2022 MID-ATLANTIC CONFERENCE

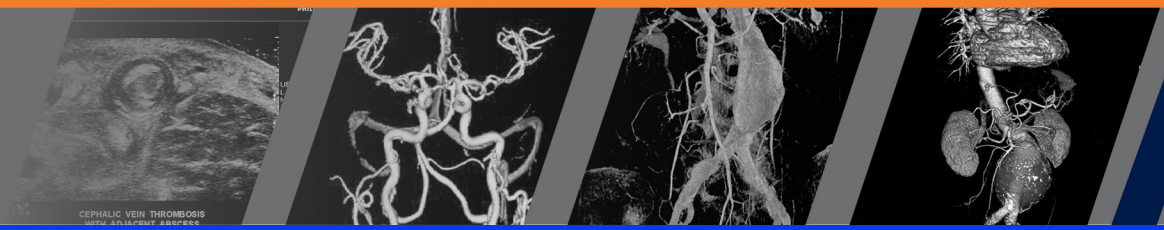
10th ANNUAL CURRENT CONCEPTS IN

VASCULAR THERAPIES

2022

Hilton Virginia Beach Oceanfront
Virginia Beach, Virginia

APRIL 28-30



Sentara Vascular Specialists

New Frontiers in Hyperlipidemia

Deepak Talreja, MD, FACC

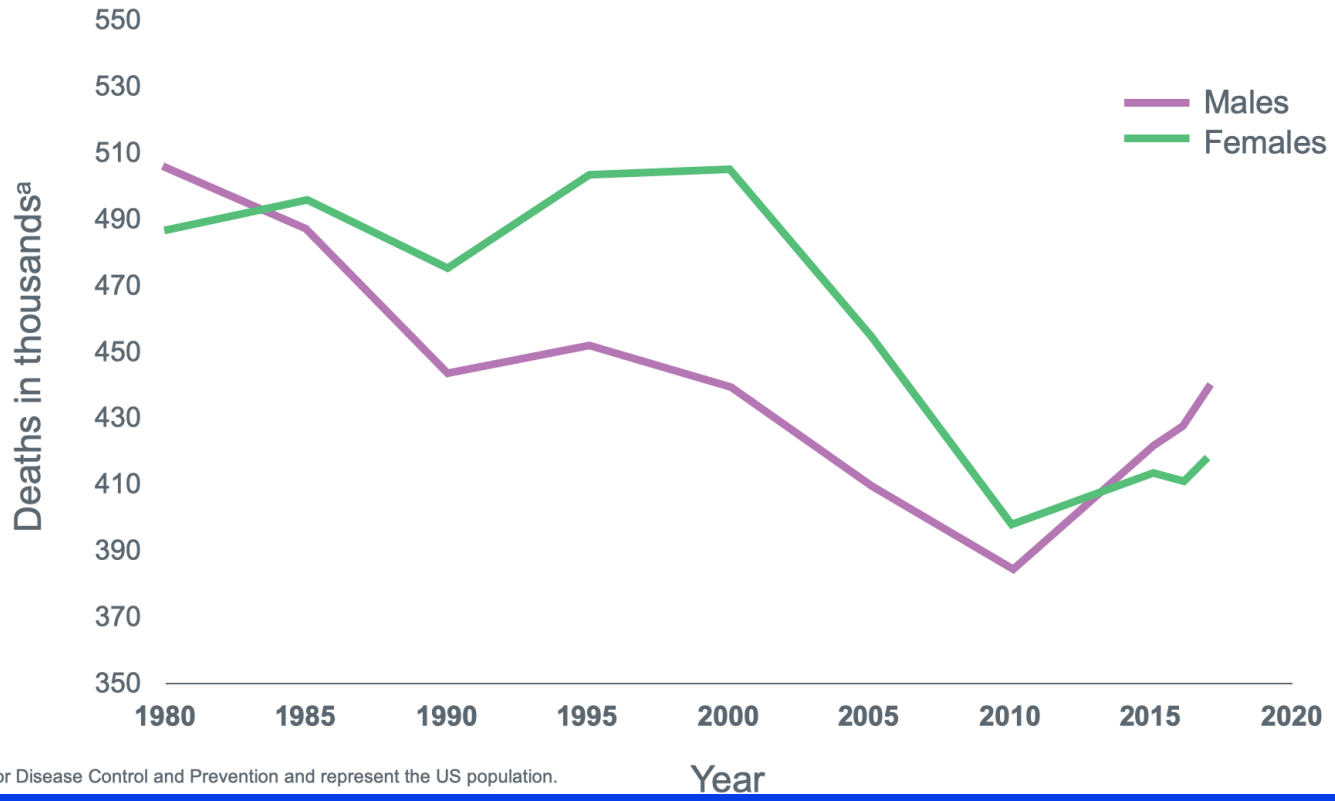
Sentara Cardiology Specialists

Disclosures

- PI/Sub-I and then Speakers Bureau and Educational Programs: Pfizer, GSK, Amgen, Esperion, AZ, BI/Lily, Medtronic, Edwards, Boston Scientific, Abbott, EKO

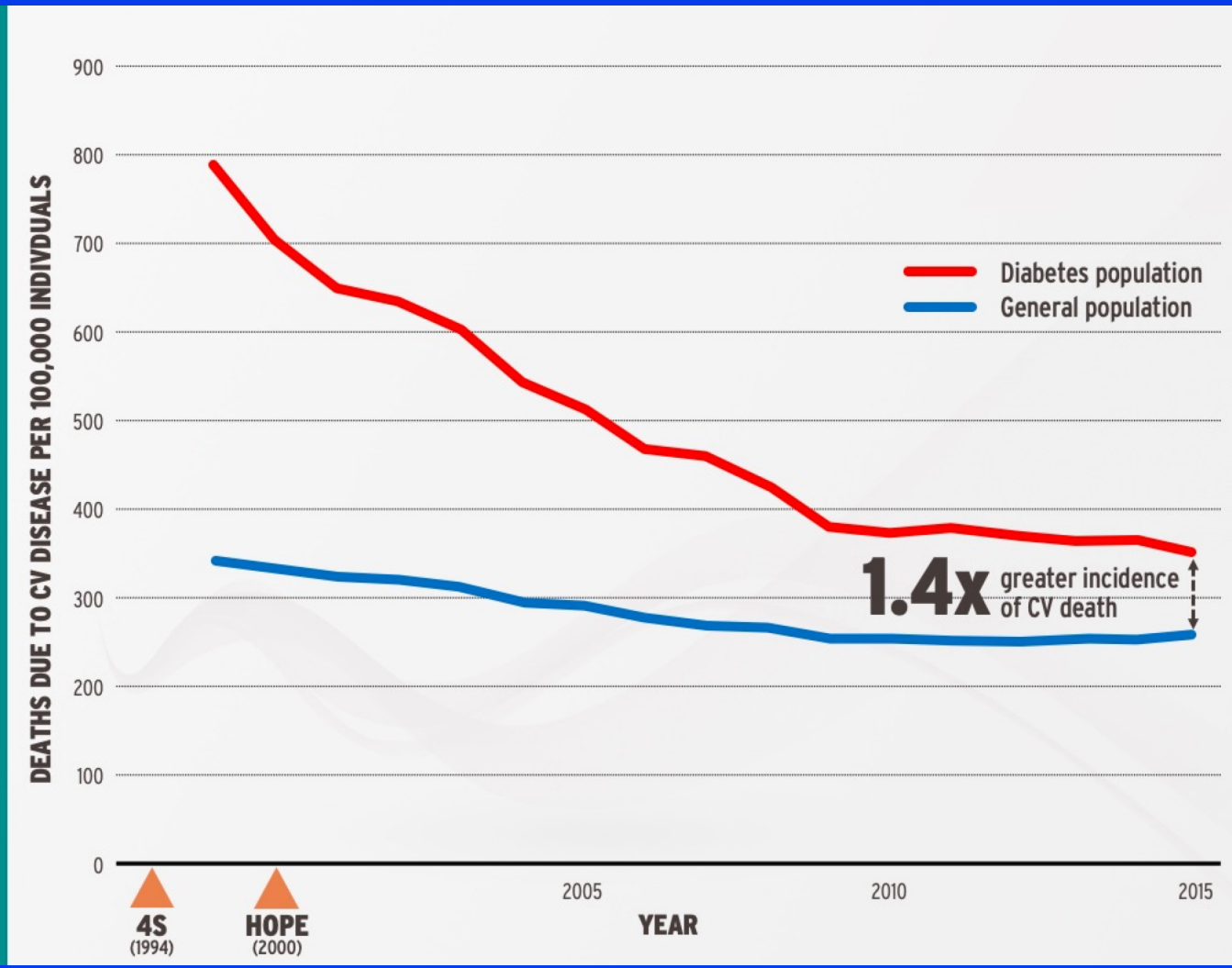
Cardiovascular disease deaths have increased in recent years in the US

DEATHS ATTRIBUTABLE TO CARDIOVASCULAR DISEASE (US, 1980-2017)



[a]The data are from the US Centers for Disease Control and Prevention and represent the US population.

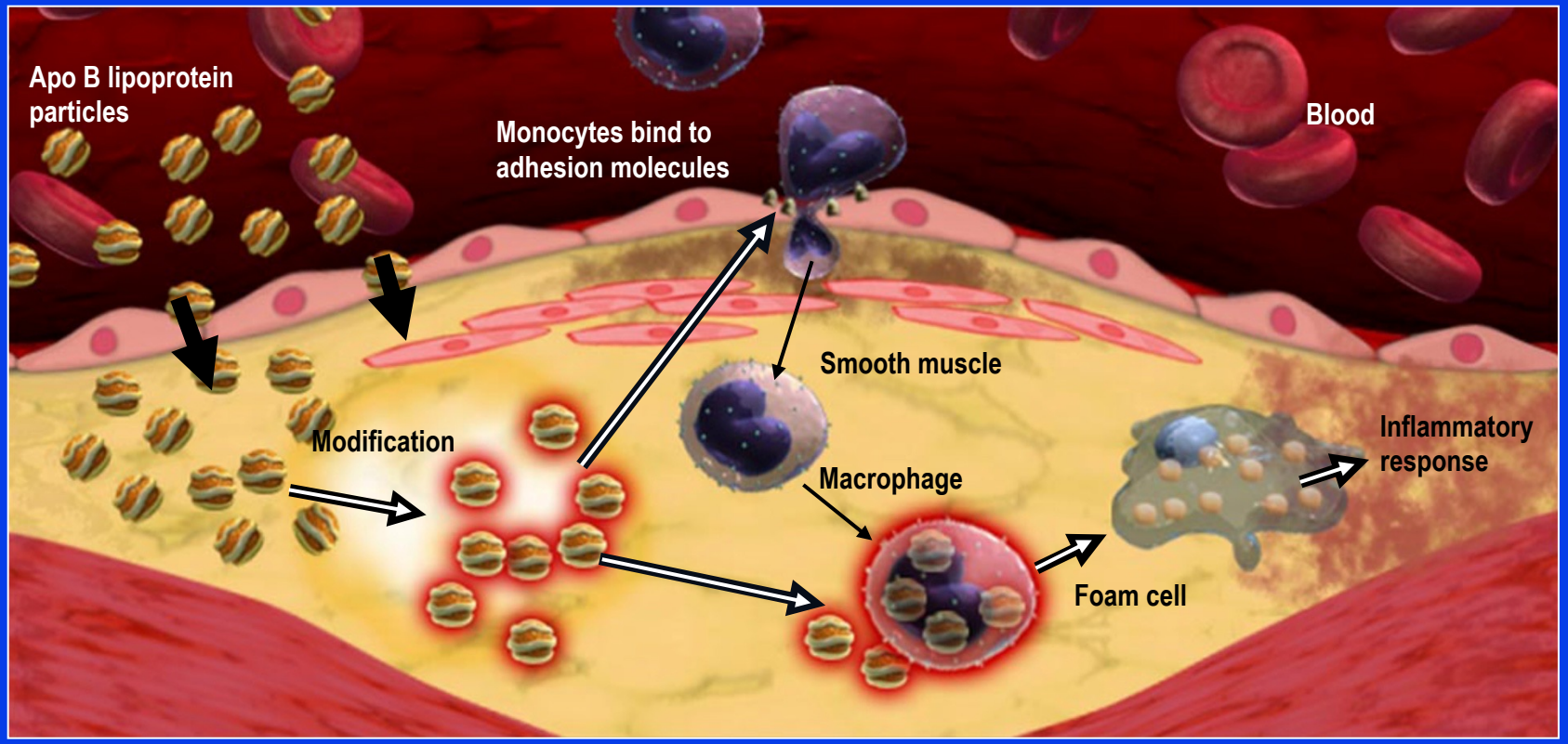
INCIDENCE OF CV DEATH REMAINS GREATER IN PATIENTS WITH DIABETES DESPITE ADVANCES IN STANDARD OF CARE



1. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2016 on CDC WONDER Online Database, released December, 2017. Data are from the Multiple Cause of Death Files, 1999-2016, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/mcd-icd10.html on May 8, 2018;
2. Centers for Disease Control and Prevention. Long-term trends in diabetes. http://www.cdc.gov/diabetes/data. Published April 2017. Accessed on May 10, 2018;
3. 4S Investigators. Lancet. 1994;344:1383-90;
4. HOPE Investigators. N Engl J Med. 2000;342(3):145-53.

