AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Merits of Targeting LDL-C, Triglycerides, HDL-C, and Non-HDL-C, and Addressing Residual Risk

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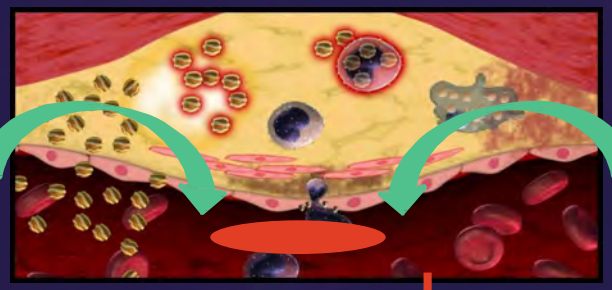
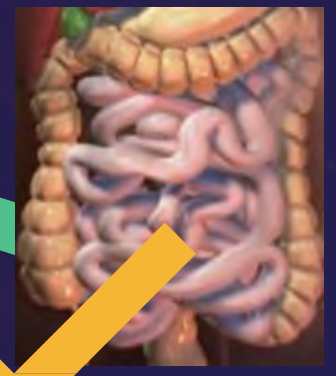
Introduction

- What risk factors contribute to a patient's total risk profile for cardiometabolic disease, including residual CAD risk?
- How does targeting HDL-C vs HDL-P affect risk?
- What are the merits of targeting (reducing) TG and how does the setting of high cholesterol contribute to risk associated with high TGs?
- What are the benefits of lowering LDL-C, non-HDL-C, Apo B, and LDL-P? How low should LDL-C lowering go?

Apo = apolipoprotein; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; HDL-P = high-density lipoprotein particle; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; TG = triglyceride.

Close Interrelationship of Metabolic Pathways





Apo A-1

Apo A-1

HDL interconversion

HDL maturation

HDL

VLDL B-100

CE TG

HDL

TG CE

Chylomicrons B-48

Lipolysis

Lipid exchange

Lipid exchange

VLDL Remnant

Delivery of HDL constituents PLTP, PL, Apos: C1, CII, CIII AV

Lipolysis

Lipolysis

HDL

Hepatic Lipase

LDL

Small dense LDL

LDL

Small dense LDL

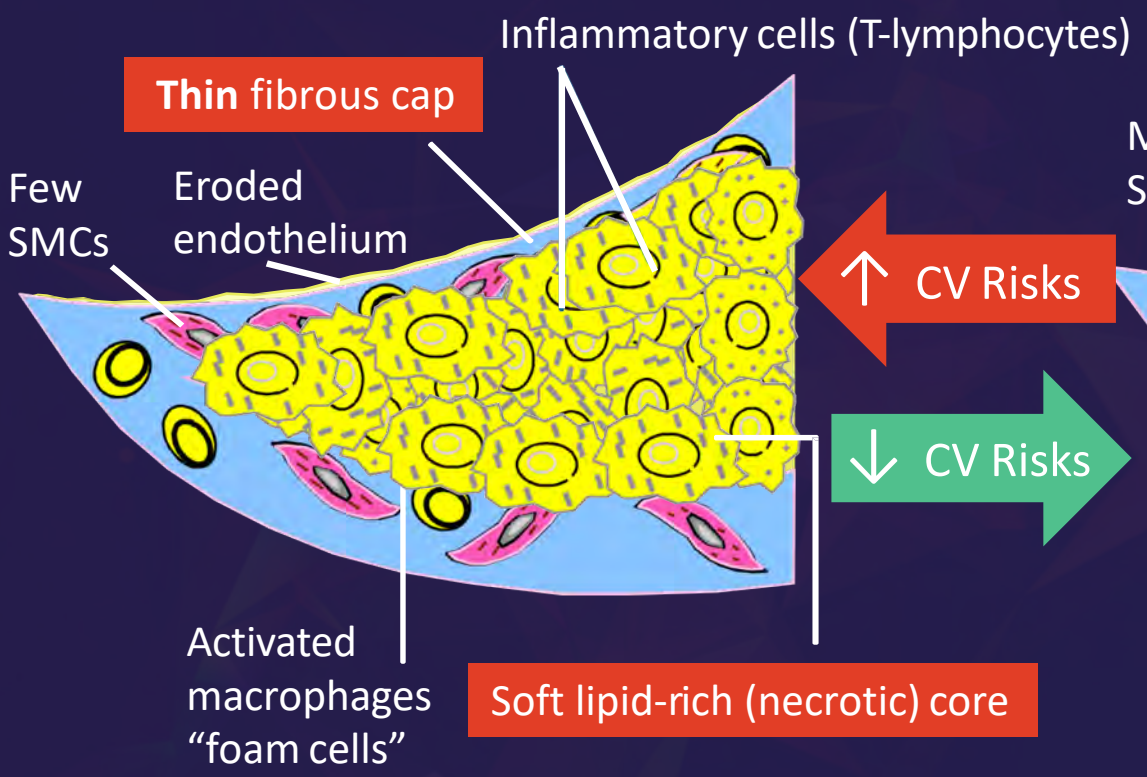
Chylomicron remnant

Apo = apolipoprotein; CE = cholesteryl ester; HD L= high-density lipoprotein; HTG = hypertriglyceridemia LDL = low-density lipoprotein; PL = phospholipid; PLTP = phospholipid transfer protein; TG = triglyceride; VLDL = very-low-density lipoprotein.

Modified from Chapman, et al. *European Heart Journal.* (2011) 32(11):1345–1361f.

Secondary Prevention: Characteristics of Unstable and Stable Plaque

Unstable Plaque

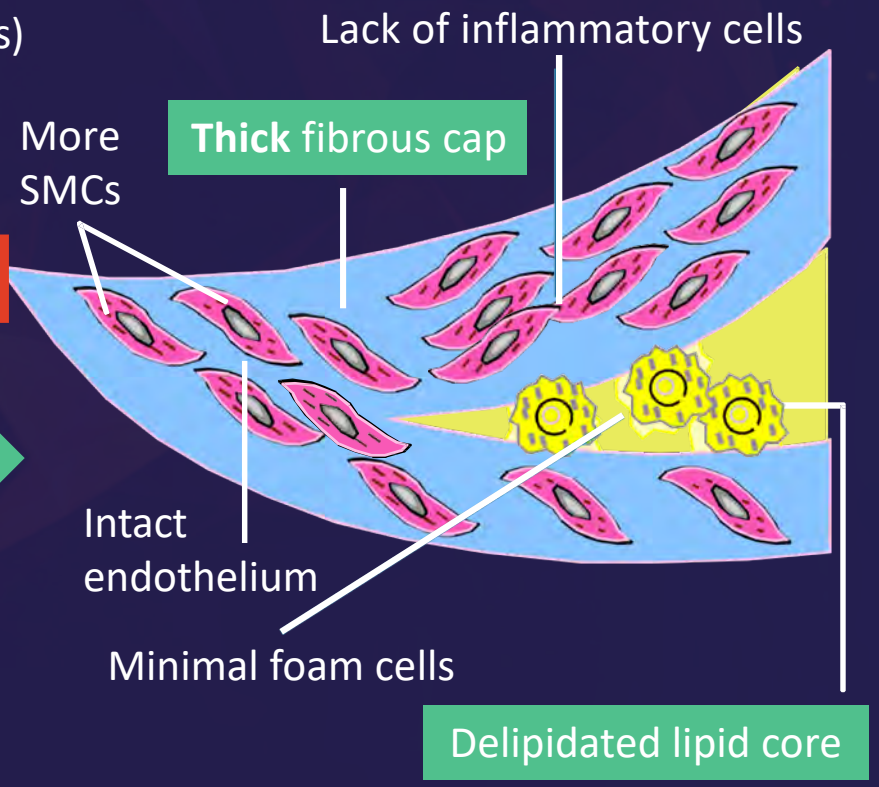


- Unstable plaques have a thin fibrous cap and are at greater risk for rupture; the lipid-rich core represents the majority of plaque volume.[1]

