Current Lipid Management: The AACE Guidelines

A Cased-Based Approach

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Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease

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Selected Updated Topics in 2017 AACE Lipid Guidelines Update

- Advances in LDL Goal categorization
  - The **"Extreme Risk"** category
- Assessing CVD Risk: CAC score
- Treating elevated triglyceridemia for CVD reduction
- Treating dyslipidemia in Type 1 diabetes
- Special considerations in children, adolescents and women.
- PCSK9 inhibitors
- Familial Hypercholesterolemia

Case 1…

A 68-year-old male seeks your advice for evaluation of “pre-diabetes”. He has persistent fasting plasma glucose levels between 105 and 115 for many years and a recent A1C of 6.1. He has been treated for hypertension for > 10 years. At age 62 he experienced a L sided TIA. He has no known hx of CAD. No family hx of premature ASCVD. He feels well.

Meds:
Ramipril 10 mg for hypertension
Aspirin 162 mg daily.
Atorvastatin 40 mg/daily

PE:
BMI 33. BP 134/76. Physical exam is unremarkable except for 2+ peripheral pulses , absent DTR’s and mildly diminished peripheral vibratory sensation. There is a questionable R carotid bruit.

Case 1… (cont'd.)

Current laboratory values:

FBS 112 mg/dl, A1c 6.1%,
serum creatinine 1.5, eGFR 45
cholesterol 148 mg/dl
HDL-C 40 mg/dl
triglycerides 165 mg/dl
LDL-C 78 mg/dl
hs CRP 1.6

What is his LDL goal?

A. < 70 mg/dl
B. <100 mg/dl
C < 55 mg/dl
D. Doesn't matter, goals are not important; just Rx with statins.

ASCVD Risk Categories and LDL-C Treatment Goals

Risk category	Risk factors/10-year risk	Treatment goals		
		LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	– Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL – Established clinical cardiovascular disease in individuals with DM, stage 3 or 4 CKD, or HeFH – History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% – DM or stage 3 or 4 CKD with 1 or more risk factor(s) – HeFH	<70	<100	<80
High risk	– ≥2 risk factors and 10-year risk 10%-20% – DM or stage 3 or 4 CKD with no other risk factors	<100	<130	<90
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

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

Barter PJ, et al. *J Intern Med*. 2006;259:247-258; Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Brunzell JD, et al. *Diabetes Care*. 2008;31:811-822; Cannon CP, et al. *N Engl J Med.* 2015;372(25):2387-2397; Grundy SM, et al. *Circulation.* 2004;110:227-239; Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497; Lloyd-Jones DM, et al. *Am J Cardiol*. 2004;94:20-24; McClelland RL, et al. *J Am Coll Cardiol*. 2015;66(15):1643-1653; NHLBI. NIH Publication No. 02-5215. 2002; Ridker PM, *J Am Coll Cardiol*. 2005;45:1644-1648; Ridker PM, et al. *JAMA*. 2007;297(6):611-619; Sever PS, et al. *Lancet*. 2003;361:1149-1158; Shepherd J, et al. *Lancet*. 2002;360:1623-1630; Smith SC Jr, et al. *Circulation*. 2006;113:2363-2372; Stevens RJ, et al. *Clin Sci*. 2001;101(6):671-679; Stone NJ. *Am J Med*. 1996;101:4A40S-48S; Weiner DE, et al. *J Am Soc Nephrol.* 2004;15(5):1307-1315.

What is Clinical ASCVD?

2014 ACC/AHA definition of clinical ASCVD as one or more of the following:

Coronary Heart Disease (CHD)

- Acute coronary syndrome (ACS)
- History of myocardial infarction (MI)
- Stabile or unstable angina
- Coronary or other arterial revascularization

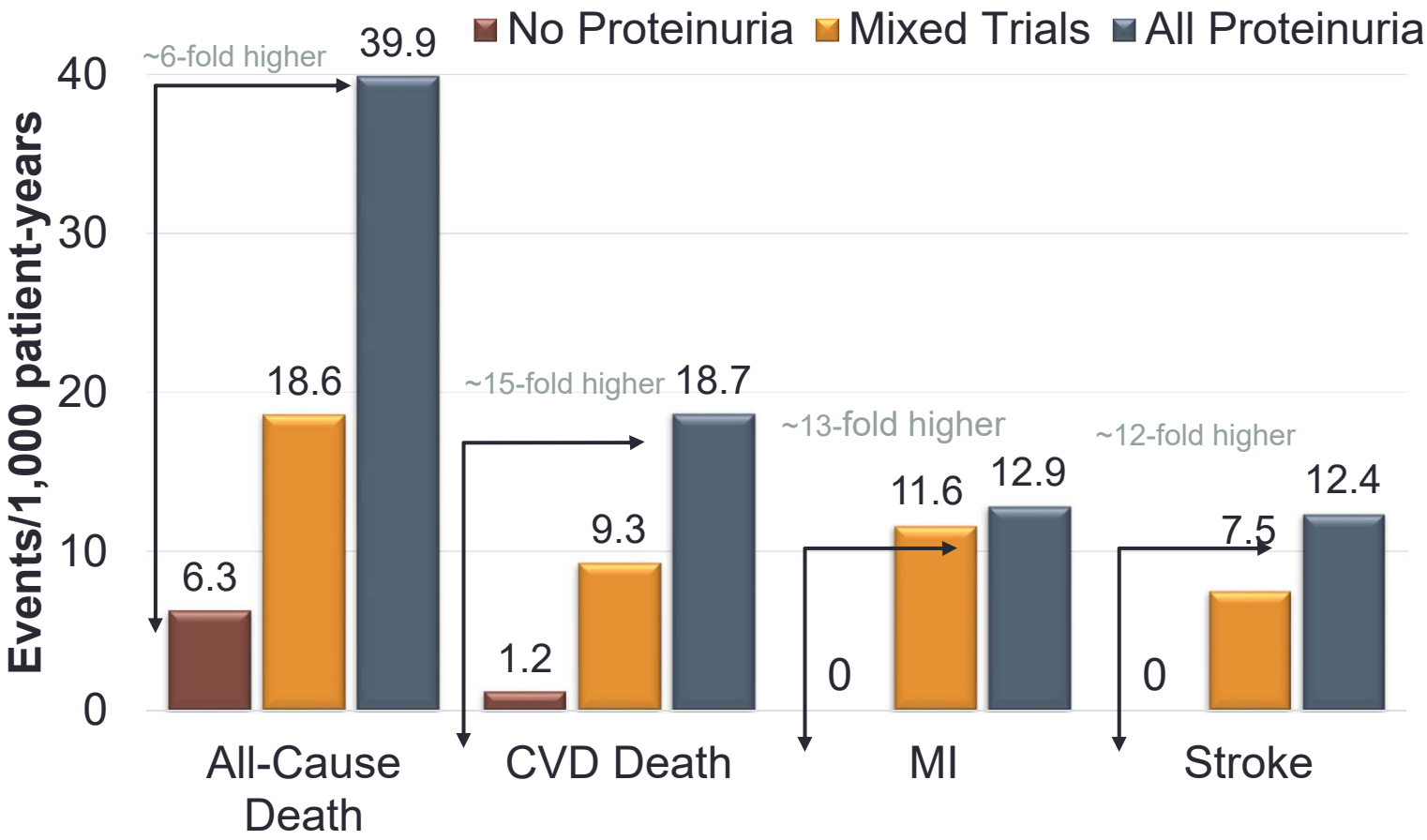
Stroke or transient ischemic attack

Peripheral arterial disease

Stone NJ et *al J Am Coll Cardiol* 2014;63:2889-2934

Systematic Review, Summary of Event Rates in Trial Participants With Diabetes, Stratified by Absence or Presence of Baseline Proteinuria