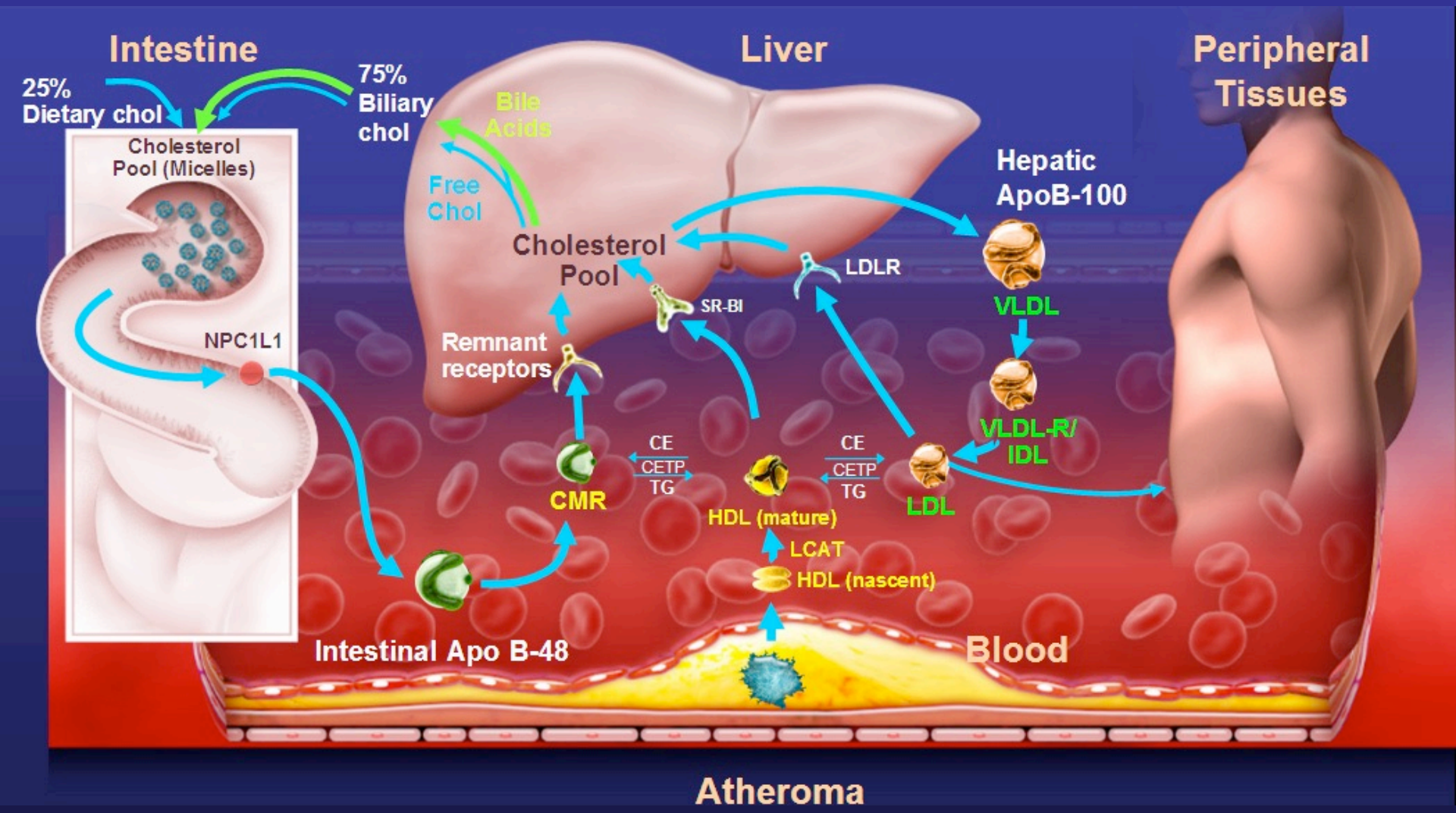
High Plasma Apo B Lipoprotein Levels Promote Atherogenesis

Rationale for therapeutic lowering of Apo B lipoproteins: decrease the probability of inflammatory response to retention



Tabas I et al. *Circulation.* 2007;116:1832-1844.
Williams KJ et al. *Arterioscler Thromb Vasc Biol.* 1995;15:551-561.
Hoshiga M et al. *Circ Res.* 1995;77:1129-1135.
Williams KJ et al. *Arterioscler Thromb Vasc Biol.* 2005;25:1536-1540.
Merrilees MJ et al. *J Vasc Res.* 1993;30:293-302.
Nakata A et al. *Circulation.*1996;94:2778-2786.
Steinberg D et al. *N Engl J Med.* 1989;320:915-924.

Lipoprotein Metabolism[1–5]



1. Goldstein JL et al. *Science*. 2001;292:1310–1312. **2.** Shepherd J. *Eur Heart J*. 2001;3(suppl E):E2–E5. **3.** Turley SD, et al. *Prev Cardiol*. 2003;6:29–33, 64. **4.** Mudd JO et al. *J Am Coll Cardiol*. 2007;50:1735–1741. **5.** Altmann SW et al. *Science*. 2004;303:1201–1204.

Cardiovascular Rehab and Nutrition Programs

2018 ACC/AHA guideline on the management of blood cholesterol[a]

PRIMARY PREVENTION

10-year ASCVD risk should guide therapeutic considerations:

- For intermediate-risk patients, moderate- to high-intensity statin therapy[b] should be considered
- For high-risk patients, LDL-C should be reduced ≥50%
- It may be reasonable to add ezetimibe to maximally tolerated statin therapy in patients with intermediate risk who would benefit from more aggressive LDL-C lowering

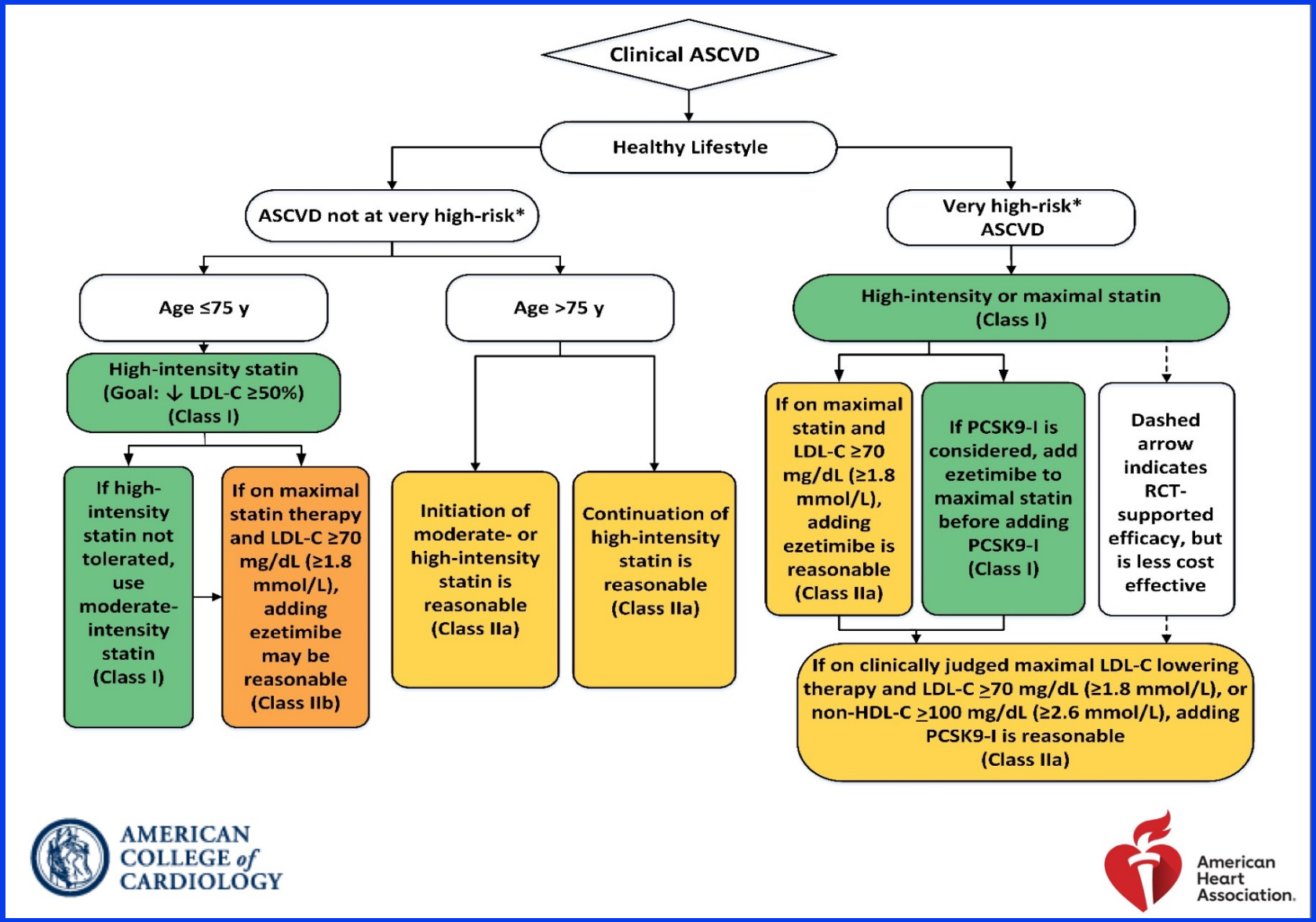
For patients with diabetes mellitus age 40 to 75 years:

- Start moderate-intensity statin therapy if LDL-C ≥70 mg/dL

SECONDARY PREVENTION

- High-intensity statin therapy is indicated for clinical ASCVD, but if this cannot be used, moderate-intensity statin therapy can be utilized
- The first goal is to achieve ≥50% reduction in LDL-C
- If LDL-C remains ≥70 mg/dL, adding ezetimibe may be reasonable

2018 ACC/AHA Secondary Prevention



AMERICAN COLLEGE of CARDIOLOGY

American Heart Association.