↑ CV Risks

↓ CV Risks

Stable Plaque

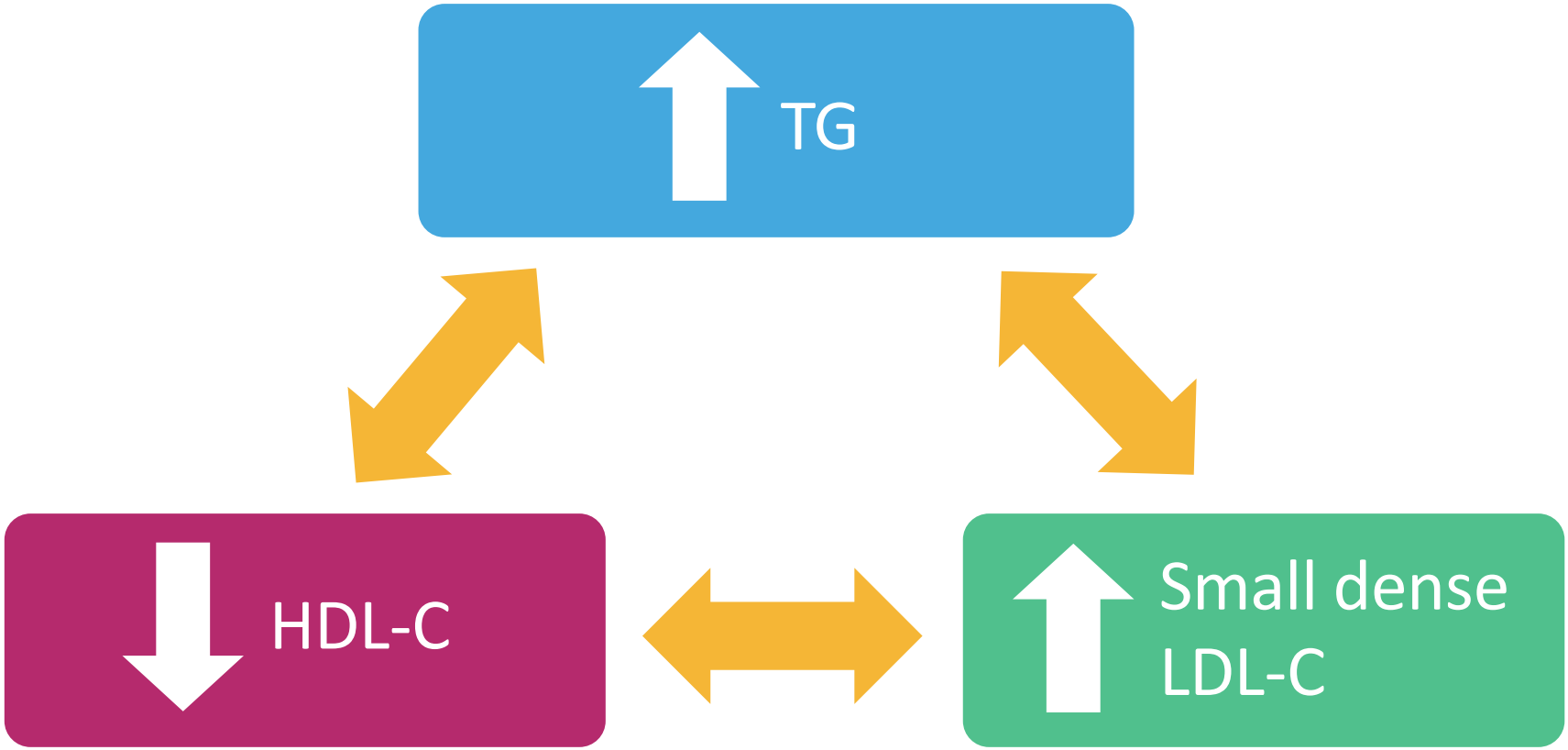


- In stable plaques, a thick fibrous cap represents >70% of plaque volume. It stabilizes the plaque and prevents it from undergoing rupture.[1]

CV = cardiovascular; SMC = smooth muscle cell.

Adapted from Libby P. *Circulation.* (1995) 91:2844-2850; Naghavi M, et al. *Circulation.* (2003) 108:1664-1672.

Classic Atherogenic Lipid Triad



HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride.

LDL-C

LDL-C = low-density lipoprotein cholesterol.

Low-Density Lipoprotein Cholesterol

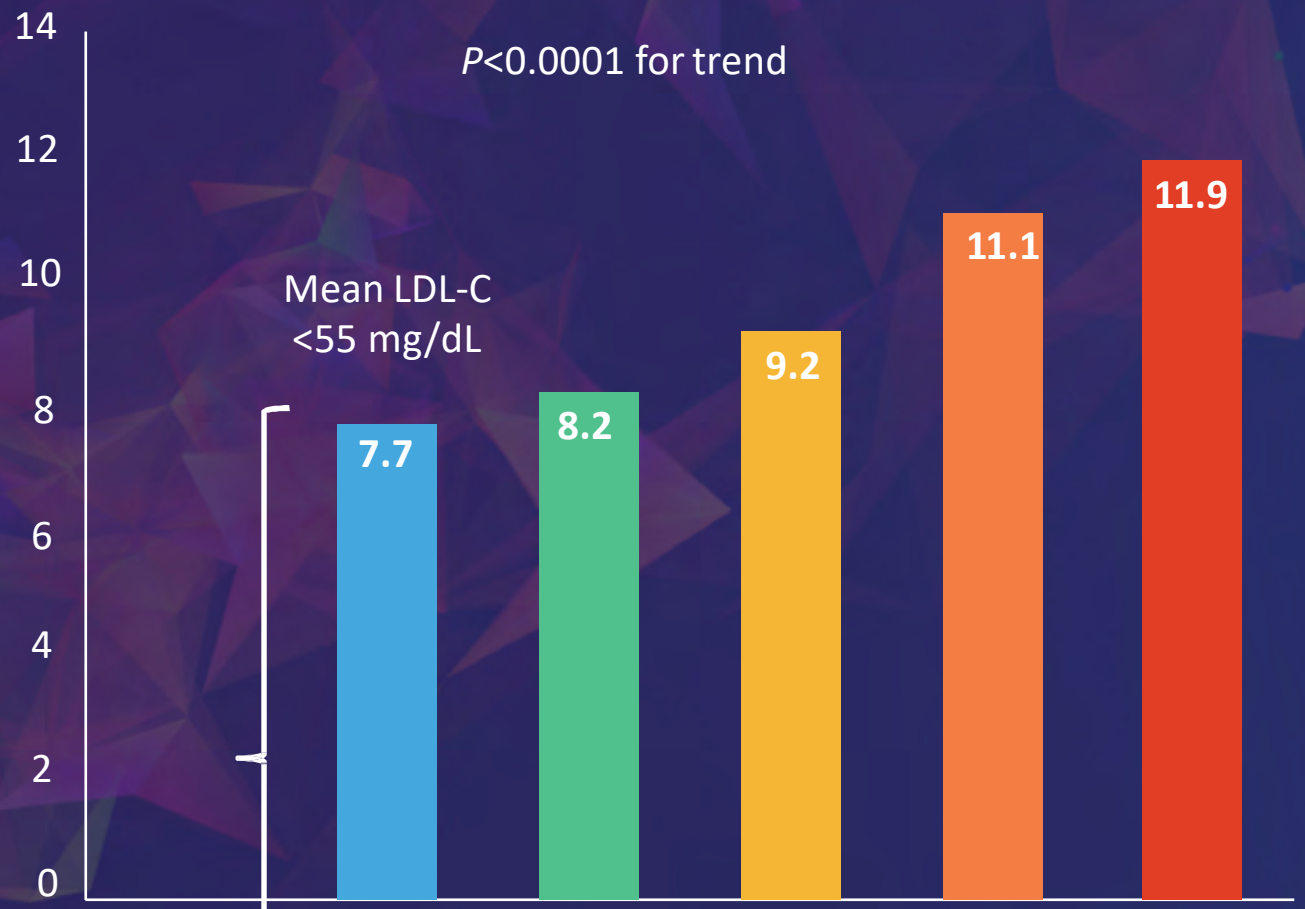
- Elevated LDL-C is a major ASCVD risk factor[1]
- LDL-C comprises ~75% of circulating cholesterol carried by lipoprotein particles other than HDL-C[2]
  - This percentage may be ↓ in patients with HTG
- 70% of U.S. adults have suboptimal LDL-C levels (>100 mg/dL)[1]

