-C) reduction of up to 75% from baseline to day 84, with duration of LDL-C reduction up to at least 6 months.
- Mild localized injection site reactions

Fitzgerald K, White S, Borodovsky A, et al. A Highly Durable RNAi Therapeutic Inhibitor of PCSK9. The New England journal of medicine. 2016. doi: 10.1056/NEJMoa1609243. PubMed PMID: 27959715

Inclisiran Cardiovascular Outcomes

- Inclisiran is a RNAi that inhibits PCSK9 synthesis specifically in the liver
- Inclisiran lowers low-density lipoprotein cholesterol levels on average by >50% with a duration of effect that enables twice-yearly dosing.
- The ongoing ORION program includes Phase III trials evaluating inclisiran's safety and efficacy in individuals at high risk of atherosclerotic cardiovascular disease (ASCVD), including established ASCVD and familial hypercholesterolemia.
- The ORION-4 trial will assess the impact of inclisiran on cardiovascular outcomes in approximately 15,000 ASCVD subjects.

Stoekenbroek RM, Kallend D, Wijngaard PL, Kastelein JJ. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. Future Cardiol. 2018 Nov;14(6):433-442.

National Lipid Association Statement

Enhancing the Value of PCSK9 Monoclonal Antibodies by Identifying Patients Most Likely to Benefit

Purpose:

- Update for clinical decision-making based on new information
  - PCSK9 mAb discounting
  - Potential for net ASCVD risk reduction benefit from added LDL-C lowering therapy
    - Systematic review to identify heterogeneity in benefits observed in subgroup analyses

Extremely high risk ≥40% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
EXTREMELY HIGH ATHEROSCLEROTIC BURDEN	**EXTREMELY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	

• Polyvascular clinical ASCVD (coronary heart disease†, ischemic stroke, and symptomatic peripheral arterial disease)
• Symptomatic peripheral arterial disease** in addition to a coronary heart disease† or ischemic stroke
• A clinical ASCVD event (coronary heart disease†, stroke, or symptomatic peripheral arterial disease**) with multi-vessel coronary artery disease defined as ≥40% stenosis in ≥2 large vessels
• Recurrent myocardial infarction within 2 years
	• Heterozygous familial hypercholesterolemia with clinical ASCVD (or coronary artery calcium >100)
	• History of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** with at least one of:
	  ○ Diabetes
	  ○ LDL-C >100 mg/dl
	  ○ Less than high intensity statin therapy
	  ○ High sensitivity C-reactive protein >3 mg/L
	• Poorly controlled hypertension and clinical ASCVD

† Clinically evident coronary heart disease includes myocardial infarction, history of angina with objective evidence of coronary artery disease (electrocardigraphic, positive stress test, wall motion abnormality on ultrasound, coronary angiographic evidence of significant atherosclerotic lesions), or prior revascularization including coronary artery bypass grafting or percutaneous coronary intervention)

Very high risk 30-39% 10-year ASCVD risk

Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	**Adverse or poorly controlled cardiometabolic risk factors**
VERY HIGH ATHEROSCLEROTIC BURDEN	**VERY HIGH RISK FACTORS**
Majority had at least 1 additional adverse or poorly controlled cardiometabolic risk factor	
• Recent acute coronary syndrome (only if no subsequent event within 2 years) • Coronary heart disease† and ischemic stroke without symptomatic peripheral arterial disease** • Coronary artery bypass grafting	Clinical ASCVD and one or more of: • Age ≥65 years • Chronic kidney disease • Lipoprotein(a) ≥37 nmol/L • High sensitivity C-reactive protein 1-3 mg/L • Metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease** • Smoking