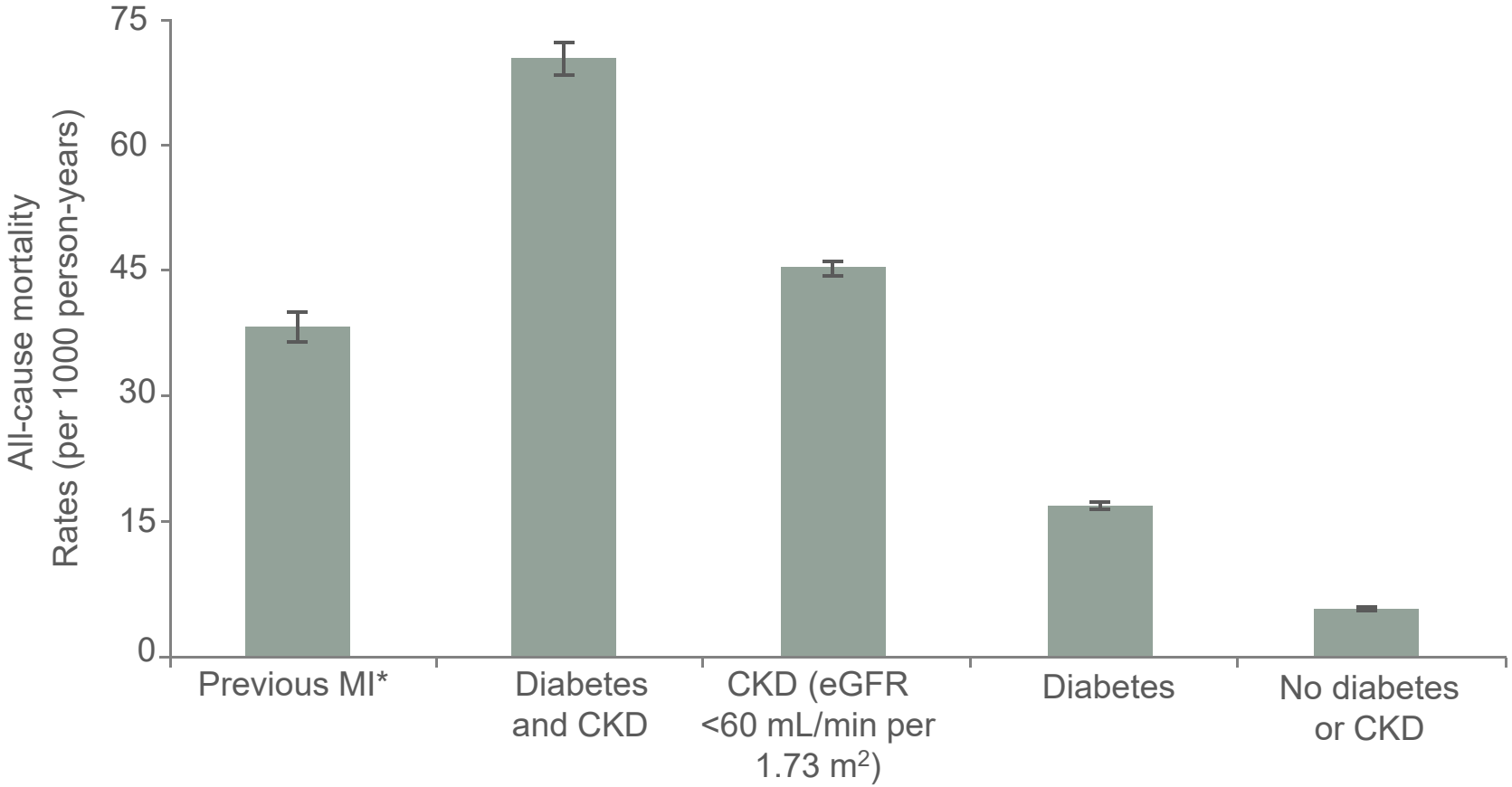
Randomized controlled trials (N=29), 116,790 patients with diabetes,
~518,611 patient-years of follow-up



Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction.

Preiss D, et al. *Am Heart J*. 2011;161:210-219.

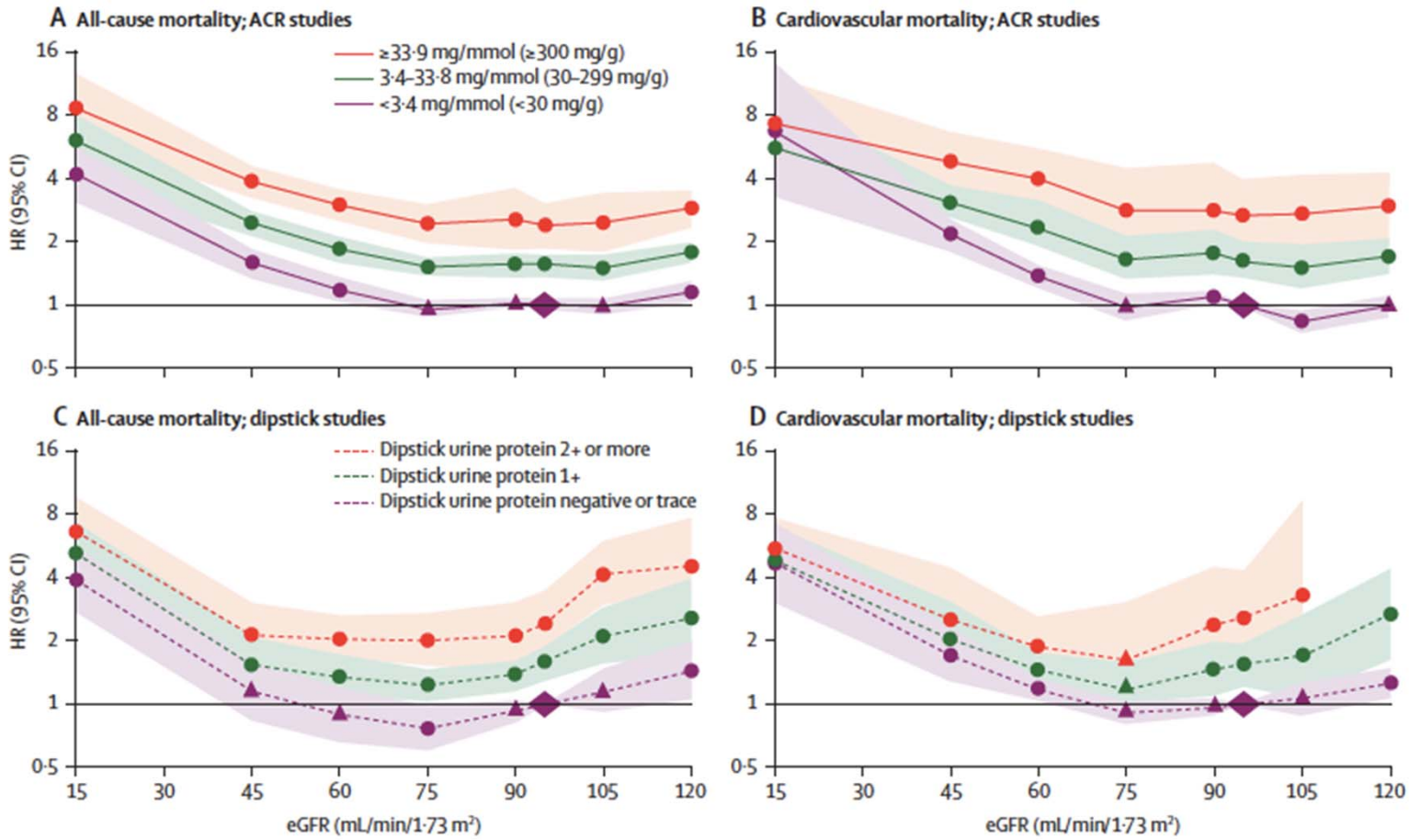
Renal Disease is Associated with Increased All-cause Mortality



*Includes participants with or without diabetes and chronic kidney disease.