Lipid Lowering Medications

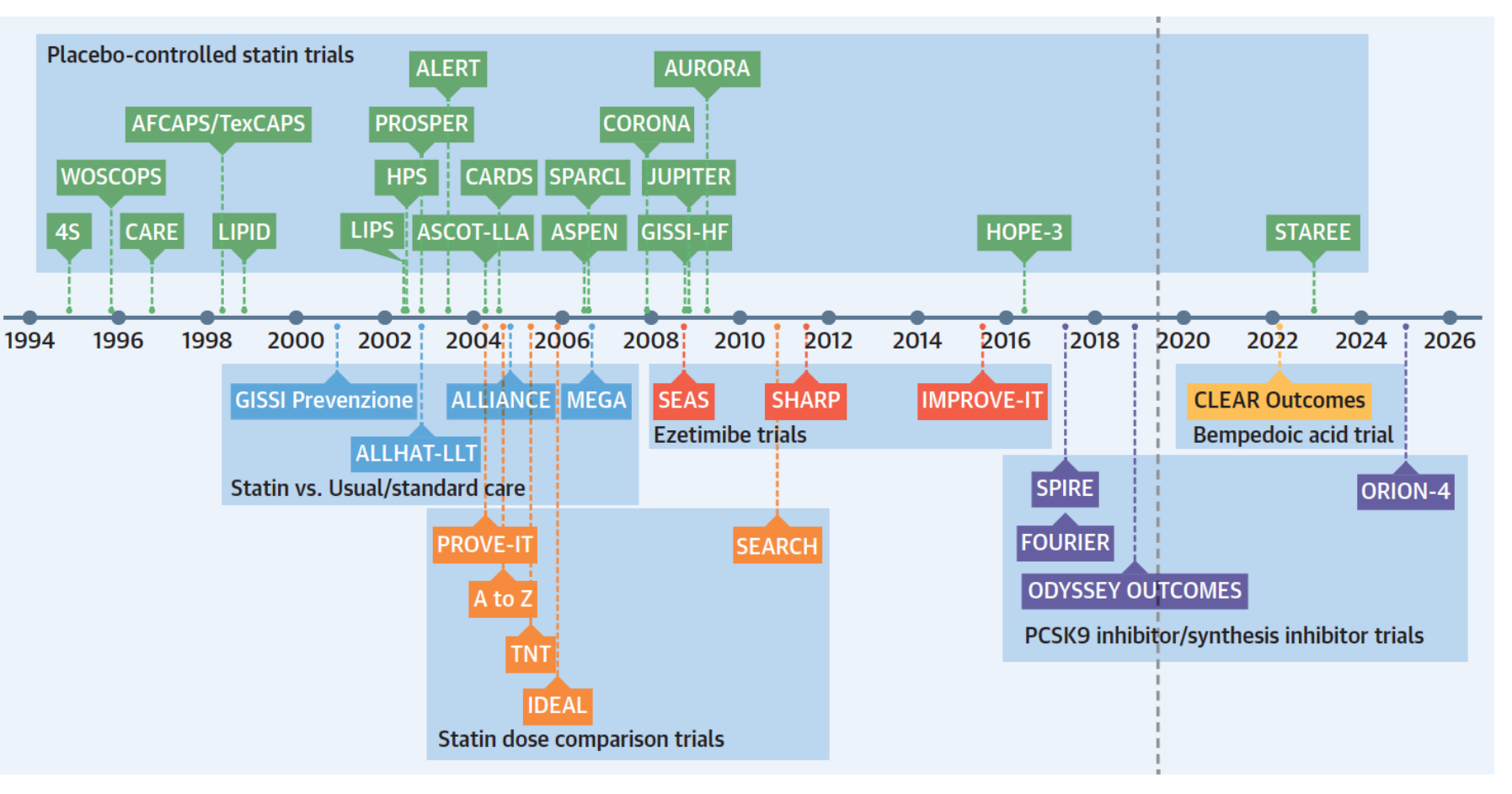
Class	HMG-CoA Reductase Inhibitors (Statins)	Cholesterol Absorption Inhibitor	PCSK9 Inhibitors	Bile Acid Sequestrants	ACL Inhibitor	Omega-3 Fatty Acids	Fibric Acid Derivatives	Niacin
Agents	Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin	Ezetimibe	Alirocumab, evolocumab	Cholestyramine, colestipol, colesevelam	Bempedoic acid	IPE, omega-3 acid ethyl esters (EPA + DHA)	Fenofibrate, fenofibric acid, gemfibrozil	Immediate, slow, extended release
LDL-C effect	↓ to ↓↓↓	↓ to ↓↓	↓↓↓ to ↓↓↓↓	↓ to ↓↓	↓ to ↓↓	IPE: — EPA + DHA: ↑	↑↓	↓ to ↓↓
Triglyceride effect	↓ to ↓↓	—	– to ↓	↑	—	↓ to ↓↓	↓↓↓	↓↓ to ↓↓↓
Non-HDL-C effect	↓↓	↓	↓↓↓	– to ↓	↓ to ↓↓	IPE: ↓↓ EPA + DHA: ↓	↓↓	↓↓ to ↓↓↓
CV outcome	++ to +++	+	++	– to +	—	IPE: ++ to +++ EPA + DHA: —	– to +	– to +
Glucose intolerance/ diabetes risk	↑	—	—	↓ to ↓↓	↓	—	—	↑
Muscle effect	↑ to ↑↑	—	—	—	—	—	– to ↑	—
Liver effect	—	—	—	—	—	—	—	↑ to ↑↑
Kidney effect	—	—	—	—	↑	—	Fenofibrate ↑creatinine	—
GI effect	—	Mild diarrhea	—	Bloating, constipation	—	Dyspepsia	Possible cholelithiasis, hepatitis	Abdominal pain, dyspepsia, jaundice
Brain effect	↑↓	—	—	—	—	—	—	—
Other effects	—	—	Injection site reaction, – to ↑	—	Tendon rupture, ↑ uric acid	Atrial fibrillation ↑ bleeding ↑	Fenofibrate may improve diabetic retinopathy	Flushing, pruritus, ↑ uric acid, gout
Interactions	CYP450i (eg, cyclosporin, rifampin, protease inhibitors; mycins)	—	—	↓ Absorption of thyroid hormones; vitamins A, D, E, K; other medications	Avoid with simvastatin >20 mg and pravastatin >40 mg	—	May potentiate anticoagulant effects; gemfibrozil ↑↑statin muscle toxicity	↑ Statin muscle toxicity

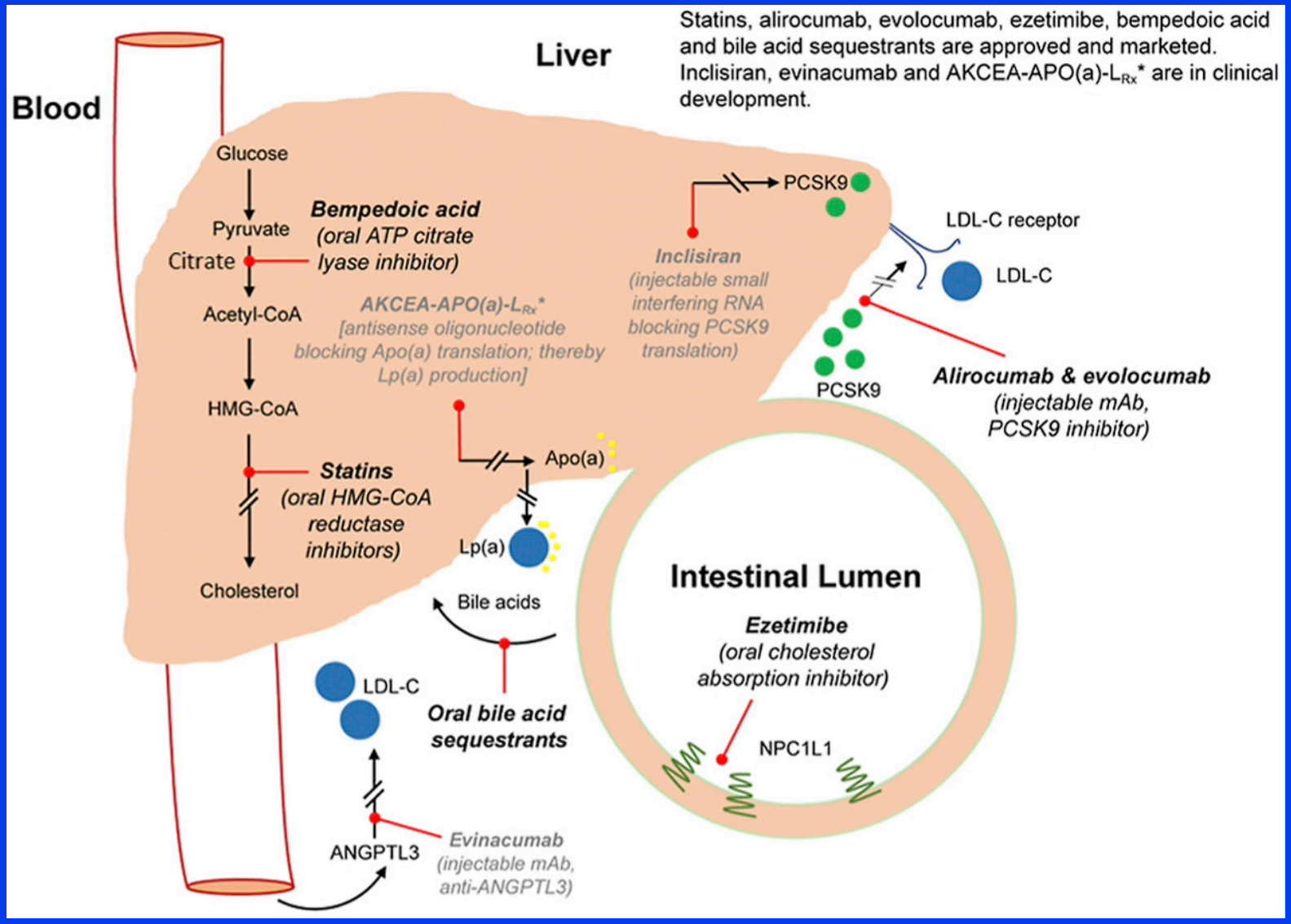
Abbreviations: ACL = ATP-citrate lyase; CV = cardiovascular; CYP450i = cytochrome P450 inhibitor; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GI = gastrointestinal; HMG-CoA = hydroxymethylglutaryl-coenzyme A; IPE = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Few adverse events or possible benefits | Potential for adverse effects | — Neutral