High risk 20-29% 10-year ASCVD risk

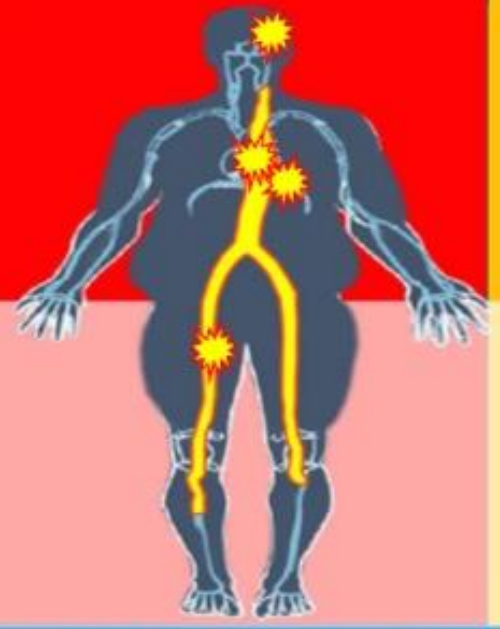
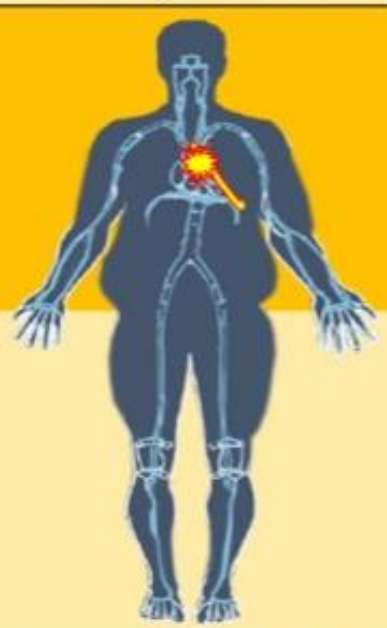
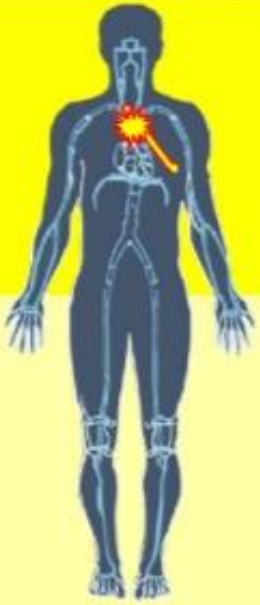
Systematic review subgroups of RCTS Moderate vs high intensity statins, PCSK9 mAbs

ON STATIN THERAPY	
Burden and activity of clinical ASCVD	
HIGH ATHEROSCLEROTIC BURDEN	**WELL-CONTROLLED RISK FACTORS**
<u>High burden (20-29% 10-year ASCVD risk)</u> • Coronary heart disease† only • Ischemic stroke only • Symptomatic peripheral arterial disease only** • Acute coronary syndrome with no subsequent ASCVD event after 2 years	

Did not find heart failure subgroups as in 2018 AHA/ACC Cholesterol Guideline "Very high ASCVD risk" group; Patients with NYHA Class 3 & 4 heart failure excluded from RCTs

NLA Statement: REASONABLE - HIGH VALUE FROM ADDING PCSK9 mAb

ON MAXIMALLY TOLERATED STATIN THERAPY (±ezetimibe)

Extremely High Risk ≥40% 10-year ASCVD risk	Very High Risk 30-39% 10-y ASCVD risk	High Risk 20-29% 10-year ASCVD risk
		
Extensive or active burden of ASCVD Usually with poorly controlled cardiometabolic risk factors	**Less extensive ASCVD & Poorly controlled cardiometabolic risk factors**	**Less extensive ASCVD & Well controlled risk factors**
Less extensive ASCVD & Extremely high risk cardiometabolic risk factors		**Primary prevention HeFH/SGH LDL-C≥220 mg/dl & Poorly controlled cardiometabolic risk factors**
LDL-C ≥70 mg/dl	**LDL-C ≥100 mg/dl**	**LDL-C ≥130 mg/dl**

Robinson JG, et al. J Clin Lipidol 2019; online ahead of print


LIPID
SPECIALIST


AMERICAN BOARD OF CLINICAL LIPIDOLOGY
ABCL
EST. 2004

Organizational Awareness & Recognition
NLA Strategic Planning

The NLA Strategic Planning meeting was convened to consider the strategic future direction of the association and related certification boards (ABCL* and ACCL**) with respect to formal recognition as a specialty or sub-specialty of medicine.

***American Board of Clinical Lipidology**

- Certifies physician knowledge and training in Clinical Lipidology
- 767 diplomates as of May 2, 2019

****Accreditation Council for Clinical Lipidology**

- Certifies physicians, nurses, nurse practitioners, physician assistants, pharmacists, registered dietitian/nutritionists, clinical exercise physiologists/specialists and other healthcare professionals knowledge and training in Clinical Lipidology
- 183 CLS as of May 2, 2019

Lipid Specialist Definition

- A Lipid Specialist is defined as a healthcare professional certified by the American Board of Clinical Lipidology (ABCL) or Accreditation Council for Clinical Lipidology (ACCL) specializing in the identification and management of dyslipidemia and related metabolic disorders which lead to atherosclerotic cardiovascular disease (ASCVD) and other morbidities.

Lipid Specialist Benefits

- Consistent nomenclature usage by the NLA, ABCL and ACCL is necessary for recognition.
- Using a single term allows for consistency across multiple disciplines.
- CMS recognition of Lipid Specialists would enable those who can bill for Medicare and Medicaid services to identify themselves Lipid Specialists and be paid for treatment of lipid related services as such.

NATIONAL LIPID ASSOCIATION

SCIENTIFIC SESSIONS

June 4-7

2020

CHICAGO