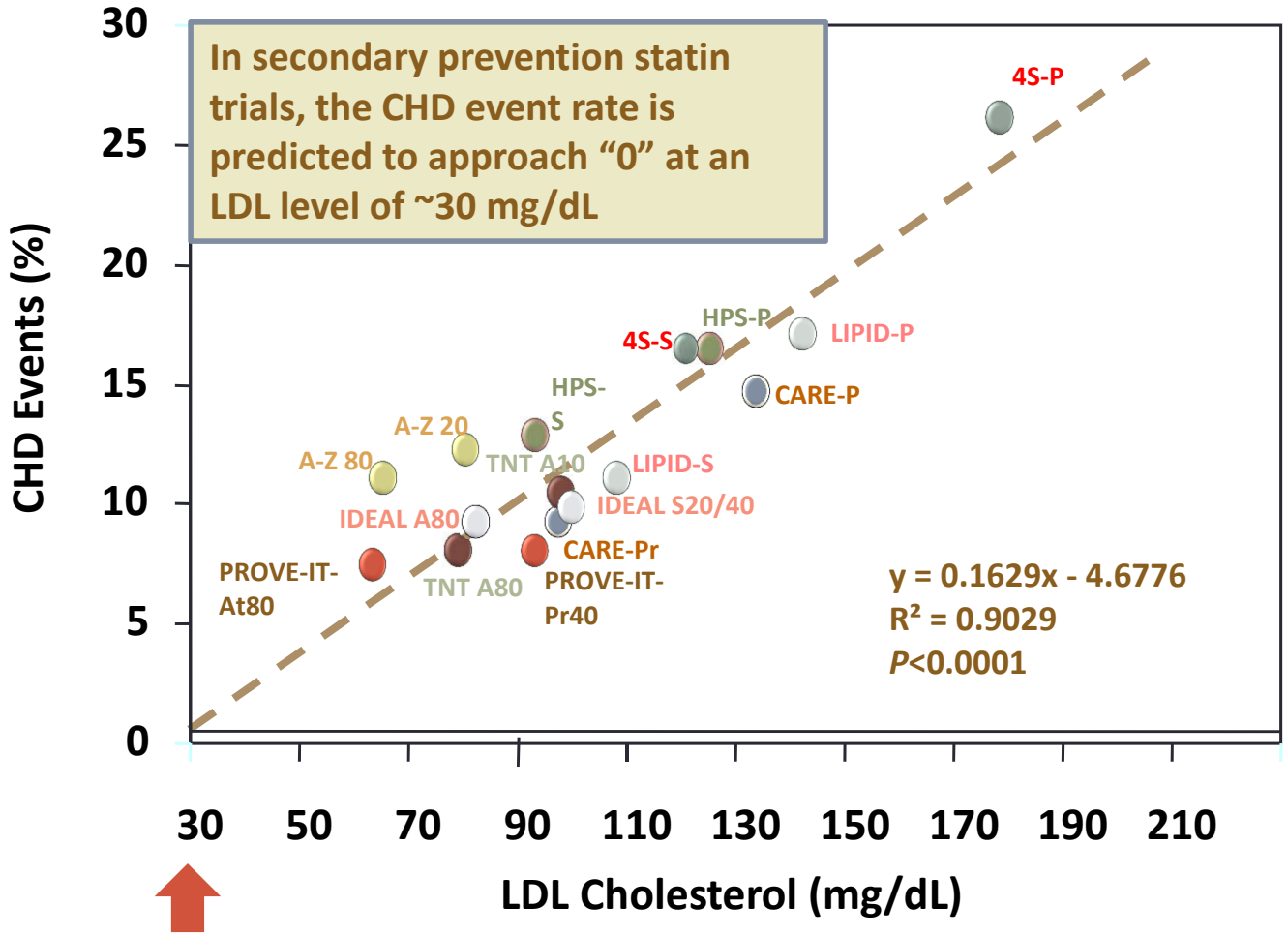
Tonelli et al. Lancet 2012;380(9844):807–14.

Meta-Analysis: Hazard Ratios and 95% CIs for All-Cause and CV Mortality According to eGFR and Categorical Albuminuria



Abbreviations: CV, cerebrovascular; eGFR, estimated glomerular filtration rate.
Chronic Kidney Disease Prognosis Consortium. *Lancet*. 2010;375:2073-2081 .

Coronary Heart Disease Event Rates in Secondary Prevention Trials Including Acute Coronary Syndrome

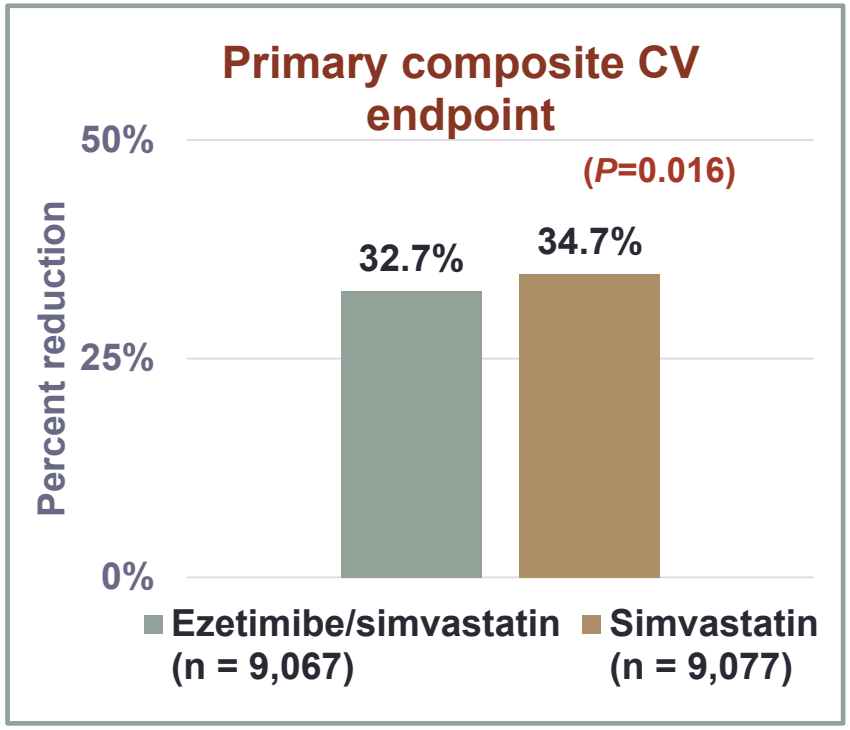


Abbreviations: CHD, coronary heart disease; LDL, low-density lipoprotein.

O'Keefe JH, et al. *J Am Coll Cardiol*. 2004;43:2142-2146.

IMPROVE-IT: Improved Reduction of Outcomes, Vytorin Efficacy International Trial

Trial design: Patients with recent ACS were randomized 1:1 to either ezetimibe 10 mg + simvastatin 40 mg or simvastatin 40 mg and followed for a median of 6 years



Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Cannon CP, et al. *N Engl J Med.* 2015;372:2387-2397.

Results

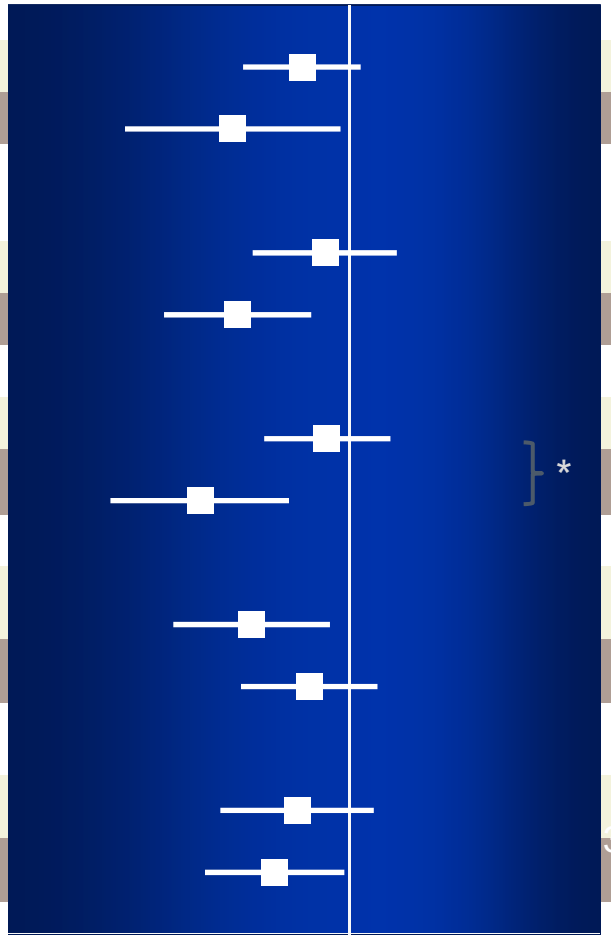
- Primary endpoint (CV death/MI/UA/coronary revasc/stroke/moderate/severe bleeding) for ezetimibe/simvastatin vs. simvastatin: 32.7% vs. 34.7% (HR 0.94, 95% CI 0.89-0.99; *P*=0.016)
- MI:13.1% vs.14.8%, *P*=0.002; stroke: 4.2% vs. 4.8%, *P*=0.05; CVD/MI/stroke: 20.4% vs. 22.2%, *P*=0.003
- Median LDL follow-up average: **53.7** vs. 69.5 mg/dL

Conclusions

- In patients with high-risk ACS, ezetimibe 10 mg/ simvastatin 40 mg was superior to simvastatin 40 mg alone in reducing adverse CV events
- This is the first study powered for clinical outcomes to show a benefit with a non-statin agent
- **Reaffirms the "lower is better" LDL-C hypothesis**

Major Prespecified Subgroups: IMPROVE-IT

Baseline data	Simva† Mean LDL 69.5	EZE/Simva† Mean LDL 53.7
Male	34.9	33.2
Female	34.0	31.0
Age <65 years	30.8	29.9
Age ≥65 years	39.9	36.4
No diabetes	30.8	30.2
Diabetes	45.5	40.0
Prior LLT	43.4	40.7
No prior LLT	30.0	28.6
LDL-C >95 mg/dL	31.2	29.6
LDL-C ≤95 mg/dL	38.4	36.0