 | DOI 10.4158/CS-2020-0490

Key Trials in the Lipid Space



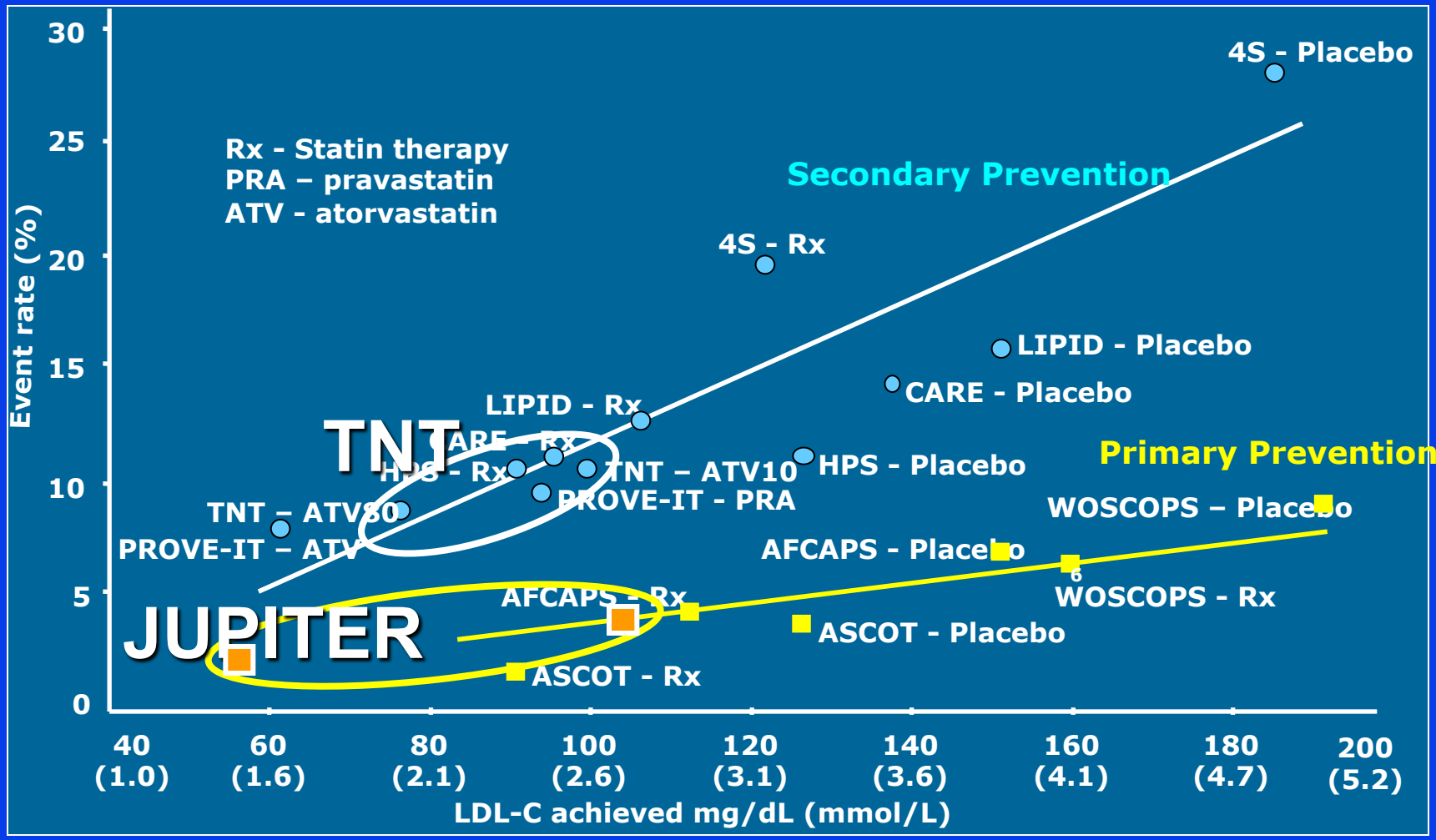

Statins, alirocumab, evolocumab, ezetimibe, bempedoic acid and bile acid sequestrants are approved and marketed.
Inclisiran, evinacumab and AKCEA-APO(a)-LRx* are in clinical development.
Blood
Liver
Glucose
Pyruvate
Citrate
Acetyl-CoA
HMG-CoA
Cholesterol
Bempedoic acid (oral ATP citrate lyase inhibitor)
AKCEA-APO(a)-LRx* [antisense oligonucleotide blocking Apo(a) translation; thereby Lp(a) production]
Statins (oral HMG-CoA reductase inhibitors)
Apo(a)
Lp(a)
Bile acids
Oral bile acid sequestrants
LDL-C
ANGPTL3
Evinacumab (injectable mAb, anti-ANGPTL3)
PCSK9
Inclisiran (injectable small interfering RNA blocking PCSK9 translation)
LDL-C receptor
LDL-C
PCSK9
Alirocumab & evolocumab (injectable mAb, PCSK9 inhibitor)
Intestinal Lumen
Ezetimibe (oral cholesterol absorption inhibitor)
NPC1L1

Cholesterol Treatment Trialists' (CCT) Collaboration: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins (The Lancet 9/27/05)

Over 5 year treatment period (average reduction in LDL-C by 40 mg/dl) showed:

- 12% reduction in all-cause mortality
- 19% reduction in coronary mortality
- 23% reduction in MI or CHD death
- 17% reduction in stroke
- 21% reduction in major vascular events

LDL cholesterol and benefit in clinical trials
Is lower better ?

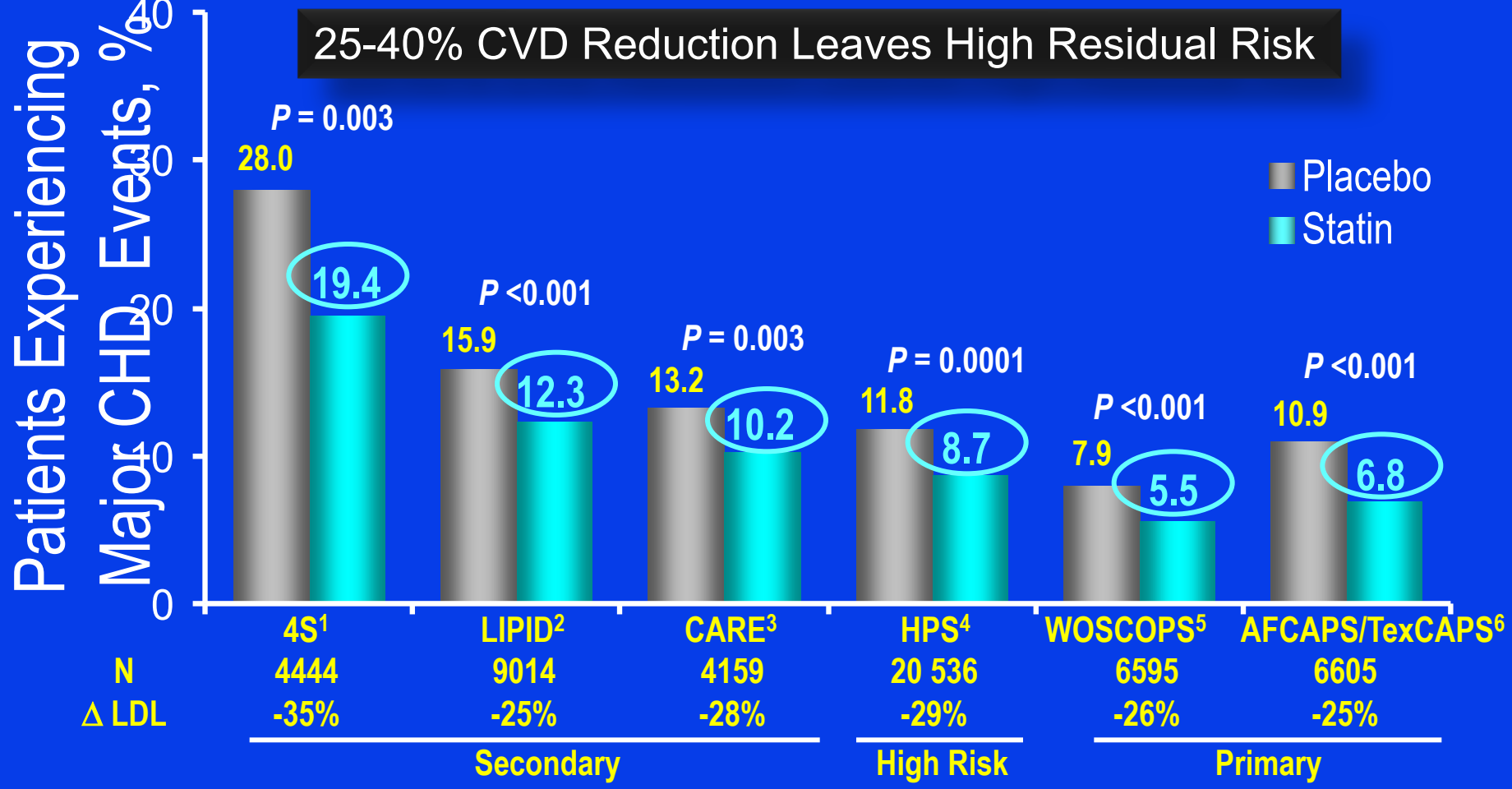


Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004;9(2):269-279

LaRosa JC *et al. N Engl J Med* 2005;352:e-version

Trials of Statin vs Placebo

Many CHD Events Still Occur in Statin-Treated Patients



[1]4S Group. *Lancet.* 1994;344:1383-1389.
[2]LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357.
[3]Sacks FM et al. *N Engl J Med.* 1996;335:1001-1009.
[4]HPS Collaborative Group. *Lancet.* 2002;360:7-22.
[5]Shepherd J et al. *N Engl J Med.* 1995;333:1301-1307.
[6] Downs JR et al. *JAMA.* 1998;279:1615-1622.

IMPROVE-IT: Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

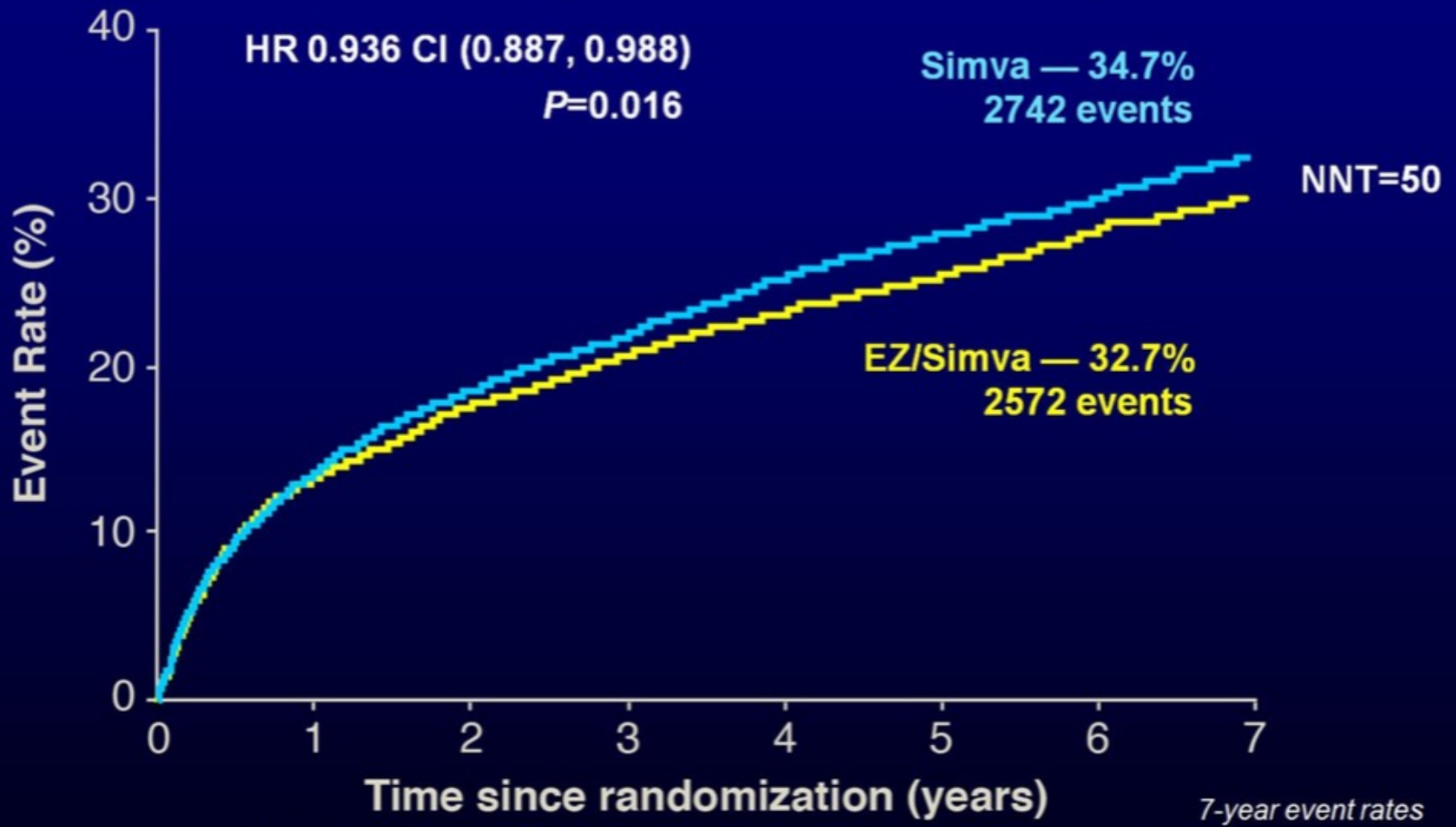
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Blazing MA, *Am Heart J.* 2014;168:205-212