ASCVD = atherosclerotic cardiovascular disease;
HDL-C = high-density lipoprotein Cholesterol;
HTG = hypertriglyceridemia; LDL-C = low-density lipoprotein cholesterol.

1. Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497;
2. Bays H, et al. *J Clin Lipidol.* (2016) Jan-Feb;10(1 Suppl):S1-43.

Major Cardiovascular Event Outcomes According To Quintile of On-treatment LDL-C in TNT

Mean LDL-C (mg/dL):
101 (10-mg atorvastatin);
77 (80-mg atorvastatin)
49% of patients on atorvastatin 80 mg/day did not reach LDL-C <70 mg/dL



* = CHD death, myocardial infarction, resuscitated cardiac arrest, and stroke.
Trends for rates of CHD death (*P*<0.01), nonfatal MI (*P*<0.0001), fatal or nonfatal stroke (*P*<0.05)

LDL-C Range	<64	64-76	77-89	90-105	≥106
Mean LDL-C, mg/dL	54	70	83	97	122
Quintile	1	2	3	4	5
No of Pts, Atorva (80mg/10mg	1722/114	1403/529	968/1019	515/1515	266/1718

CHD = coronary heart disease; CV = cardiovascular; HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TNT=treating to new targets.

AACE 2017 LDL-C Risk Categories and Treatment Goals

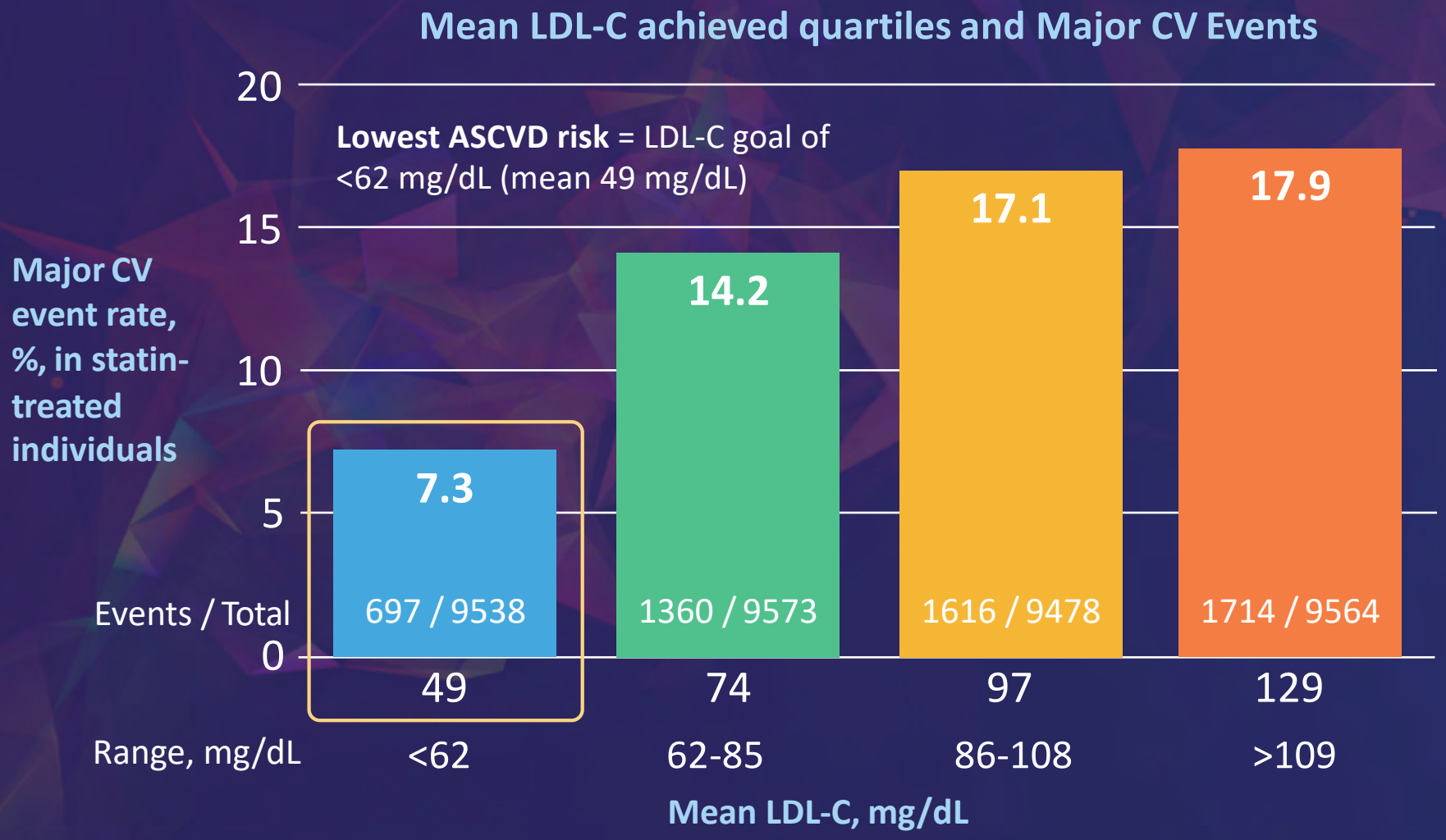
Risk category[1,2]	Risk factors/10-year risk[1,2]	Treatment goals[1,2] LDL-C (mg/dL)
Extreme risk	• Progressive ASCVD, including unstable angina in patients after achieving an LDL-C <70 mg/dL • Established clinical CVD in patients with DM, CKD 3/4, or HeFH • History of premature ASCVD (<55 male, <65 female)	<55
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% • Diabetes or CKD 3/4 with ≥1 risk factor(s) • HeFH	<70
High risk	• ≥2 risk factors and 10-year risk 10%-20% • Diabetes or CKD 3/4 with no other risk factors	<100
Moderate risk	• ≤2 risk factors and 10-year risk <10%	<100
Low risk	• 0 risk factors	<130

AACE = American Association of Clinical Endocrinologists; ACS = Acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

NR=not recommended.