†*7-year event rates*

**P-interaction=0.023, otherwise >0.05*

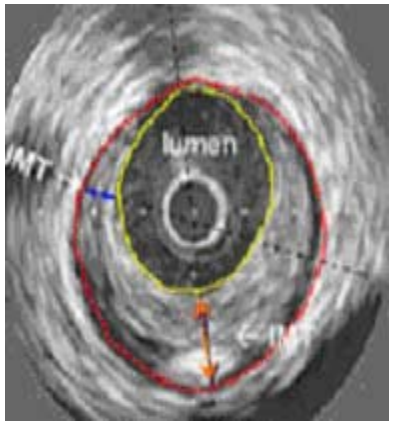
Abbreviations: LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

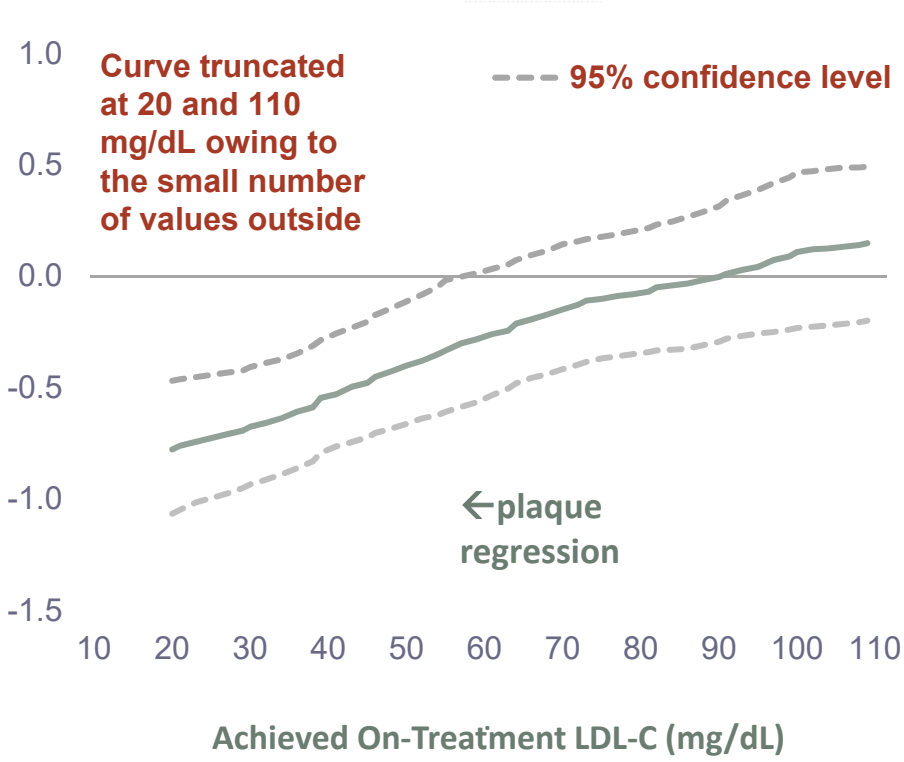
NNT=56

Cannon CP, et al. *N Engl J Med.* 2015;372:2387-2397. Supplementary Appendix.

GLAGOV: Mean On-Treatment LDL-C vs. Change in Percent Atheroma Volume

The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment 5/2013 to 1/2015) conducted at 197 academic and community hospitals in 6 continents, enrolling 968 patients (mean age 59.8 years, 27.8% female) with CAD





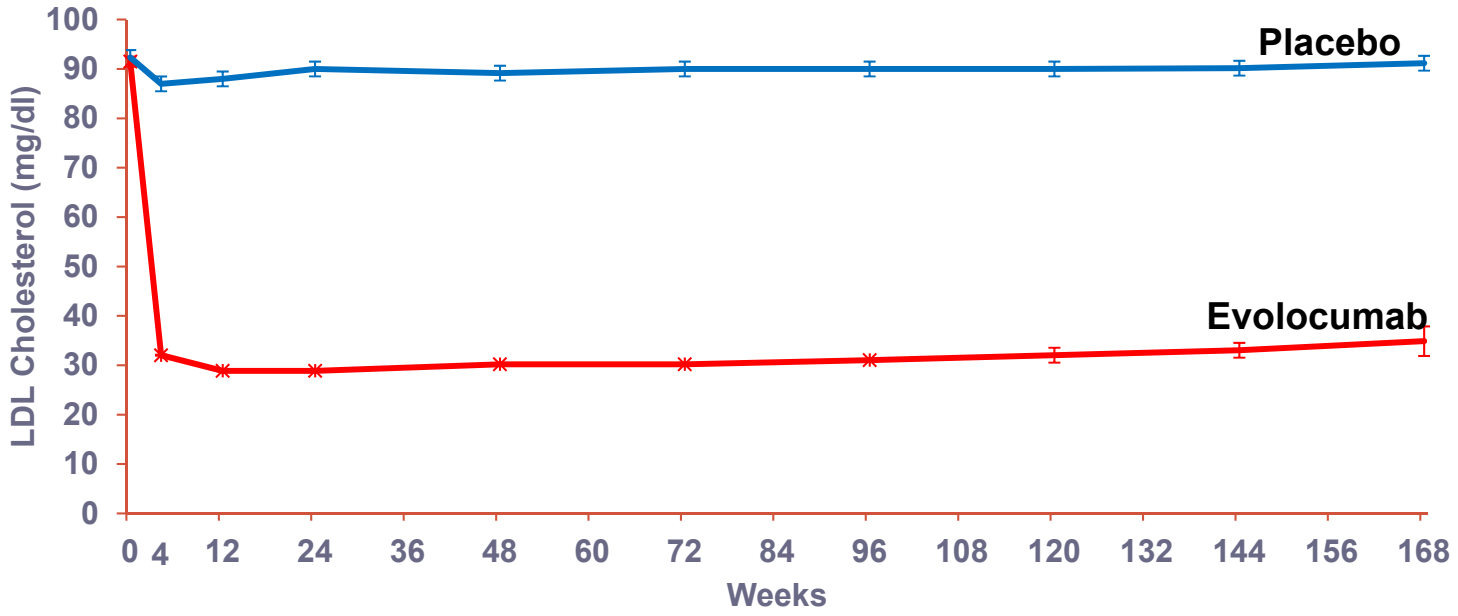
Patients with angiographic CAD were randomized to receive monthly evolocumab (420 mg) (n=484) or placebo (n=484) SQ for 76 weeks, in addition to statins

Locally weighted polynomial regression (LOESS) plot demonstrates a linear continuous relationship between achieved LDL-C level and PAV progression/ regression for levels of LDL-C ranging from 110 mg/dL to as low as 20 mg/dL

Abbreviations: CAD, coronary artery disease; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody ;LDL-C, low-density lipoprotein
cholesterol; SQ, subcutaneous.

Nicholls SJ. *JAMA*. 2016;316(22):2373-2384.

FOURIER Evolocumab Study
LDL-C Levels Over time



No. at Risk

Placebo	13,779	13,251	13,151	12,954	12,596	12,311	10,812	6926	3352	790
Evolocumab	13,784	13,288	13,144	12,964	12,645	12,359	10,902	6958	3323	768

Absolute difference (mg/dL)	54	58	57	56	55	54	52	53	50
Percentage difference	57	61	61	59	58	57	55	56	54
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol.

Sabatine MS, et al. *NEJM*. 2017; epub ahead of print.