IMPROVE-IT: Primary Endpoint (ITT)

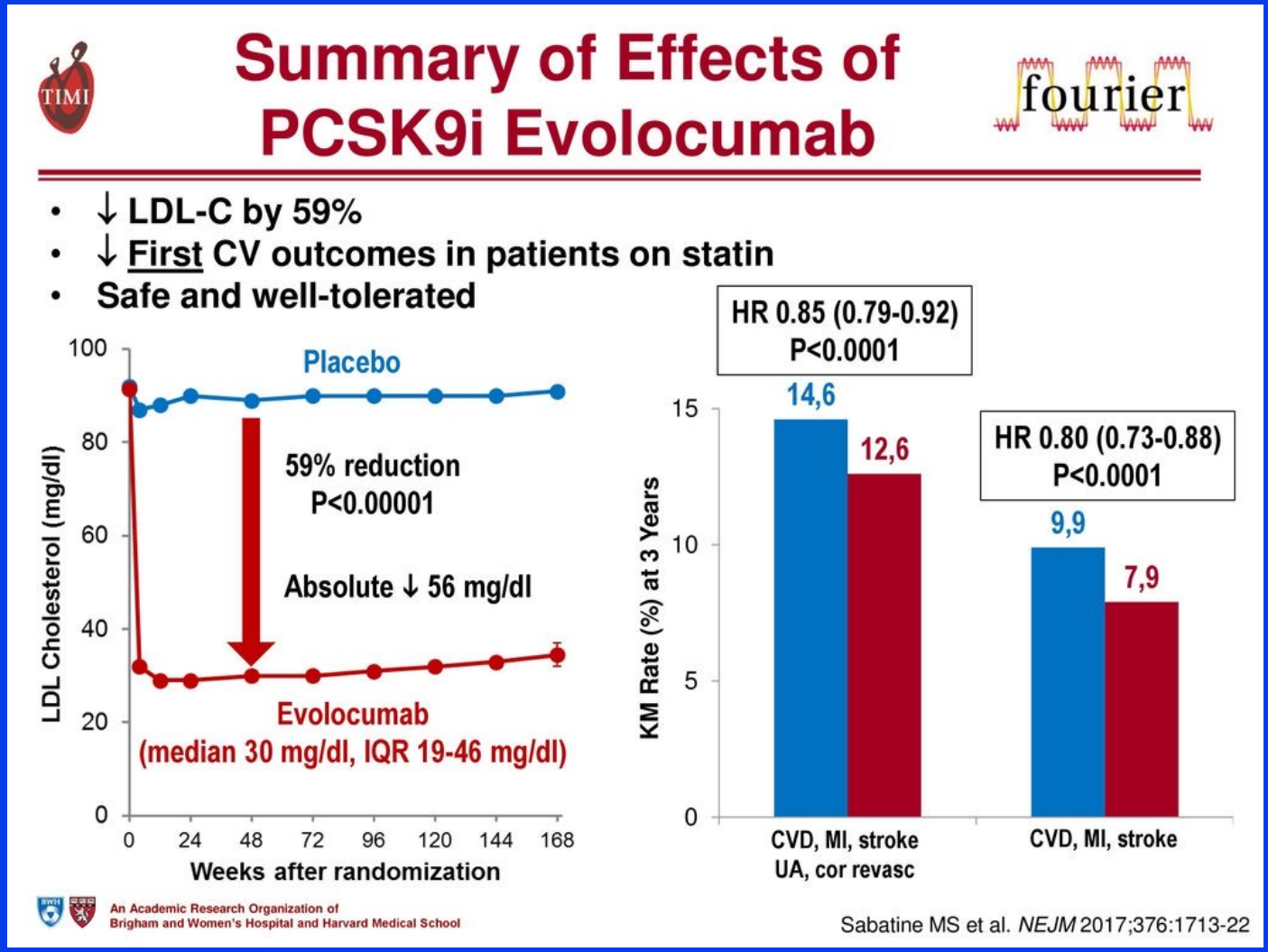
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

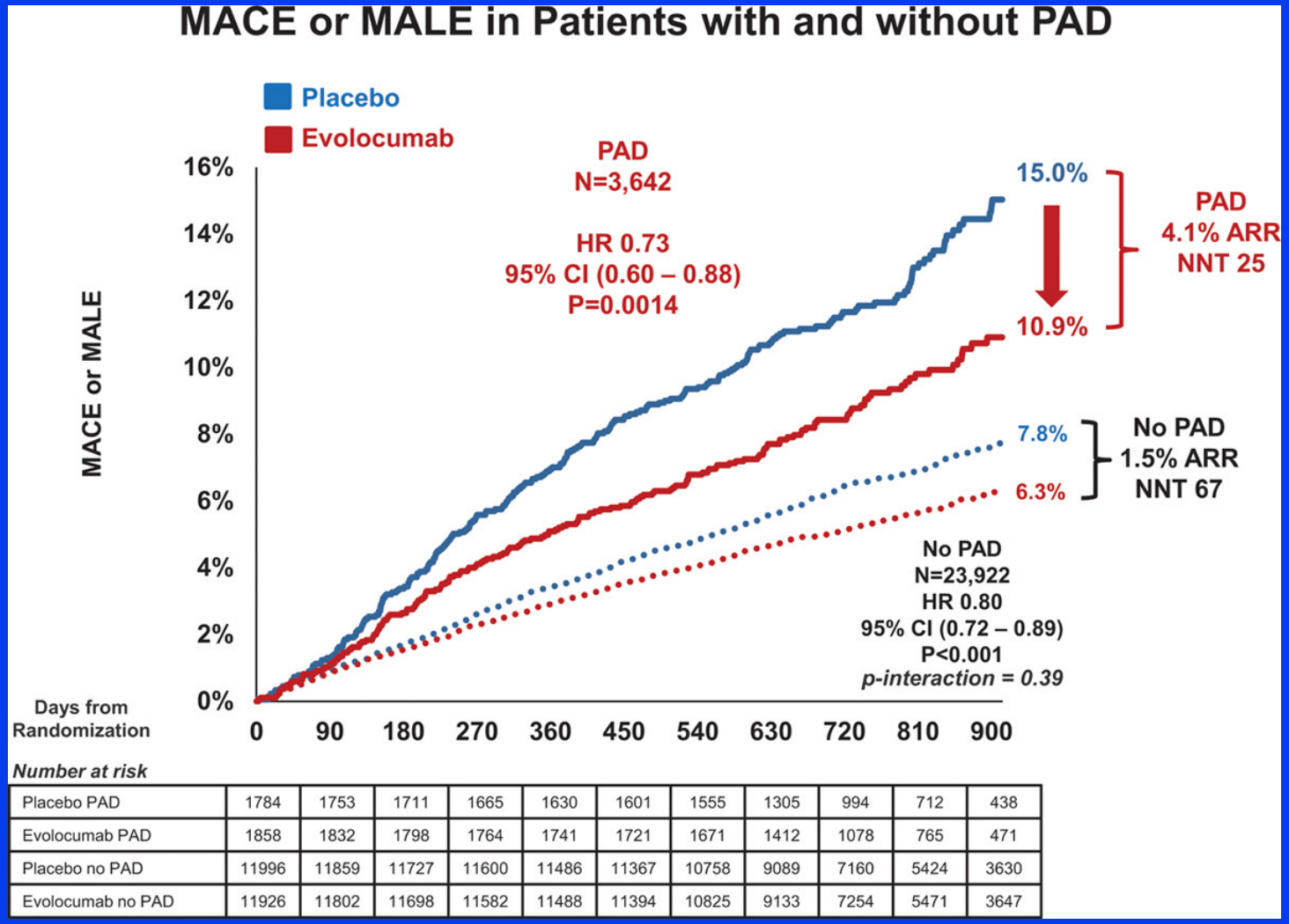
Adapted from Cannon CP, et al. Presented at: American Heart Association Scientific Sessions 2014; November 17, 2014; Chicago, IL.

Fourier Cardiovascular Outcomes Trial



Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722

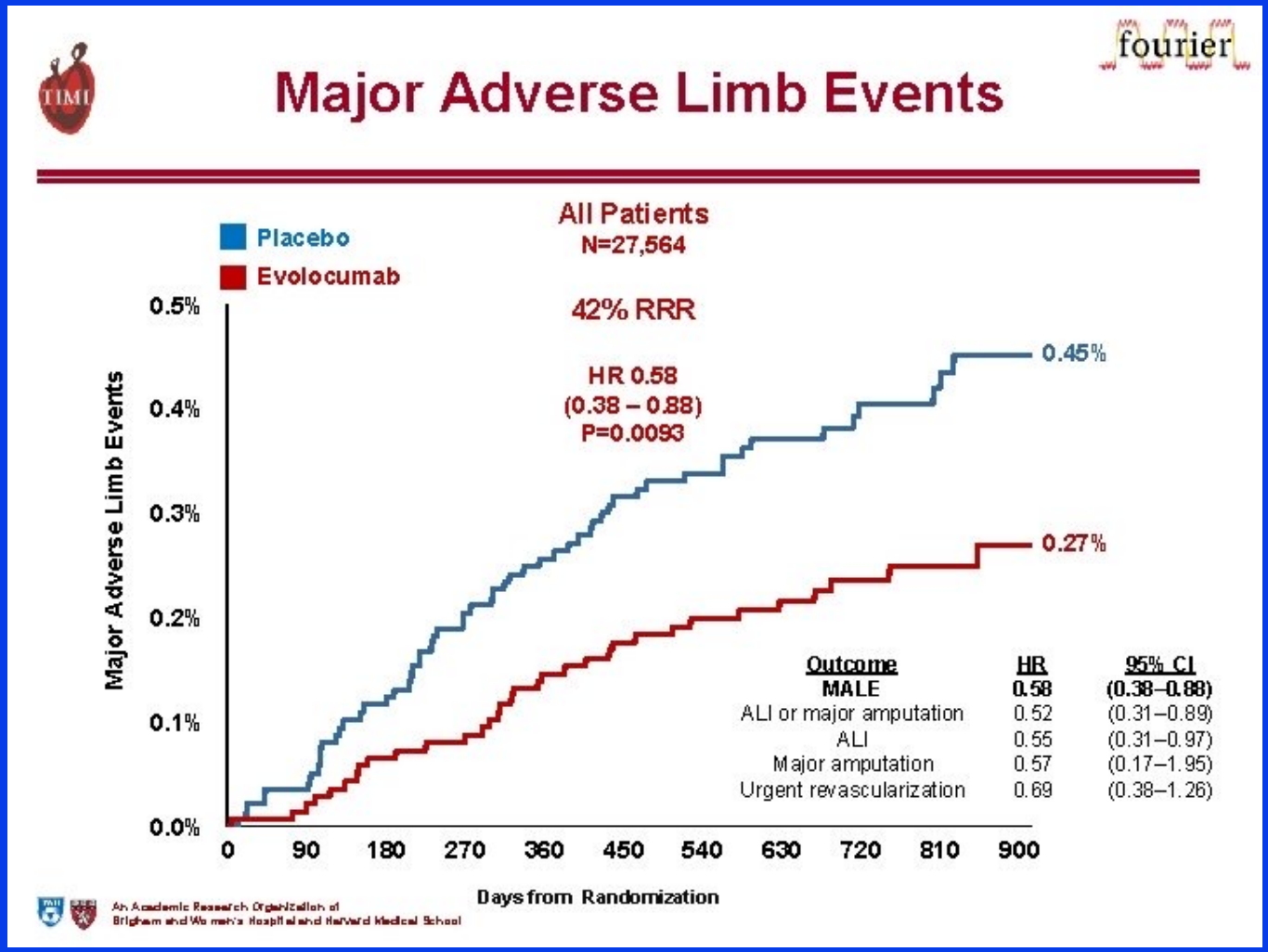
Fourier Cardiovascular Outcomes Trial



Placebo PAD	1784	1753	1711	1665	1630	1601	1555	1305	994	712	438
Evolocumab PAD	1858	1832	1798	1764	1741	1721	1671	1412	1078	765	471
Placebo no PAD	11996	11859	11727	11600	11486	11367	10758	9089	7160	5424	3630
Evolocumab no PAD	11926	11802	11698	11582	11488	11394	10825	9133	7254	5471	3647

Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722

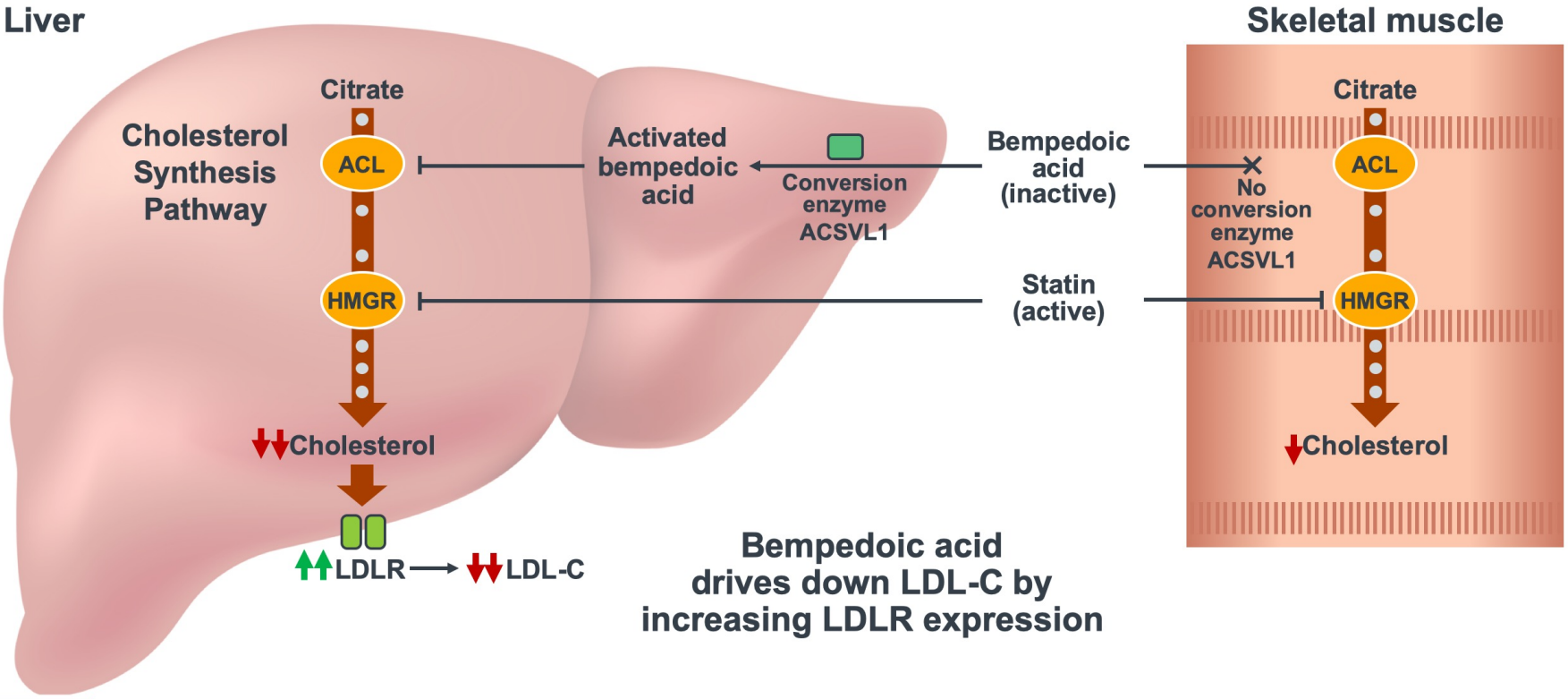
Fourier Cardiovascular Outcomes Trial

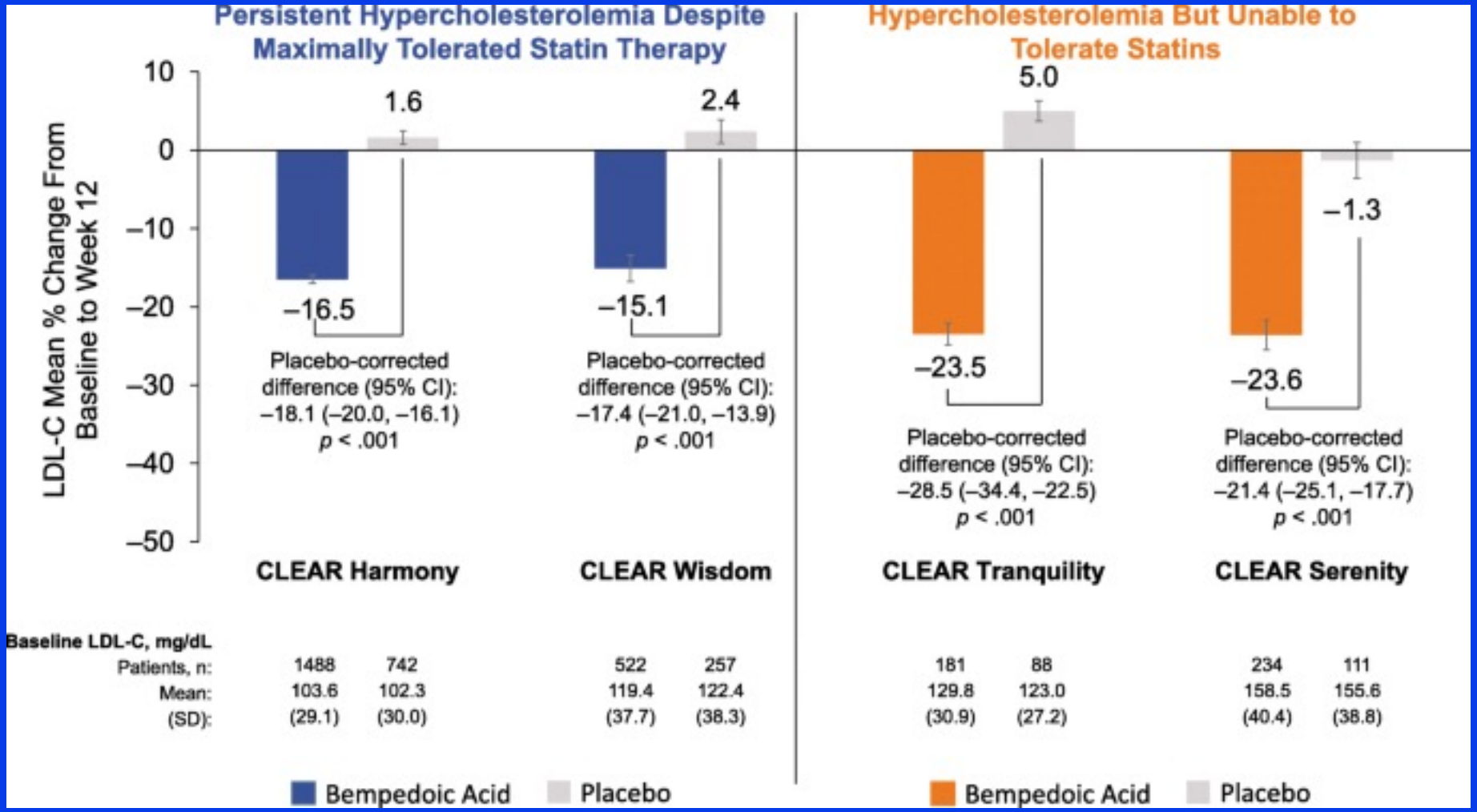


Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722

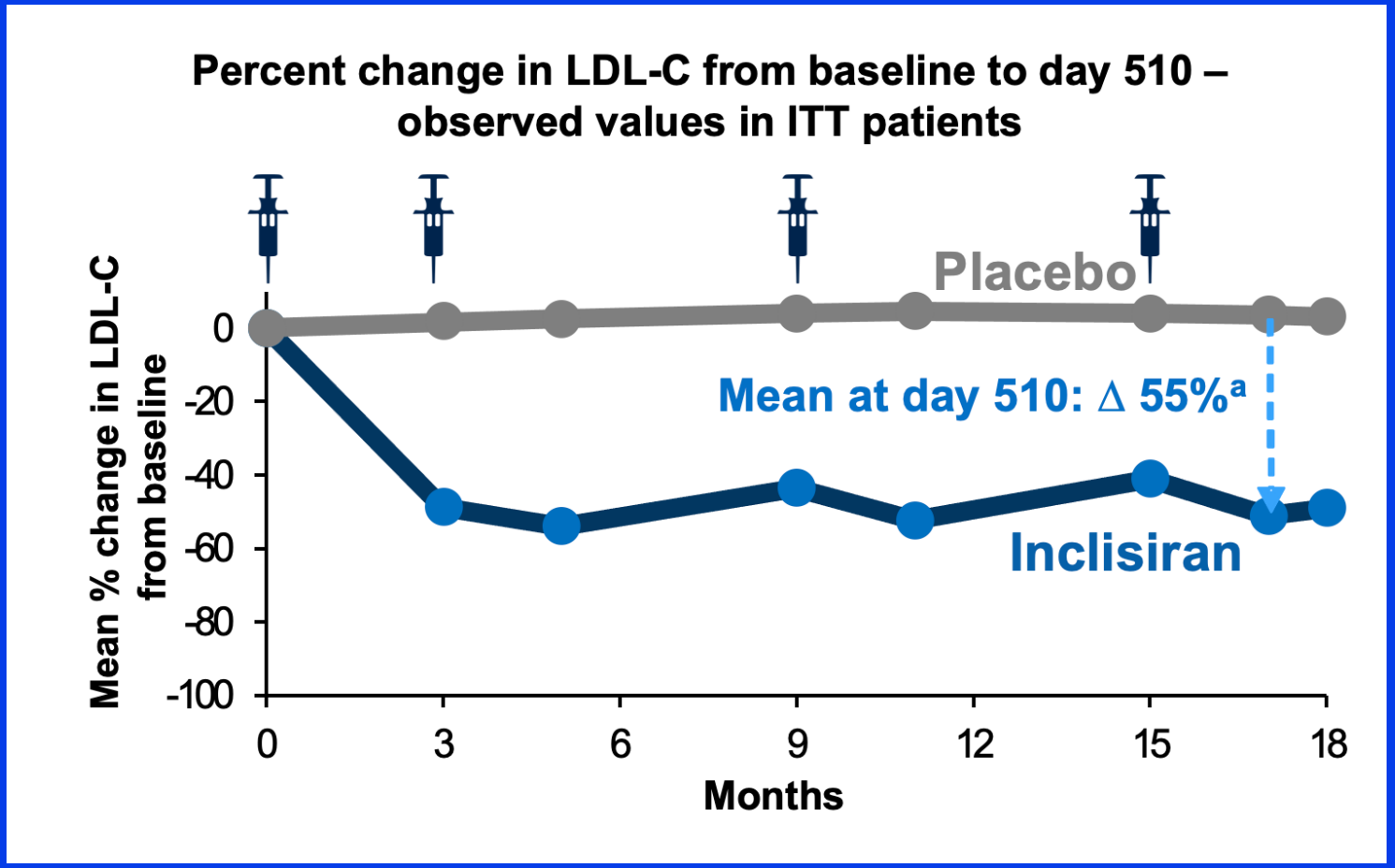
Bempedoic acid reduces cholesterol synthesis by inhibiting ACL 2 steps upstream from HMG-CoA reductase