1. Garber A, et al. *Endocr Pract*. (2017) 23:207-38.
2. Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497.;

Lipid Levels and Risk of Major Cardiovascular Events in Statin-Treated Individuals



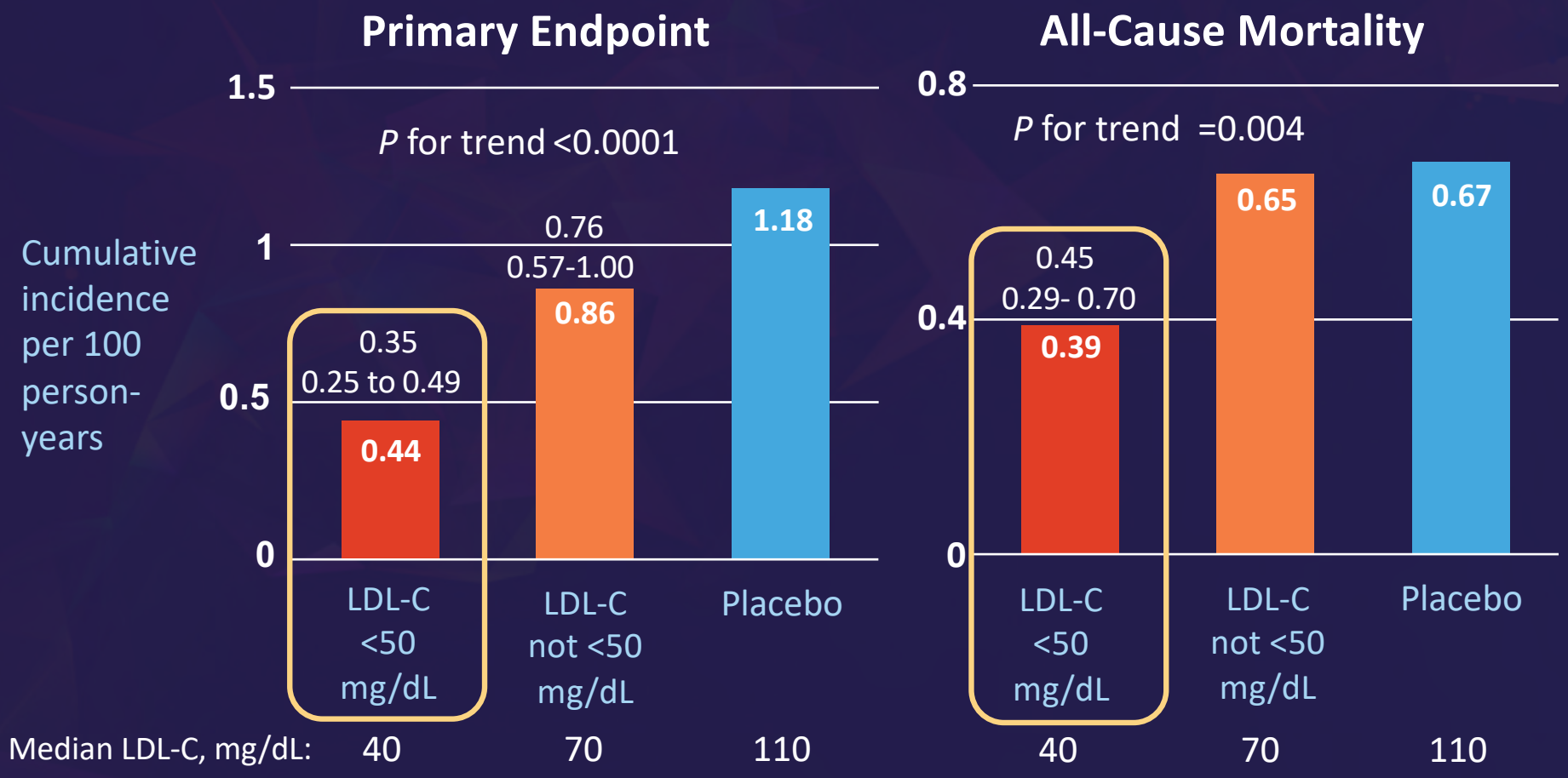
P<0.001 for trend and per 1 SD increase from lowest mean LDL-C

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; SC = stratum corneum; SD = standard deviation.

Boekholdt S, et al *JAMA.* (2012) 307(12):1302-1309.

JUPITER: Rosuvastatin-Allocated Participants Attaining LDL-C <50 mg/dL had a Lower Risk of CV Events

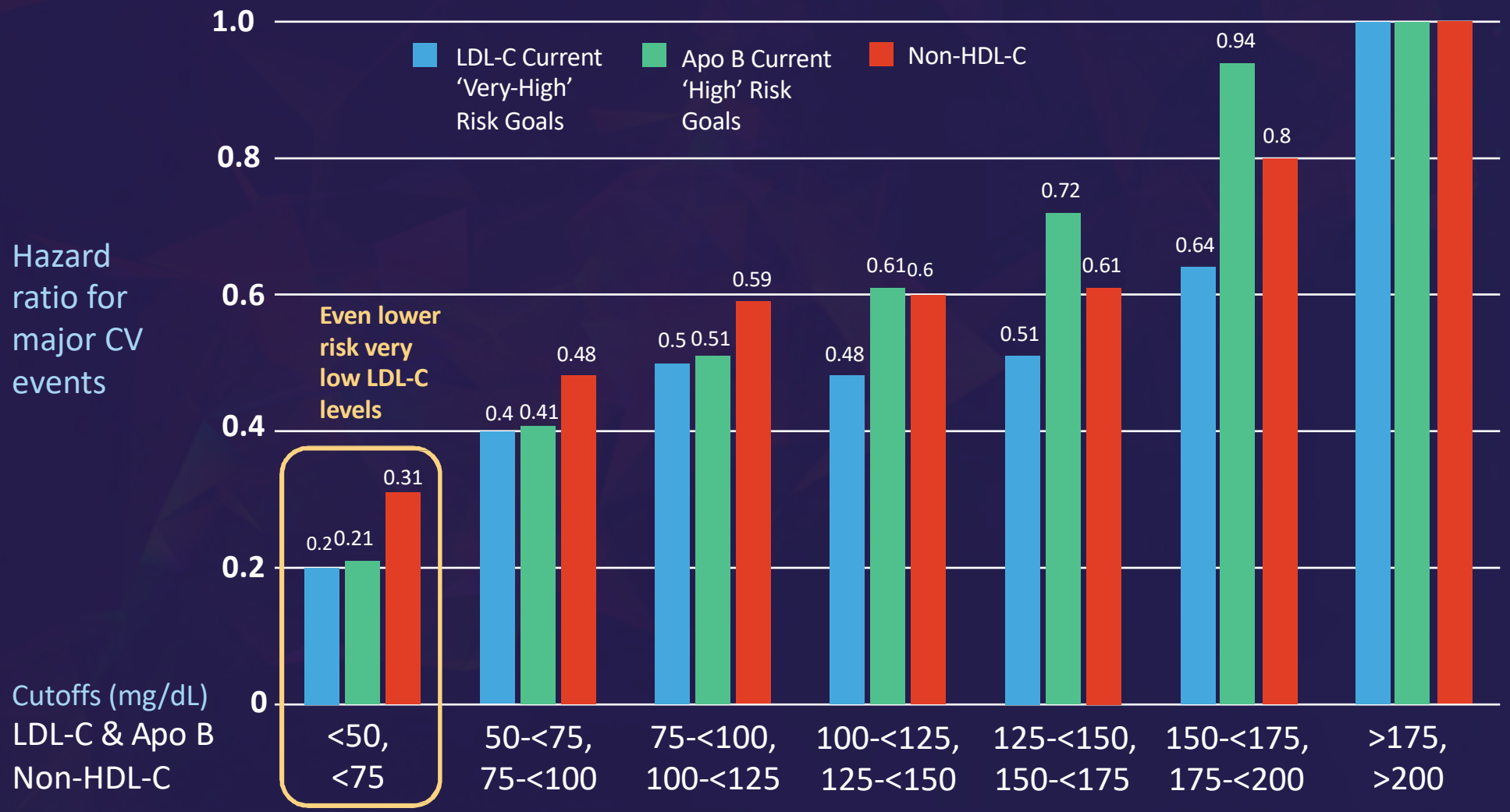
A cohort (N=17,802) of apparently healthy individuals with hsCRP ≥2 mg/dL and LDL-C <130 mg/dL randomized to rosuvastatin 20 mg/day or placebo. Primary endpoint = composite of MI, stroke, arterial revascularization, unstable angina, or CV death.