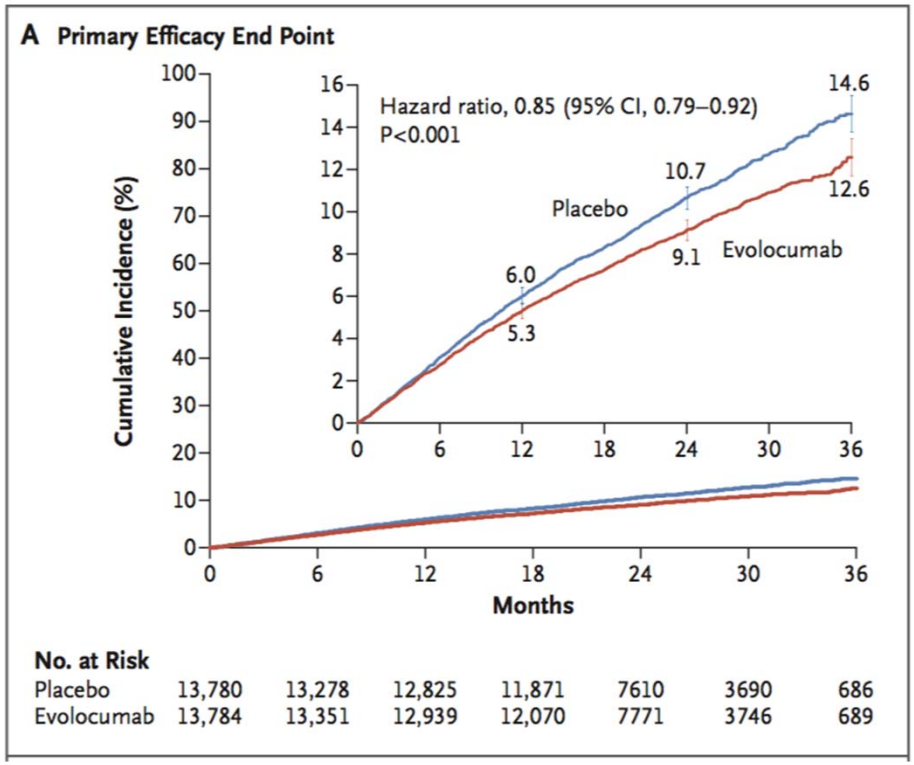
FOURIER Primary and Secondary Endpoints

- **At 26 months, extremely tight lipid control with evolocumab led to a 15% decrease in risk for the primary composite endpoint and 20% decrease in risk for a secondary composite endpoint**
  - **The primary endpoint included MI, cardiovascular death, stroke, coronary revascularization, or hospitalization for unstable angina**
  - **The secondary endpoint included cardiovascular death, MI, or stroke**
- **Beyond the second year of follow-up, the risk reduction increased to 20% for the primary endpoint and to 25% for the secondary endpoint**
- **For singular endpoints at 26 months, very tight lipid control reduced the risk of MI by 27%, stroke by 21%, and coronary revascularization by 22%**
- **NNT 74; NNT extended to 36 months ~50**

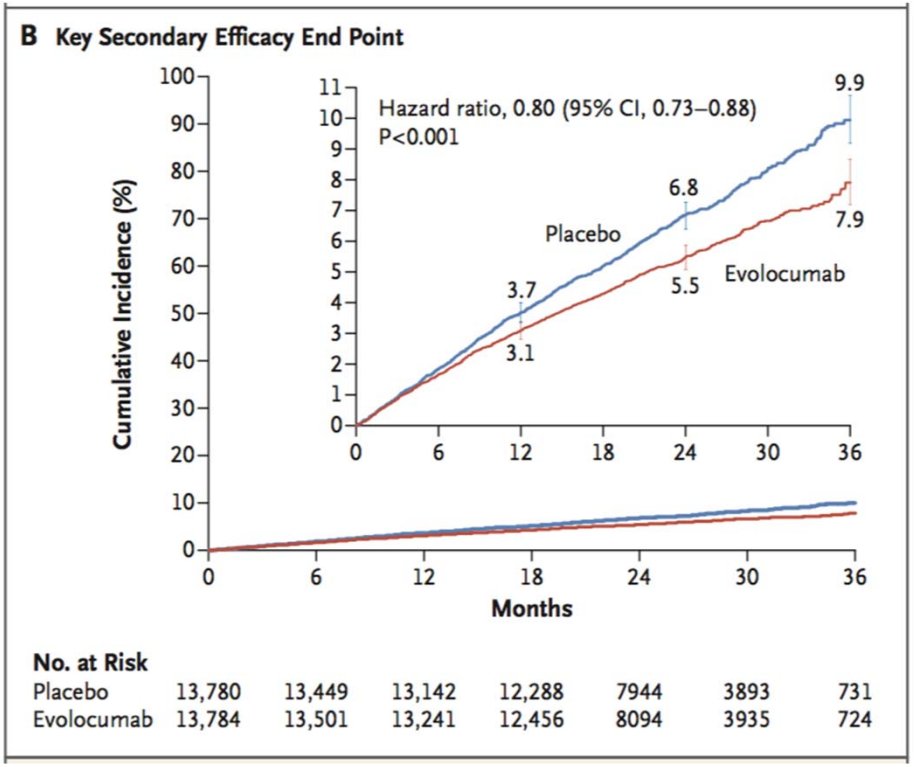
Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Sabatine MS, et al. *NEJM.* 2017; epub ahead of print.

FOURIER Evolocumab Study Endpoints



Cumulative event rates for the primary efficacy endpoint
(Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)



Cumulative rates for the key secondary efficacy endpoint
(Composite of cardiovascular death, MI, or stroke)

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI, myocardial infarction.

Sabatine MS, et al. *NEJM*. 2017; epub ahead of print.

ODYSSEY OUTCOME TRIAL, 2018

Conclusions:

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL and allowing levels as low as 15 mg/dL:

- **Reduced MACE (15%), MI (14%), ischemic stroke (27%) and unstable angina (39%).**
- **Was associated with a lower rate of all-cause death (15%,)**
- **Was safe and well-tolerated over the duration of the trial**

Clinical Perspective:

- **In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions**
- **Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%, NNT 29) and all-cause death by 29% (ARR 1.7%, NNT 60) compared with placebo. These are the patients who may benefit most from treatment ARR, absolute risk reduction**

Cholesterol Treatment Trialists' 2010: Efficacy of Intensive LDL-C Lowering in Patients With Low Baseline LDL-C

Meta-analysis of randomized controlled trials of major vascular events (coronary death, myocardial infarction, coronary revascularization, and ischemic stroke) with at least 1,000 patients and ≥2 years of more vs. less intense statin dosage (N=169,138)

For each 39 mg/dL reduction in LDL-C:

- Individuals with baseline LDL-C <77 mg/dL had a **29%** further reduction in major vascular events (*P*=0.007)
- Those with baseline LDL-C <70 mg/dL had a **37%** further reduction in major vascular events (*P*=0.004)

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Cholesterol Treatment Trialists' Collaboration. *Lancet* 2010;376:1670-1681; Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Question: Which screening tests should be used?

Recommendations associated with this question:

Non-HDL-C

- **R24.** Non-HDL-C (total cholesterol minus HDL-C) should be calculated to assist risk stratification in individuals with moderately elevated TG (200 to 500 mg/dL), diabetes, and/or established ASCVD **(Grade B; BEL 2)**.
- **R25.** If insulin resistance is suspected, non-HDL-C should be evaluated to gain useful information regarding the individual's total atherogenic lipoprotein burden **(Grade D)**.

Triglycerides

- **R26.** TG levels should be part of routine lipid screening: moderate elevations (≥150 mg/dL) may identify individuals at risk for insulin resistance syndrome and levels ≥200 mg/dL may identify individuals at substantially increased ASCVD risk **(Grade B; BEL 2)**.

Apolipoproteins

- **R27.** Apo B and/or an apo B/apo A1 ratio calculation and evaluation may be useful in at-risk individuals (TG ≥150, HDL-C <40, prior ASCVD event, T2DM, and/or insulin resistance syndrome [even at target LDL-C levels]) to assess residual risk and guide decision-making **(Grade A; BEL 1)**.
- **R28.** Apo B measurements (reflecting the particle concentration of LDL and all other atherogenic lipoproteins) may be useful to assess the success of LDL-C–lowering therapy **(Grade A; BEL 1)**.

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Case 1…(cont'd)

What further information would you like?