INHIBITION OF CHOLESTEROL SYNTHESIS BY BEMPEDOIC ACID[1,2]




Persistent Hypercholesterolemia Despite Maximally Tolerated Statin Therapy
Hypercholesterolemia But Unable to Tolerate Statins
LDL-C Mean % Change From Baseline to Week 12
10
0
−10
−20
−30
−40
−50
1.6
2.4
5.0
−1.3
−16.5
−15.1
−23.5
−23.6
Placebo-corrected difference (95% CI): −18.1 (−20.0, −16.1) p < .001
Placebo-corrected difference (95% CI): −17.4 (−21.0, −13.9) p < .001
Placebo-corrected difference (95% CI): −28.5 (−34.4, −22.5) p < .001
Placebo-corrected difference (95% CI): −21.4 (−25.1, −17.7) p < .001
CLEAR Harmony
CLEAR Wisdom
CLEAR Tranquility
CLEAR Serenity
Baseline LDL-C, mg/dL
Patients, n: 1488 742 522 257 181 88 234 111
Mean: 103.6 102.3 119.4 122.4 129.8 123.0 158.5 155.6
(SD): (29.1) (30.0) (37.7) (38.3) (30.9) (27.2) (40.4) (38.8)
Bempedoic Acid
Placebo
Bempedoic Acid
Placebo

Inclisiran: Orion Phase 3 Trials



P value for placebo-inclisiran comparison at each time point <.0001

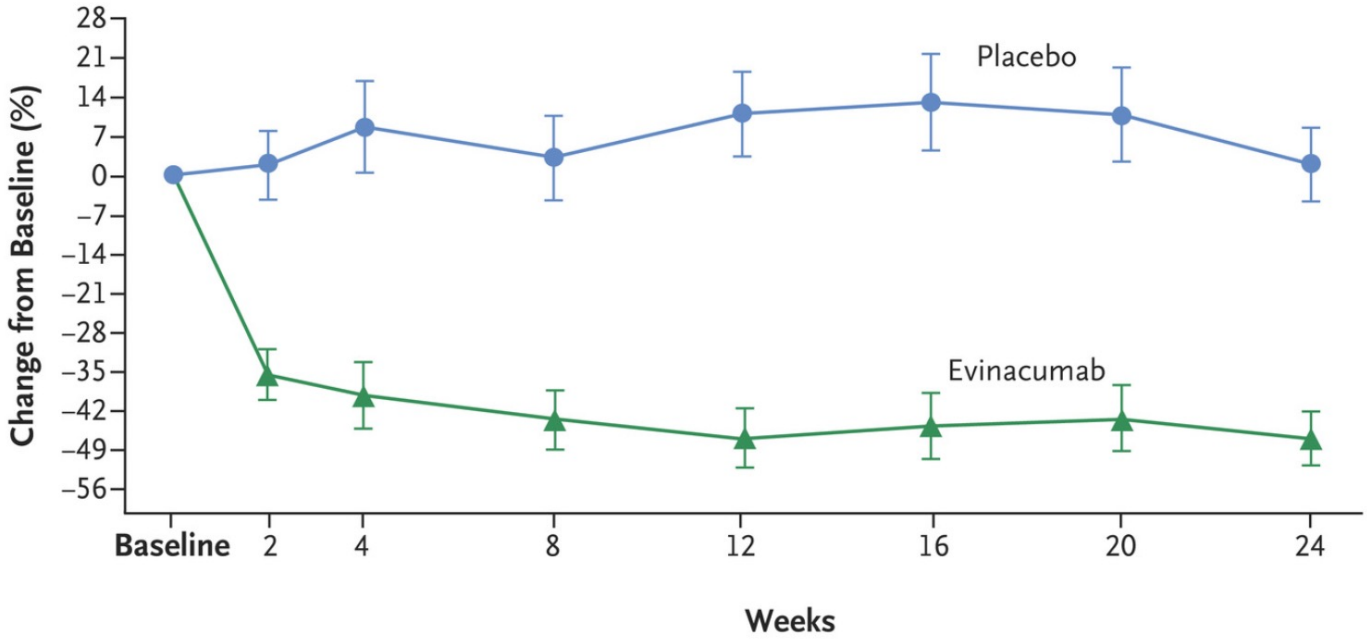
Wright RS et al. LBCT presented at ACC 2020, March 28-30, 2020, Chicago, IL.
Orion-8, Orion-9, Orion-10.

ORIGINAL ARTICLE

Evinacumab for Homozygous Familial Hypercholesterolemia

Frederick J. Raal, M.D., Ph.D., Robert S. Rosenson, M.D., Laurens F. Reeskamp, M.D., G. Kees Hovingh, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., Paolo Rubba, M.D., Shazia Ali, Pharm.D., Poulabi Banerjee, Ph.D., Kuo-Chen Chan, Ph.D., Daniel A. Gipe, M.D., Nagwa Khilla, M.S., Robert Pordy, M.D., et al., for the ELIPSE HoFH Investigators*

A Percent Change in LDL Levels



No. at Risk								
Placebo	22	19	20	21	20	20	20	21
Evinacumab	43	38	43	42	42	40	43	43

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS and the AMERICAN COLLEGE OF ENDOCRINOLOGY

AACE/ACE MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE ALGORITHM

2020

Yehuda Handelsman, MD, Chair; Paul Jellinger MD, Co-Chair; Chris Guerin, MD, Co-Chair; Zachary Bloomgarden, MD; Eliot Brinton, MD; Matthew Budoff, MD; Michael Davidson, MD; Daniel Einhorn, MD; Sergio Fazio, MD; Vivian Fonseca, MD; Alan Garber, MD, PhD; George Grunberger, MD; Ronald Krauss, MD; Jeffrey I. Mechanick, MD; Paul Rosenblit, MD, PhD; Donald Smith, MD, MPH; Kathleen Wyne, MD, PhD

Please refer to the Executive Summary for full details, including evidence citations, supporting each slide in the algorithm.

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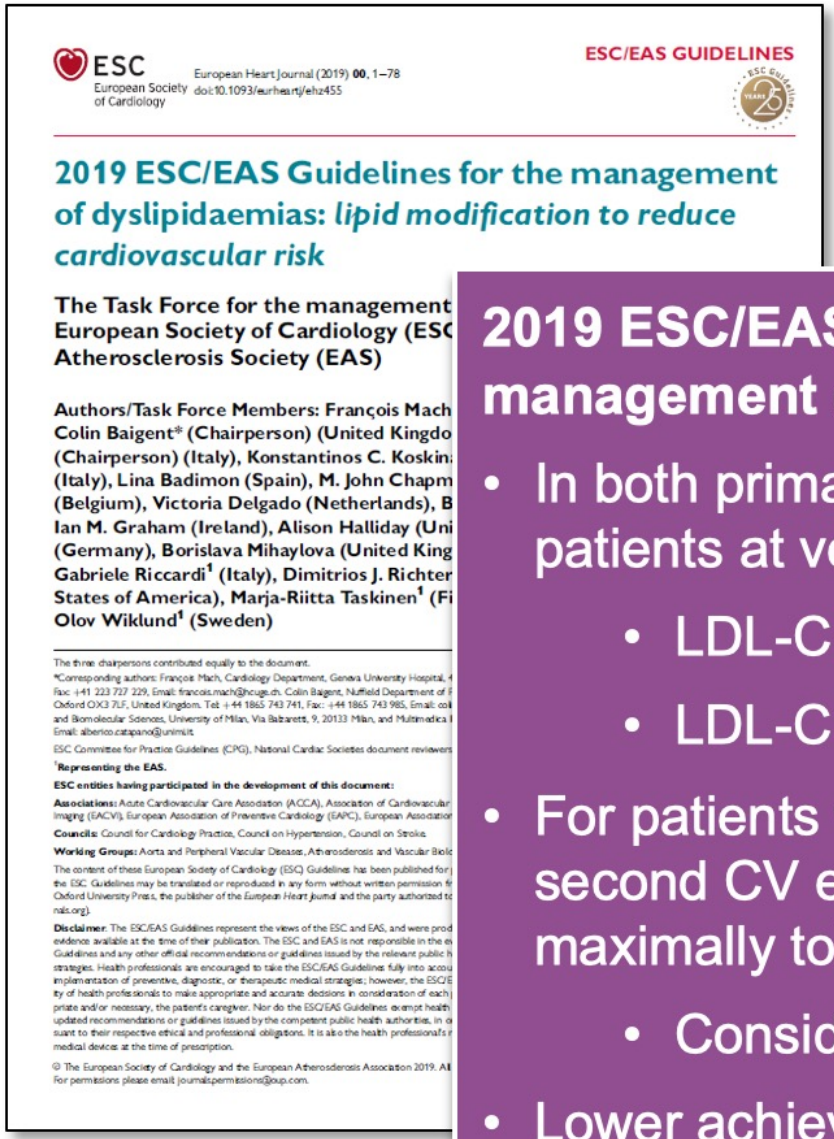
ASCVD Risk Categories and Goals

Risk category	Risk factors[a] and 10-year risk	Treatment goals (mg/dL)			
		LDL-C	Non-HDL-C	Apo B	TG
Extreme risk	• Progressive ASCVD including unstable angina • Established clinical ASCVD plus diabetes or CKD ≥3 or HeFH • History of premature ASCVD (<55 years, male; <65 years, female)	<55	<80	<70	<150
Very high risk	• Established clinical ASCVD or recent hospitalization for ACS, carotid, or peripheral vascular disease, or 10-year risk >20% • Diabetes with ≥1 risk factor(s) • CKD ≥3 with albuminuria • HeFH	<70	<100	<80	<150
High risk	• ≥2 risk factors and 10-year risk 10-20% • Diabetes or CKD ≥3 with no other risk factors	<100	<130	<90	<150
Moderate risk	• <2 risk factors and 10-year risk <10%	<100	<130	<90	<150
Low risk	• No risk factors	<130	<160	NR	<150

[a]Major risk factors: advancing age, elevated non-HDL-C, elevated LDL-C, low HDL-C, diabetes, hypertension, CKD, cigarette smoking, family history of ASCVD.

Abbreviations: ACS = acute coronary syndrome; apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; NR = not recommended; TG = triglyceride.



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
European Society of Cardiology (ESC
Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach
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Ian M. Graham (Ireland), Alison Halliday (Uni
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ESC Committee for Practice Guidelines (CPG), National Cardiac Societies document reviewers

[1]Representing the EAS.

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular
Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Associatio

Councils: Council for Cardiology Practice, Council on Hypertension, Council on Stroke.