CV = cardiovascular; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol.

Hsia J, et al. *JACC.* (2011) 57(16):1666-1675.

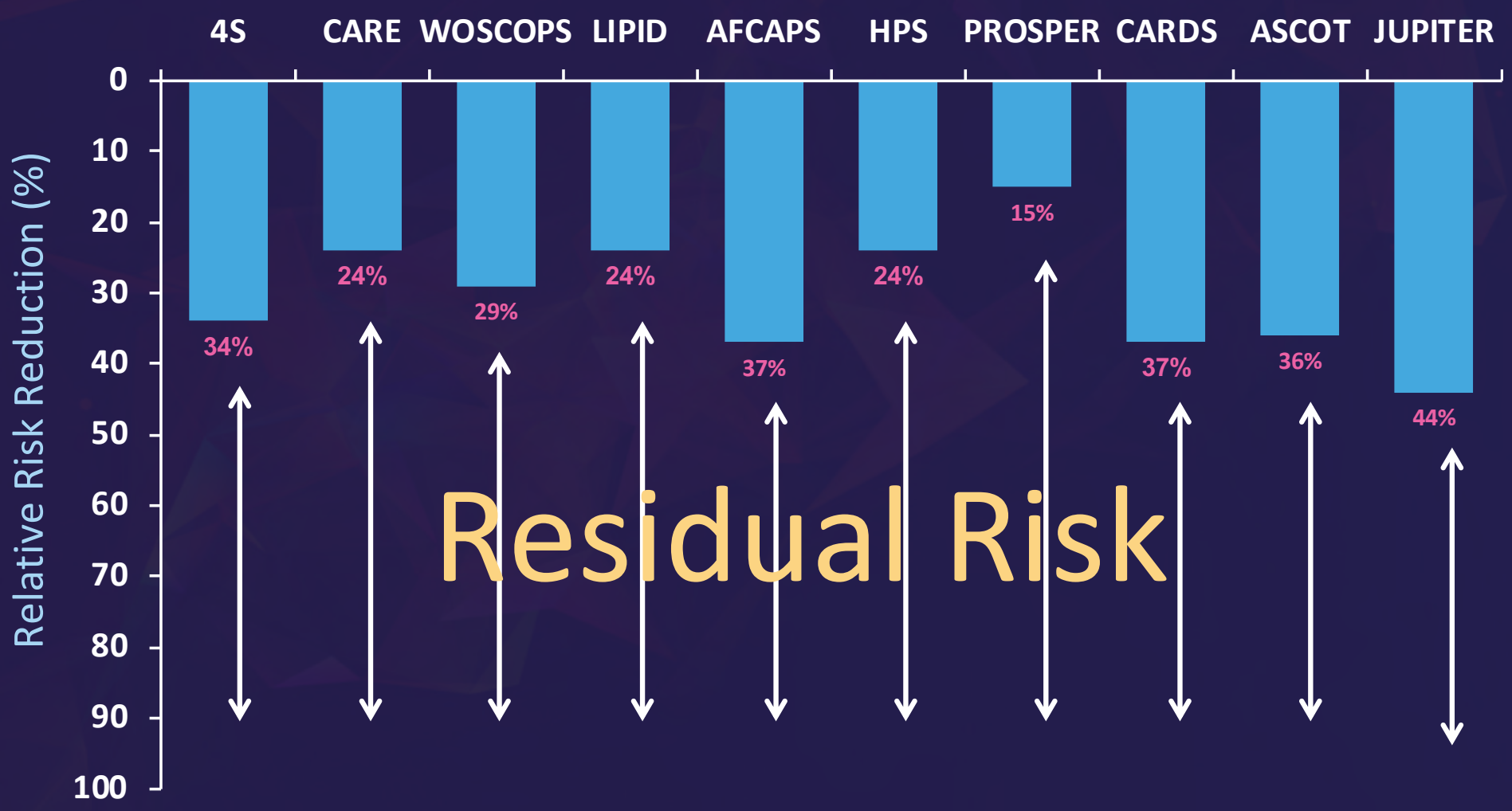
Patients Who Achieved Very-Low vs Moderately Low LDL-C Levels Had Lower Risk for Major CV Events: Meta-Analysis of 8 Statin Trials



Apo = apolipoprotein; CV = cardiovascular; HDL = high-density lipoprotein; LDL-C = low-density lipoprotein cholesterol.

Boekholdt S, et al. *JACC.* (2014) 64(5):485-494.