A. 2 hr. GTT
B. CAC score
C. Apo B measurement
D. Stress test
E. Carotid ultrasound.
F. All of the above
G. A, B, C, E

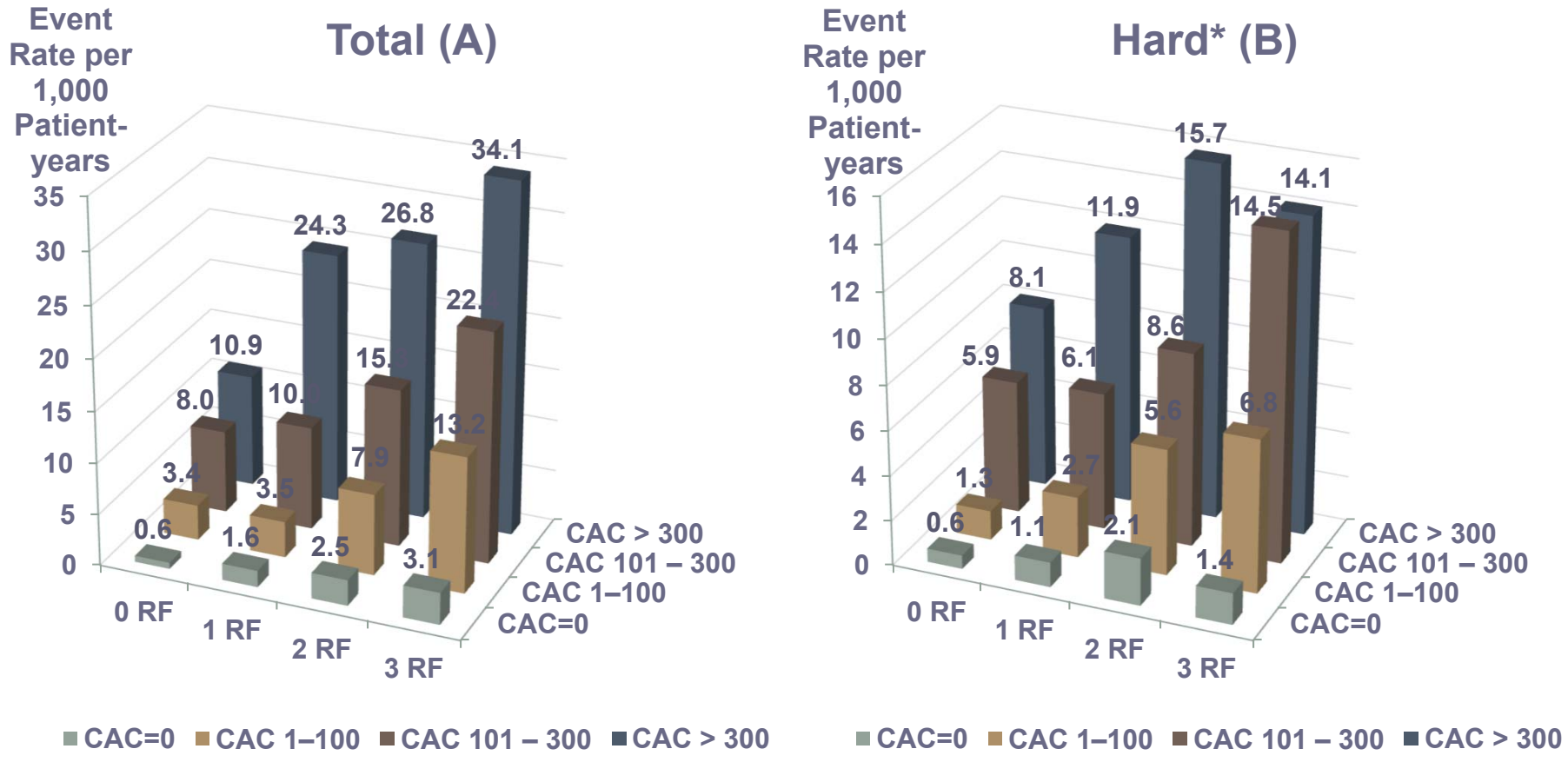
Case 1…(cont'd)

- CAC score was 527.
- A 2 hr GTT revealed DM with a 215 mg/dl 2 hr post challenge glucose.

Does either change the LDL goal?

A. Yes
B. No

MESA: CHD Event Rates With Increasing CAC Score and Based on Risk Factor Burden



***Hard events = MI, resuscitated cardiac arrest, CHD death**

Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction

Silverman MG, et al. *Eur Heart J*. 2013;35(33):2232-2241.

Coronary Artery Calcium Score for Long-term Risk Classification in Individuals With Type 2 Diabetes and Metabolic Syndrome From the Multi-Ethnic Study of Atherosclerosis (MESA)

Malik, Zhao, Budoff et al. JAMA. Cardiol 4239#December 23=4 (34):3554–1340

CONCLUSIONS AND RELEVANCE

- "In a large multiethnic cohort, the addition of CAC score to global risk assessment was associated with significantly improved risk classification in those with MetS and diabetes, even if diabetes duration was longer than a decade, suggesting a role for the CAC score in risk assessment in such patients."

- "Our results support the clinical utility of CAC scoring in those with diabetes and MetS. In addition, the Imaging Council of the American College of Cardiology recently concluded that CAC screening is the most sensitive noninvasive risk stratification tool among asymptomatic persons with diabetes "

Case 1… (cont'd.)

FBS 112, A1c 6.1,
serum creatinine 1.5,
eGFR 45
cholesterol 148 mg/dl
HDL 40 mg/dl triglycerides
165 mg/dl
LDL 78 mg/dl
hs CRP 1.6

How would you achieve the LDL goal of <55 mg/dl?

A. Increase atorvastatin from 40 mg to 80 mg
B. Increase atorvastatin to 80 mg then add ezetimibe
C. Add ezetimibe to current atorvastatin 40 mg dose
D. Add PCSK9i

Case 2…

Retired physician 79 yo male with diabetes and PVD…

- **2001**: Hx of claudication several years worsening in recent months. Now one block. Dyslipidemia. Cholesterol mid 200's, LDL 140-160, Trig 150-170, HDL mid 40's. A1c 7.0-7.5
- Angiographic evaluation demonstrated "severe, multiple and bilateral lesions with relatively small arteries and good posterior tibial pulses with good runoff through large posterior tibial arteries".

- **2010**: R femoral endarterectomy and stent.
- Improvement in claudication to 6 blocks for apporximately 1 ½ years with subsequent progressive worsening to 1-2 blocks.
- No hx MI, TIA or CVA.
- DM. Current Rx: glargine insulin, metformin linagliptin. A1c 7.0
- **Marked intolerance to statins/ezetimibe not allowing LDL levels below 120-140 mg/dl**

Retired physician79 yo diabetic male with severe PVD…

- 9/16 CAC score 2682; 2001: 1576
- GFR 48-53, most recent 64.
- 5/16 A1c 7.4% (prior 7.1, 7.0)
- 5/16 Chol 219 mg/dl, HDL 47 mg/dl, Tri 127 mg/dl, LDL 147 mg/dl on ezetimibe 10 mgs.
- 5/16 Evolocumab (Repatha) denied by insurance; started via manufacturer's program May 2016.
- LDL 70, subsequently 31-51 mg/dl.

Retired physician79 yo diabetic male with severe PVD…

- Text message, 7/2016:

"I started exercising again after a month hiatus and usually after 10-15 minutes on the treadmill with zero elevation, I would develop cramps and have to stop. Today, after 20 minutes of pilates on an exercise ball and 15 minutes on an elevated treadmill I had no cramps and felt like I could go one for another 25 minutes with ease! I don't know if the drug manufacturer knows how effective this drug is in PVD associated with it's lipid effects but you should tell them. I haven't been able to walk uphill until this medication…."

- Text message 11/16:

"I walked 12 blocks this evening and had no problem…could have gone further but ran out of sidewalk…."

Retired physician79 yo diabetic male with severe PVD…

- Persisting to this day, there is absence of claudication including climbing inclines never possible before. LDL 31, 42.

Case 3…

A 48 yo female is seen for management of long standing elevated cholesterol. She has no known history of ASCVD. Her father had an MI at age 48 and a sister has a markedly elevated cholesterol. She is currently treated with rosuvastatin 40 mgms/day.

PE. BMI 29; BP 130/72

No arcus cornealis.

Palpable achilles tendon nodularity.

Peripheral pulses palpable 3+; no carotid bruit audible.

Lab:

FBS 94 mg/dl

HbA1c 5.4%

Cholesterol 237 mg/dl

HDL 48 mg/dl

Triglycerides 150 mg/dl

LDL 159 mg/dl

hsCRP 2.3

Case 3…

Does she have FH?

A. Yes
B. No
C. Am not sure

Familial Hypercholesterolemia: Prevalence and Risk

- **FH is caused by genetic mutations passed on by:**
  - One parent (heterozygous, HeFH)[1]
  - Both parents (homozygous, HoFH)[1]
- **HoFH prevalence ranges from 1 in 160,000 to 1 in 250,000[2,3]**
  - Individuals with HoFH have extremely high LDL-C levels (>500 mg/dL) and premature CV risk[4]
  - Many with HoFH experience their first coronary event in childhood or adolescence[4]
- **HeFH prevalence ranges from 1 in 200 to 1 in 250[3]**
  - Individuals with HeFH can present with LDL-C levels 190 to 500 mg/dL and have premature CV risk[4]
  - On average, individuals with HeFH experience their first coronary event at age 42 (about 20 years younger than the general population)[4]
- **Early treatment is recommended for all individuals with FH, with a goal of reducing LDL-C levels by 50% from baseline[3]**

Abbreviations: CV, cerebrovascular; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

1. Zimmerman MP. *Am Health Drug Benefits*. 2015;8:436-442; 2. Goldstein J, et al. *The Metabolic and Molecular Bases of Inherited Disease*. 7th ed. New York, NY: McGraw-Hill; 1995: 1981-2030; 3. Bouhairie VE, et al. *Cardiol Clin*. 2015;33:169-179; 4. Turgeon RD, et al. *Can Fam Physician*. 2016;62:32-37.