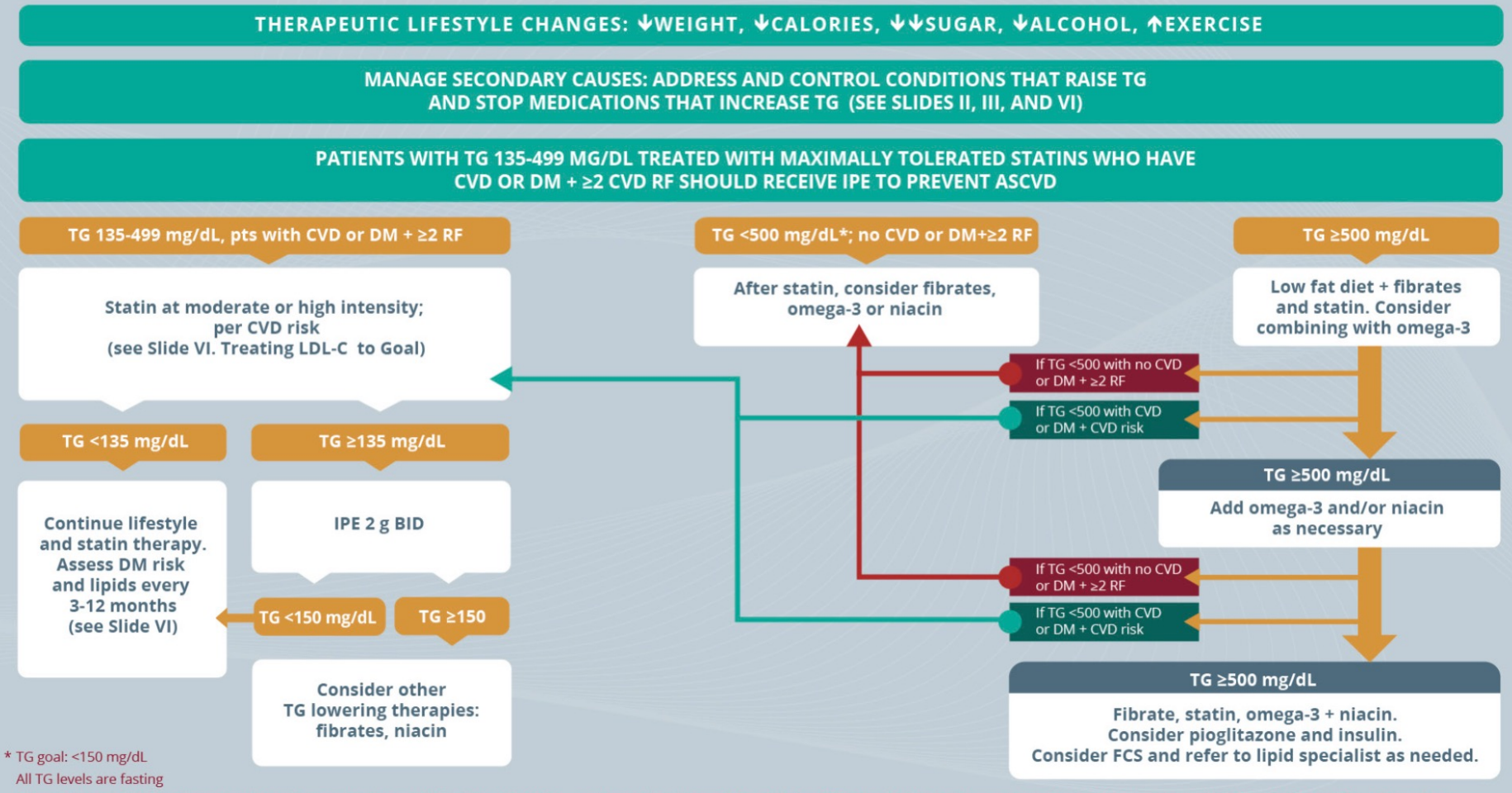
Working Groups: Aorta and Peripheral Vascular Diseases, Atherosclerosis and Vascular Biolo

Disclaimer. The ESC/EAS Guidelines represent the views of the ESC and EAS, and were prod
evidence available at the time of their publication. The ESC and EAS is not responsible in the e
Guidelines and any other official recommendations or guidelines issued by the relevant public h
strategies. Health professionals are encouraged to take the ESC/EAS Guidelines fully into accou
implementation of preventive, diagnostic, or therapeutic medical strategies; however, the ESC/E
ty of health professionals to make appropriate and accurate decisions in consideration of each
priate and/or necessary, the patient's caregiver. Nor do the ESC/EAS Guidelines exempt health
updated recommendations or guidelines issued by the competent public health authorities, in c
suant to their respective ethical and professional obligations. It is also the health professional's
medical devices at the time of prescription.

2019 ESC/EAS guidelines for the management of dyslipidemias[2]

- In both primary and secondary prevention for patients at very high risk[b]
  - LDL-C reduction of ≥50%
  - LDL-C goal of <55 mg/dL
- For patients with ASCVD who experience a second CV event within 2 years while taking maximally tolerated statin therapy
  - Consider LDL-C goal of <40 mg/dL
- Lower achieved LDL-C levels are associated with lower risk of future cardiovascular events, with no lower limit for LDL-C values[2]

Hypertriglyceridemia



* TG goal: <150 mg/dL

All TG levels are fasting

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; BID = twice daily; CVD = cardiovascular disease; DM = diabetes; FCS = familial chylomicronemia syndrome; IPE = icosapent ethyl; RF = risk factor; TG = triglycerides

 | DOI 10.4158/CS-2020-0490

Icosapent Ethyl (EPA) Fish Oil

Key Inclusion Criteria – REDUCE-IT

reduce-it

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 ≥150 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

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

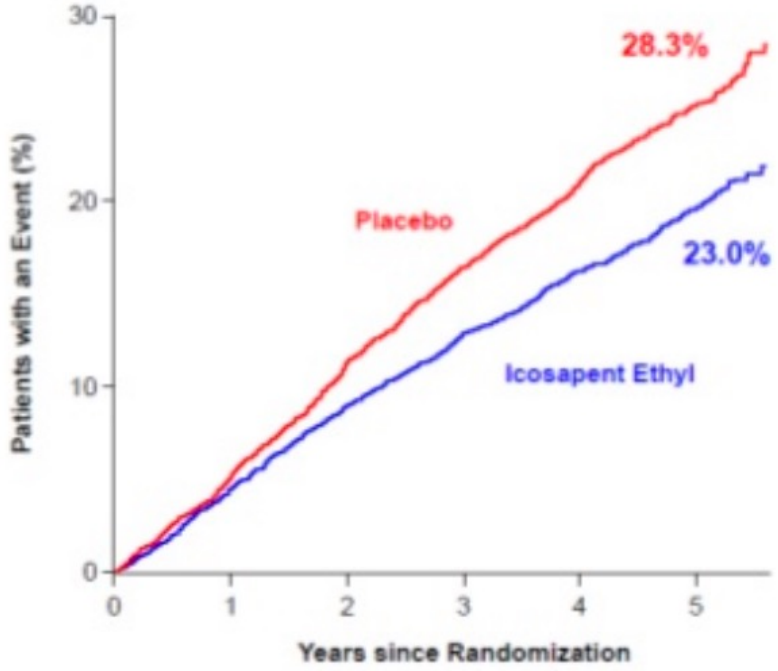
Adapted with permission* from: Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol.* 2017;40:138-148. [*https://creativecommons.org/licenses/by-nc/4.0/]

Icosapent Ethyl (EPA) Fish Oil

Primary End Point:

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

reduce-it

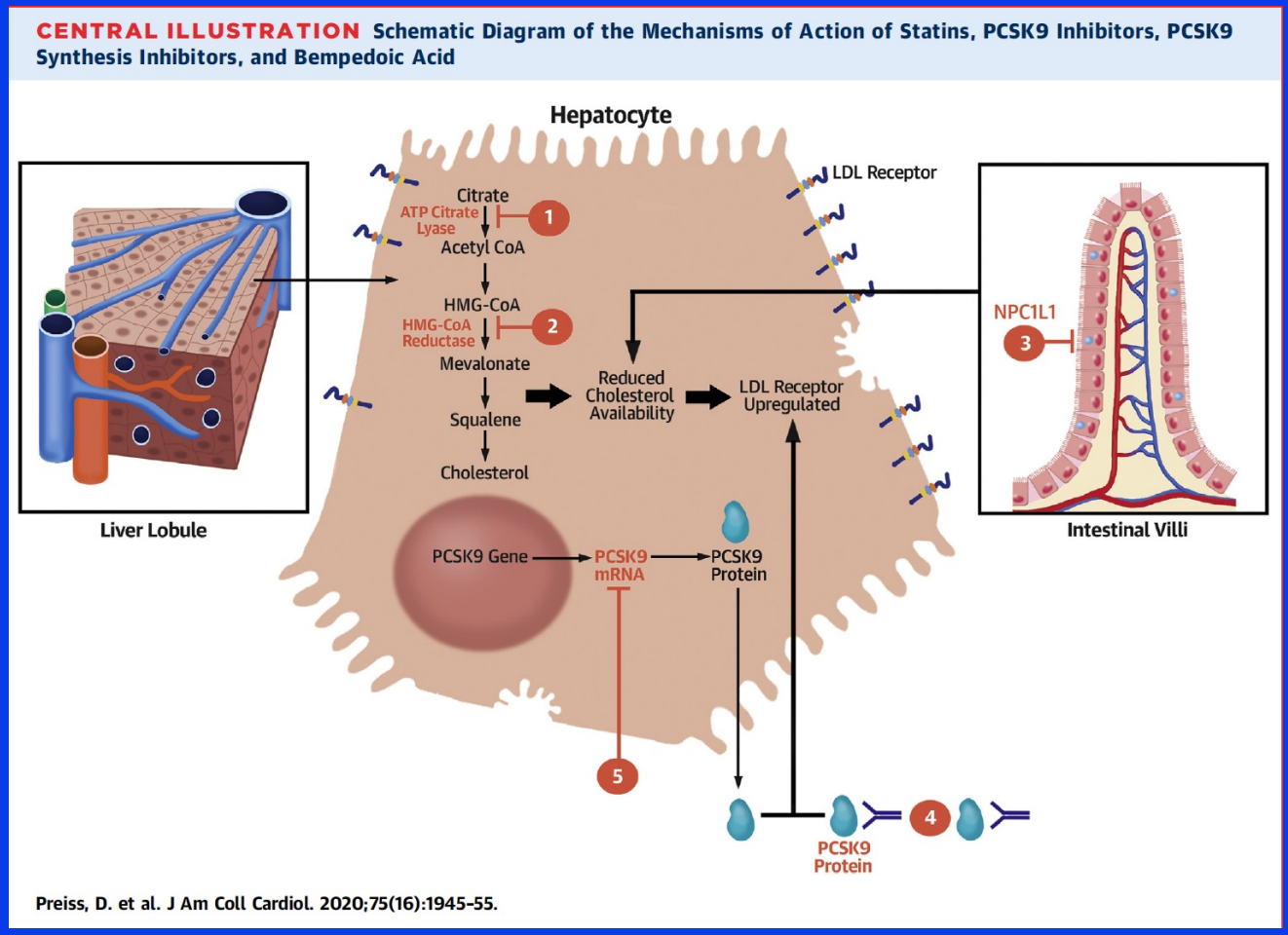


Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

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

Backup Slides

MOA for Lipid Lowering Agents



Targets of low-density lipoprotein (LDL) cholesterol-lowering agents represented are shown in **orange text**. Bempedoic acid **(1)** and statins **(2)** both inhibit steps in the synthesis of cholesterol in the hepatocyte, reducing available cholesterol; ezetimibe **(3)** inhibits the action of the transporter Niemann-Pick C1-like 1 (NPC1L1), reducing intestinal absorption of dietary and biliary cholesterol, which reduces the delivery of chylomicron cholesterol to the hepatocyte via the portal circulation; monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) **(4)** bind to PCSK9 within the circulation, whereas inclisiran **(5)** targets messenger ribonucleic acid (RNA) for PCSK9 within the hepatocyte and both strategies lower circulating PCSK9, reducing lysosomal degradation of LDL receptors. All strategies ultimately lead to up-regulation of LDL receptor expression by the hepatocyte.

The Role of PCSK9 in the Regulation of LDL Receptor Expression