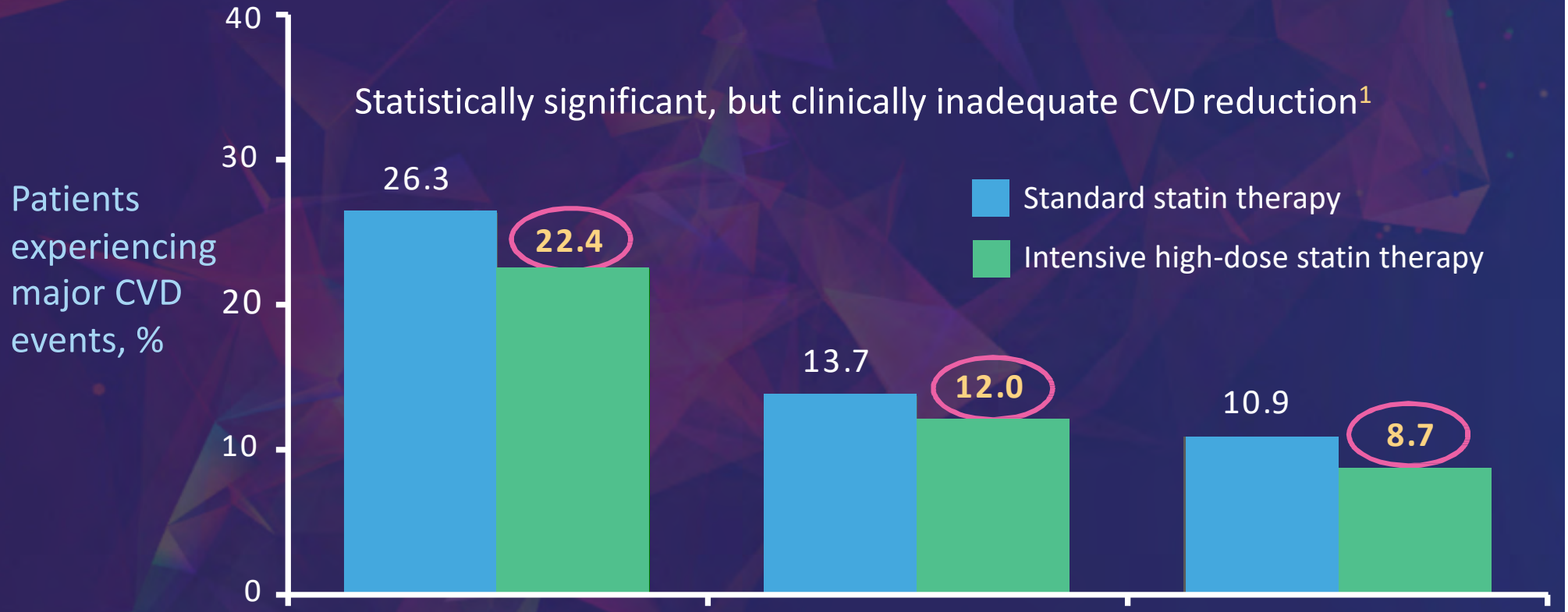
Despite Benefits of Statin-induced LDL-C Lowering, Treated Individuals have Substantial Residual Risk for CAD Events



4S = Scandinavian Simvastatin Survival Study; AFCAPS = Air Force Coronary Atherosclerosis Prevention Study; CAD = coronary artery disease; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol And Recurrent Events; HPS = Heart Protection Study; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; LDL-C = low-density lipoprotein cholesterol; PROSPER = PROspective Study of Pravastatin in the Elderly at Risk; WOSCOPS = West of Scotland Coronary Prevention Study.

Baigent C, et al. *Lancet*. (2005) 366: 1267–78. Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497.

Residual CVD Risk with Intensive Statin Therapy Less, But Still Unacceptably High



*Mean or median LDL-C after treatment

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TNT = treating to new targets.

1. Superko H. *Br J Cardiol.* (2006) 13:131-136;
2. Cannon CP, et al. *N Engl J Med.* (2004) 350:1495-15043;
3. LaRosa JC, et al. *N Engl J Med.* (2005) 352:1425-1435;
4. Pedersen T, et al. *JAMA.* (2005) 294:2437-2445.

Why Focusing on LDL-C Is Not Enough

- Residual ASCVD risk persists even in intensively treated individuals[1]
- Elevated fasting/postprandial HTG and lipoproteins other than LDL-C are involved in atherogenesis[1]
  - VLDL, IDL, and small, dense LDL-P
- Plaque instability also contributes to ASCVD[2]
  - Reducing lipid content and inflammatory cells within plaque contributes to plaque stability

ASCVD = atherosclerotic cardiovascular disease; HTG = hypertriglyceridemia; IDL = intermediate-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; VLDL = very-low-density lipoprotein.

1. Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497;
2. Dave T, et al. *Indian J Endocrinol Metab*. (2013) Nov-Dec; 17(6):983–989.

Triglycerides

Plasma TG Independently Predicts CVD Death and Total Mortality, Meta-Analysis of >1 Million Patients

- 33 studies evaluate CVD mortality (17,018 CVD deaths among 726,030 patients), and 38 studies evaluate all-cause mortality (58,419 all-cause deaths among 330,566 patients).
- Median duration of follow-up was 12.0 years; patients with diabetes, CVD, or cancer were excluded.

	CVD Mortality		All-Cause Mortality	
TG quartile/mg/dL	RR	*P*-value	RR	*P*-value
I. <90	0.83	0.001	0.94	0.150
II. 90-149 (referent)	1.00		1.00	
III. 150-199	1.15	0.015	1.09	0.011
IV. ≥200	1.25	0.013	1.20	0.011

CVD = cardiovascular disease; RR = relative risk; TG = triglyceride.

Liu J, et al. *Lipids Health Dis*. (2013) 12(159):1-11.

Algorithm for Pharmacologic Management of Dyslipidemia in Individuals with Cardiometabolic Risk and Diabetes

- Treatment Objectives for Elevated TGs[1,3]

Triglyceride Level	Rationale (Primary Goal) for Therapy[2]
"Very High" TGs ≥500 mg/dL	Prevention of Pancreatitis*
"High" or "Moderate Hypertriglyceridemia" 200-499 mg/dL	Prevention of CVD*

* To date, no large clinical outcome trials have been completed to provide support

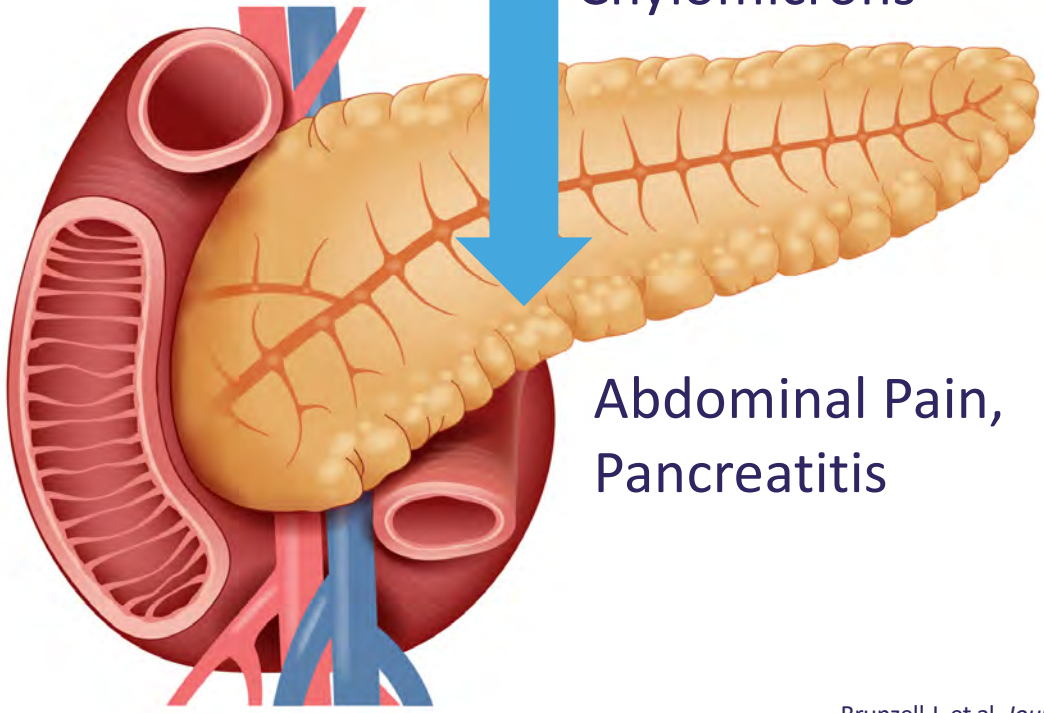
CVD = cardiovascular disease; TG = triglyceride.