Familial Hypercholesterolemia: Diagnosis

- **FH diagnostic criteria include lipid levels and family history, physical symptoms (if any), and genetic analysis (if available)[1]**
- **Three clinical diagnostic tools:[2-3]**
  - Simon Broome Register Diagnostic Criteria
  - Dutch Lipid Clinic Network Diagnostic Criteria
  - U.S. MEDPED
- **Factors that lead to an FH diagnosis include:**
  - Premature ASCVD, fasting LDL-C >190 mg/dL, the presence of tendon xanthomas, full corneal arcus in individuals <40 years of age, or a family history of high cholesterol and/or premature ASCVD[1]
- **While genetic testing may identify FH, it is not commonly used in the United States due to cost and lack of payer coverage[1]**

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MEDPED, Make Early Diagnoses Prevent Early Deaths Program Diagnostic Criteria.

1. Bouhairie VE, et al. *Cardiol Clin*. 2015;33:169-179; 2. Haralambos K, et al. *Curr Opin Lipidol*. 2016;27:367-374; 3. Turgeon RD, et al. *Can Fam Physician*. 2016;62:32-37.

Simon Broome, Dutch Lipid Clinic Network Criteria for FH

Simon Broome: LDL> 190 mg/dl

Definite FH: tendon xanthomas in patient or first or 2nd degree relative or DNA based evidence of LDL receptor mutation

Possible FH: LDL>190 mg/dl and either

family hx MI age 60 or younger in 1st degree relative or 50 or younger in 2nd degree relative

or

family hx of total cholesterol >290 mg/dl in adult 1st or second degree relative; >260 mg/dl in child, brother or sister <16 years.

Dutch Lipid Network:

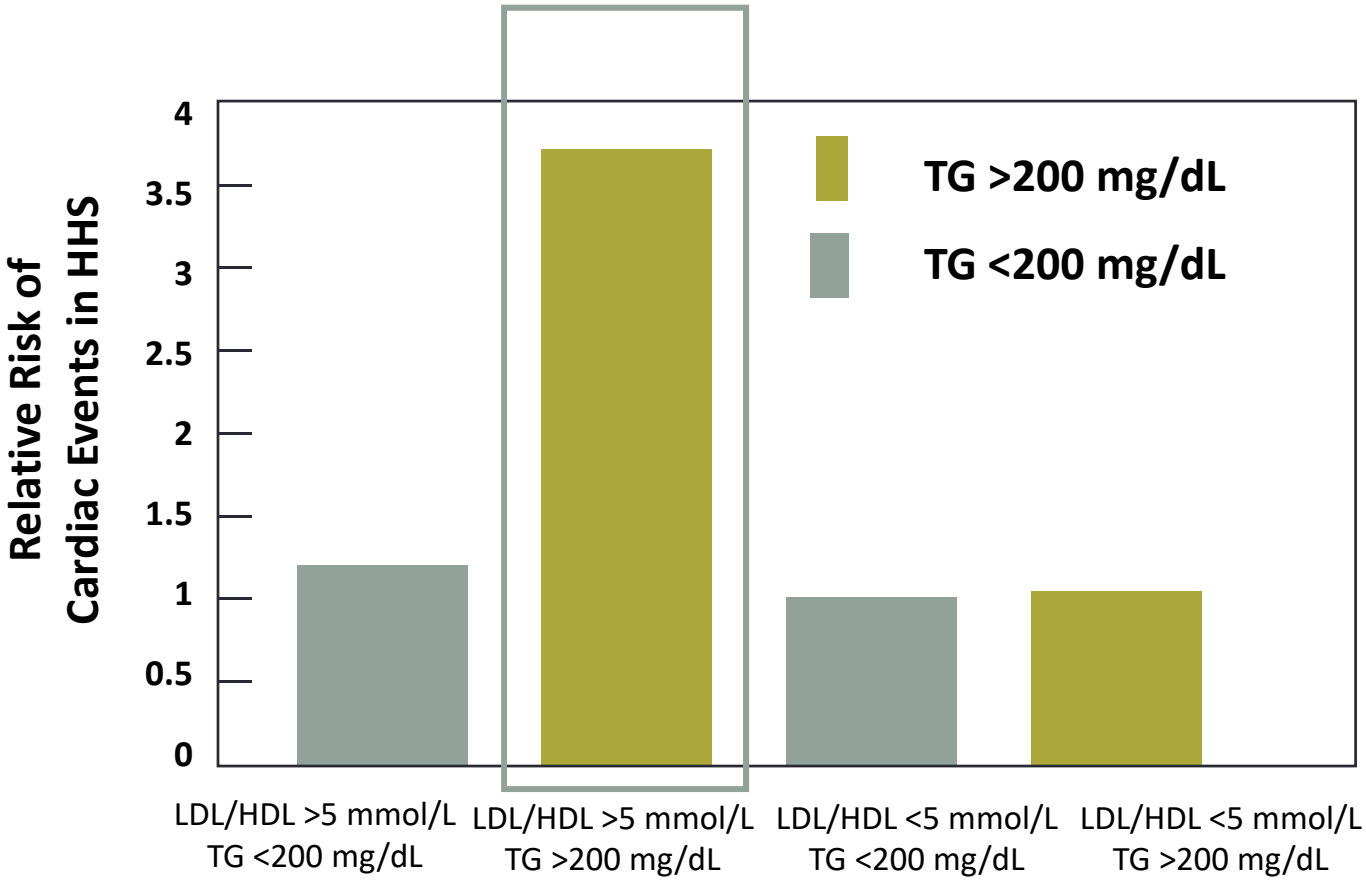
Point system based on family hx[a], clinical history[b], physical exam[c], LDL-C or DNA analysis. Tendon xanthoma (6 points), arcus cornealis < 45 years (4 points) and LDL-C levels[d] (3-8 points) most significant contributors. DNA analysis (8 points).

Definite FH >8 pts; probable FH 6-8; possible FH 3-5; unlikely FH <3

[a] 1st degree relative with premature coronary/vascular dis,1 pt or tendon xanthomas, arcus cornealis, 2 pts.
[b] patient with premature coronary dis, 2 pts; with premature CVD, PVD, 1 pt.;
[c] tendon xanthomas 6 pts, arcus cornealis <45 years 4 pts.
[d] LDL-C > 330 mg/dl, 8 pts, 250-329 mg/dl 5 pts, 190-249 mg/dl 3 pts, 155-189 mg/dl 1 pt.

Helsinki Heart Study Analysis: Joint Effects of Serum Triglycerides, LDL-C and HDL-C on CHD Risk

Relative risk of cardiac events among placebo patients



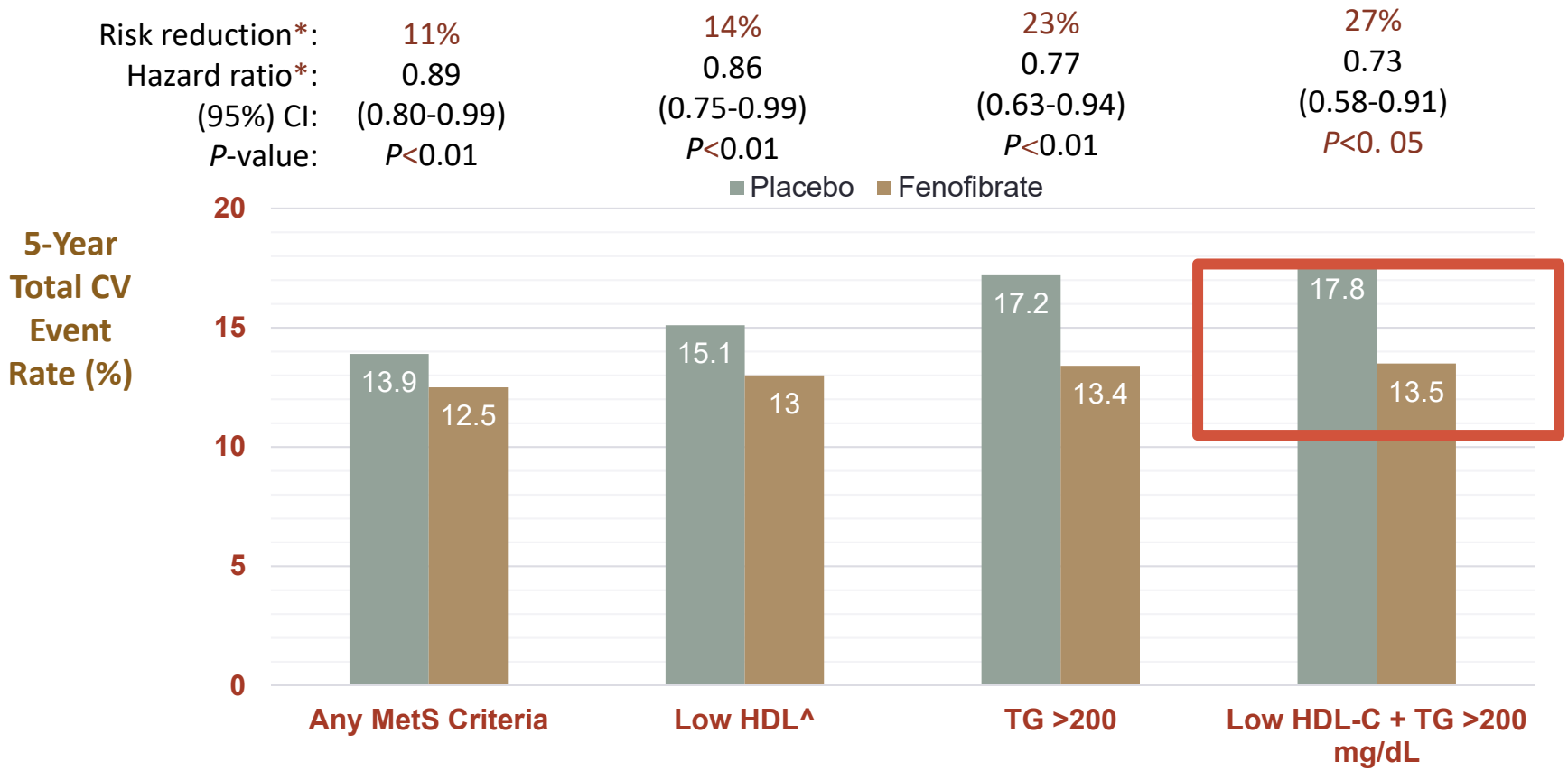
HHS population mean baseline (mg/dL):