1. Berglund L, et al. *J Clin Endocrinol Metab.* (2012) 97:2969;
2. Brunzell J, et al. *Diabetes Care*. (2008) 31:811-822;
3. NHLBI. *NIH Publication No.* (2002) 02-5215:I-1-Ref49.

Proposed Relationship Between Primary and Secondary Causes of Hypertriglyceridemia and Their Relationship to Pancreatitis

Genetic Familial HTG → Marked Hypertriglyceridemia ← Secondary HTG

Chylomicrons



Abdominal Pain, Pancreatitis

HTG = hypertriglyceridemia.

Brunzell J, et al. *Journal of Clinical Lipidology.* (2012) 6:409-12.

HDL-C and HDL-P

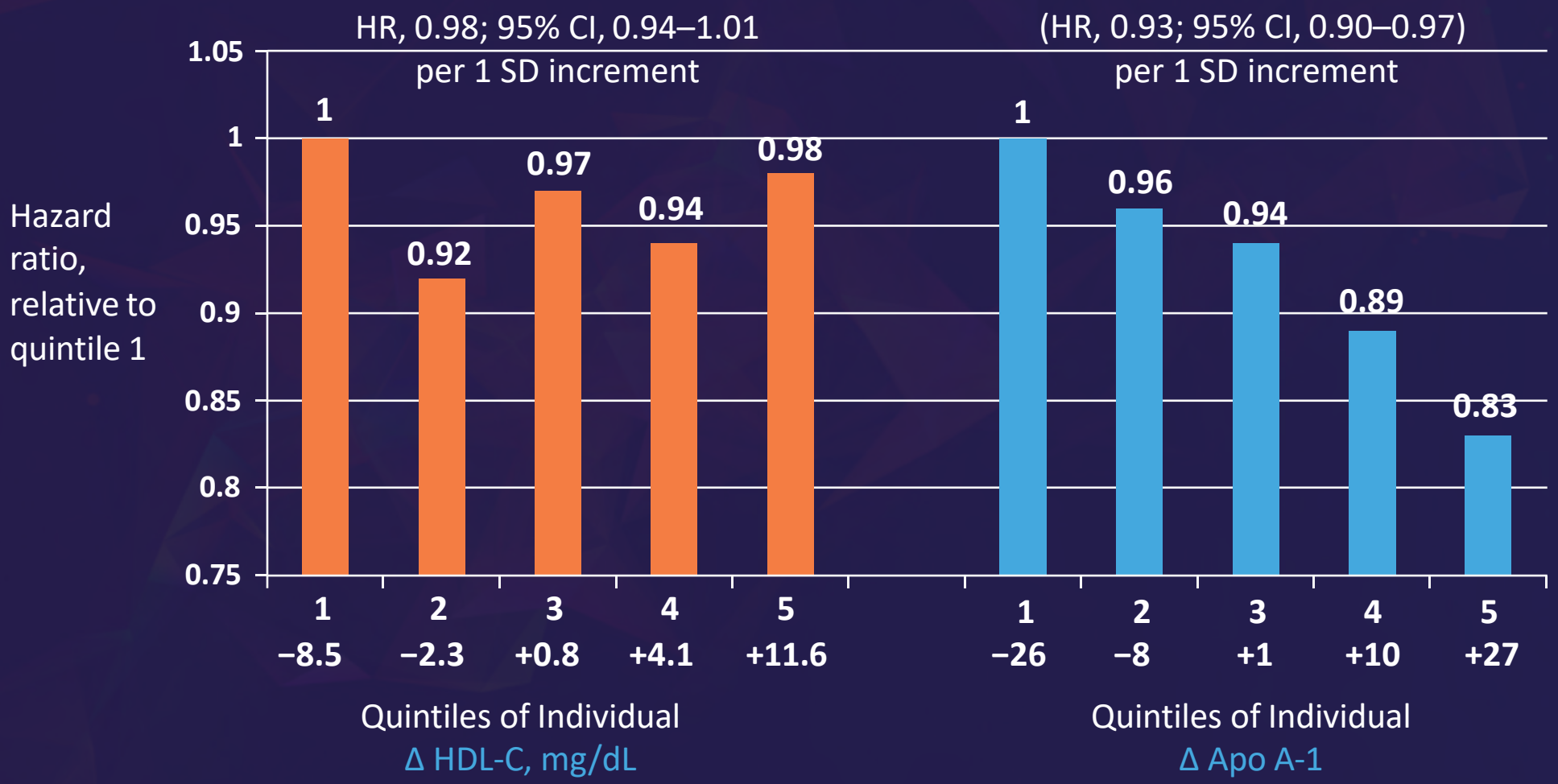
High-Density Lipoprotein Cholesterol

- Elevated non-HDL-C and low HDL-C levels constitute major ASCVD risk factors
  - Research shows a strong predictive link between higher HDL-C levels and longevity
  - Low HDL-C can act synergistically with other lipid risk factors to increase ASCVD risk
  - The atherogenicity of low HDL-C can depend on both genetic and environmental factors
- Low HDL-C is associated with:
  - Metabolic syndrome
  - HTG
  - T2D
  - Overweight or obesity
  - Physical inactivity
  - Cigarette smoking
  - Very high carbohydrate intake
  - Certain drugs (beta-adrenergic blockers, anabolic steroids, progestational agents)
  - Genetic factors

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HTG = hypertriglyceridemia; T2D = type 2 diabetes.

Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497.

Risk of Major CV Events By Absolute Change in HDL-C and Apo A-I Among Individuals on Statins