Total Chol: 289
TG: 176
HDL-C: 47
LDL-C: 189
Non-HDL-C: 242

Abbreviations: CHD, coronary heart disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Manninen V, et al. *Circulation*. 1992;85:37.s

FIELD: Highest Therapeutic Benefit of Fenofibrate Seen in Patients With Elevated TG and Low HDL-C



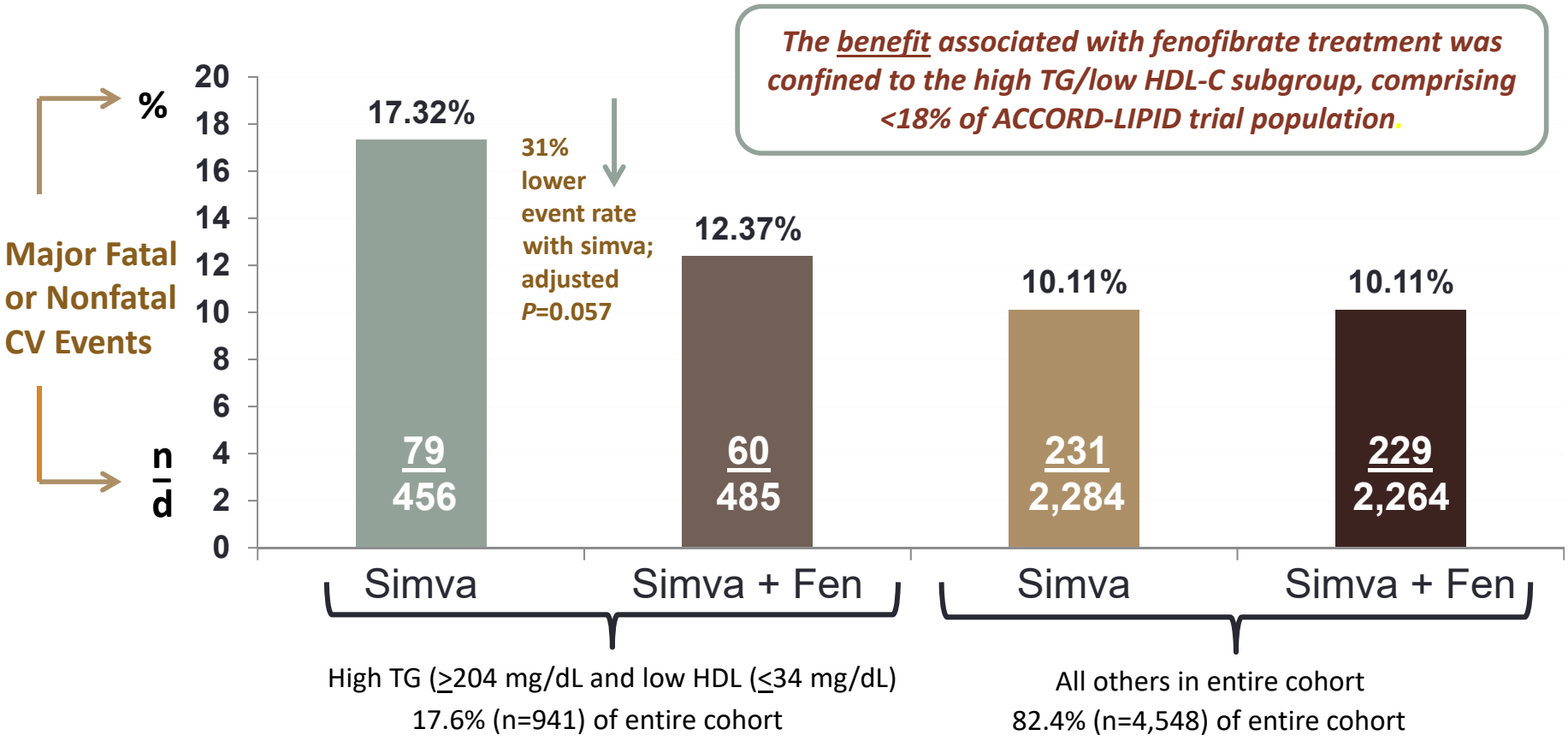
* Not corrected for large placebo group statin drop-in rate

**HDL <40 mg/dL (men) and <50 mg/dL (women)

Abbreviations: CV, cerebrovascular; FIELD, Secondary Endpoints from the Fenofibrate Intervention and Event Lowering in Diabetes trial; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides.

Scott R, et al. *Diabetes Care* 2009;32:493-498

ACCORD-LIPID: Primary Outcomes of the Prespecified Subgroups: High TG (≥204 mg/dL) and Low HDL-C (≤34 mg/dL) vs. All Others in Full Cohort



Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; CV, cerebrovascular; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Elam, et al, *Clin Lipidol*. 2011(6):9-20; Ginsberg, et al., The ACCORD Study Group. NEJM. 2010; 362:1563-1574.

Question: How is risk assessed?

Recommendations associated with this question:

R4. The 10-year risk of a coronary event (high, intermediate, or low) should be determined by detailed assessment using one or more of the following tools **(Grade C; BEL 4, upgraded due to cost-effectiveness)**:

- Framingham Risk Assessment Tool
- MESA 10-year ASCVD Risk with Coronary Artery Calcification Calculator
- Reynolds Risk Score, which includes hsCRP and family history of premature ASCVD
- UKPDS risk engine to calculate ASCVD risk in individuals with T2DM

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

R8. A classification of elevated TG should be incorporated into risk assessments to aid in treatment decisions **(Grade B; BEL 2)**.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity CRP; MESA, Multi-Ethnic Study of Atherosclerosis; T2DM, type 2 diabetes mellitus; TG, triglycerides.

Jellinger P, Handelsman Y, Rosenblit P, et al. *Endocr Practice*. 2017;23(4):479-497.

Multi-Ethnic Study of Atherosclerosis

- **MESA investigated the correlates of subclinical CVD[1]**
  - The study enrolled 6,814 patients between July 2000 and September 2002; at baseline, all patients were free of clinical CVD[2]
- **10-year outcomes showed that CAC is an independent risk factor for CVD[3]**
  - CAC predicts CVD risk in patients with or without traditional risk factors and in patients with family history of premature CHD[4-5]
  - CAC was the strongest predictor of CVD in low-risk patients[6]
- **The MESA risk score uses traditional risk factors and CAC to predict 10-year CHD risk[7]**
  - The incorporation of CAC into this risk score has improved risk prediction[7]

Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease; CVD, cardiovascular disease; MESA, Multi-Ethnic Study of Atherosclerosis.

1. Bild DE, et al. *Am J Epidemiol.* 2002;156:871-881; 2. Blaha MJ, et al. *Circulation*. 2016;133:849-858; 3. Yeboah J, et al. *J Am Coll Cardiol*. 2016;67:139-147; 4. Patel J, et al. *Circ Cardiovasc Imaging*. 2015;8:e003186; 5. Silverman MG, et al. *Eur Heart J*. 2014;35:2232-2241; 6. Joshi PH, et al. *Atherosclerosis*. 2016;246:367-373; 7. McClelland RL, et al. *J Am Coll Cardiol.* 2015;66:1643-1653.