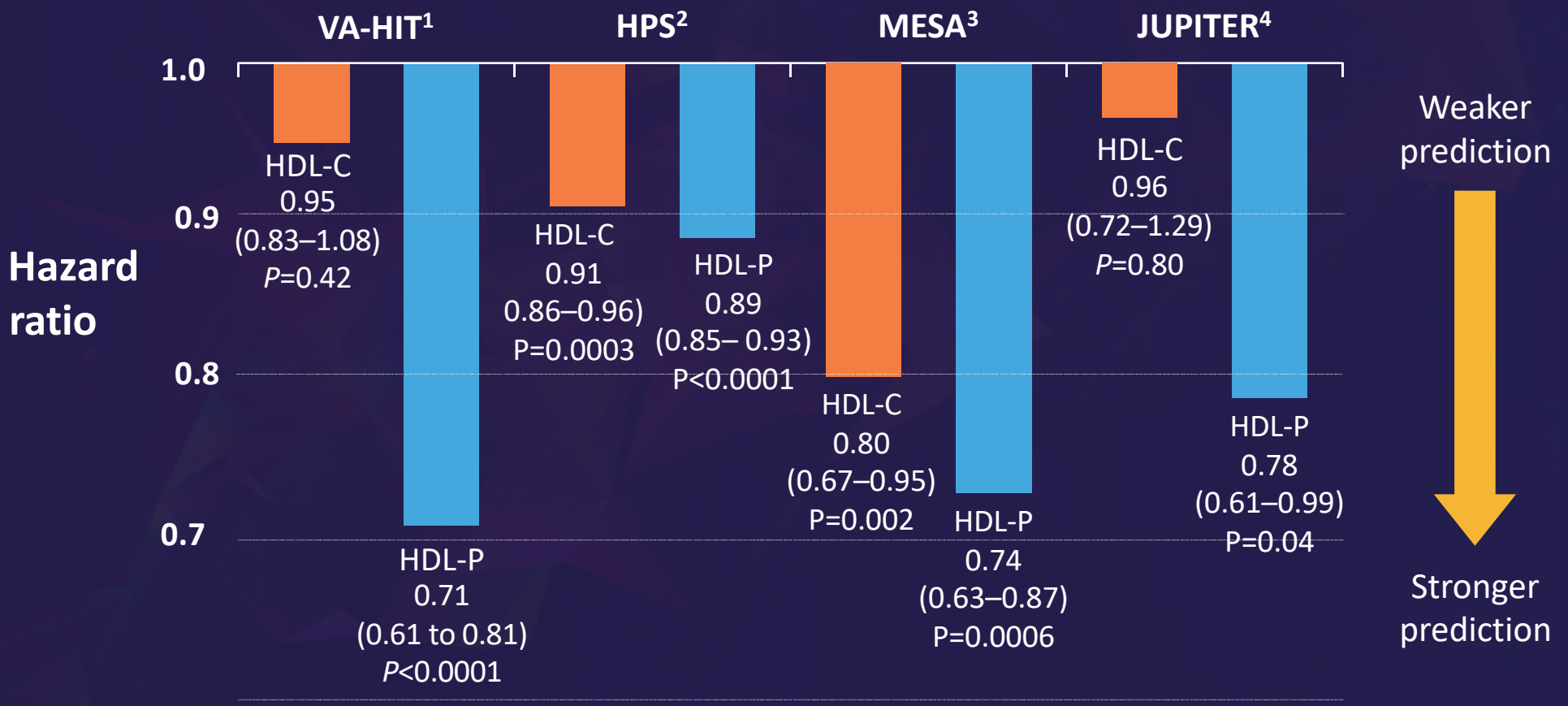


Increased Apo A-1, Not HDL-C, Associated With Reduced CV Risk

Apo = apolipoprotein; CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; SC = stratum corneum; SD = standard deviation.

Boekholdt S, et al. *Circulation.* (2013) 128:1504-1512.

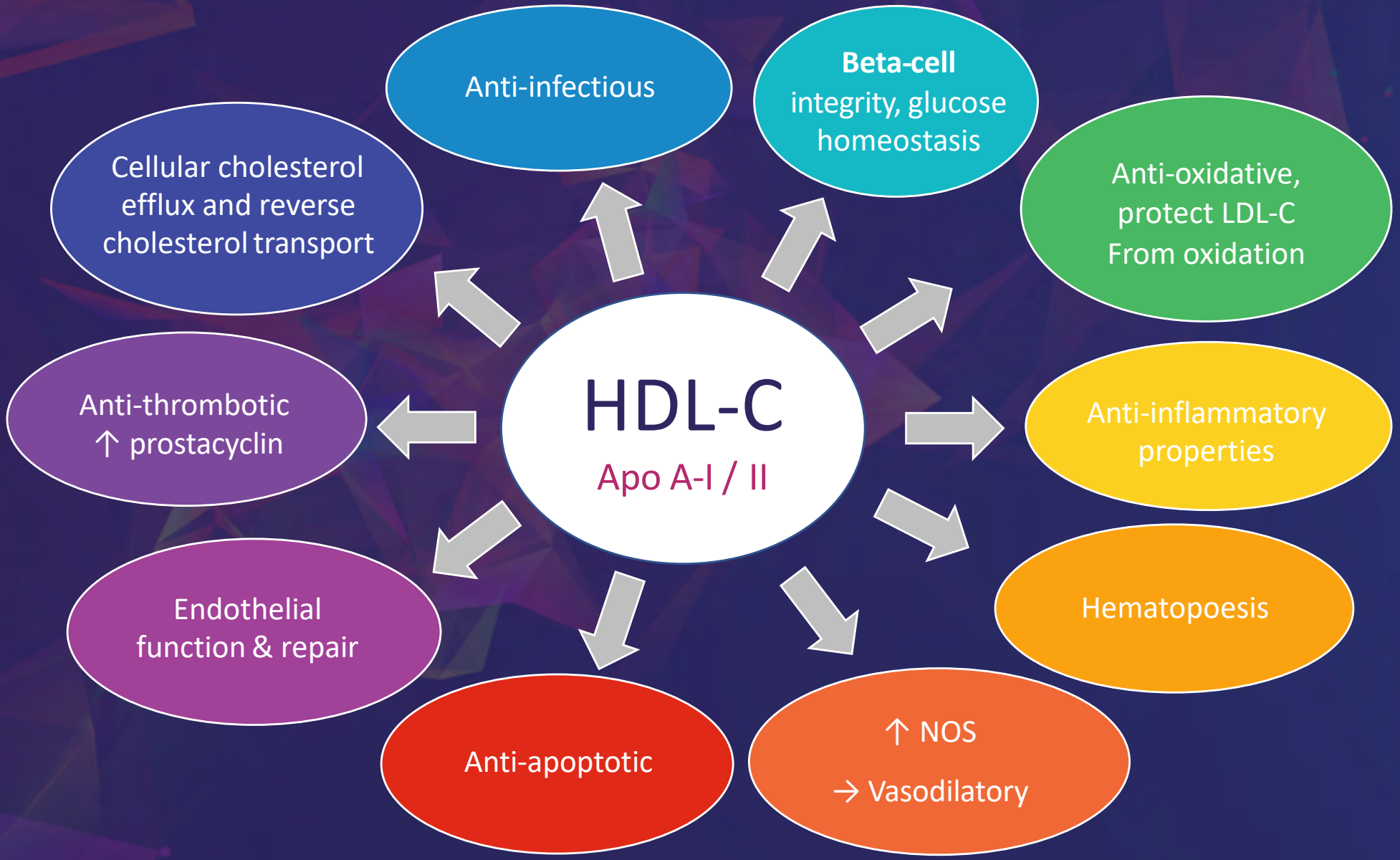
HDL-P Predicts Benefit (Reduction of Coronary Events) Better Than HDL-C in Adjusted Analyses



HDL-C = high-density lipoprotein cholesterol; HDL-P = high-density lipoprotein particle; HPS = Heart Protection Study; LDL-C = low-density lipoprotein cholesterol; JUPITER = Justi cation for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MESA = Multi-Ethnic Study of Atherosclerosis; VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial.

1. Otvos J, et al. *Circulation.* (2006) 113:1556-1563.
2. Parrish S, et al. *Circulation.* (2012) 125:2469-2478.
3. Mackey R, et al. *JACC.* (2012) 60(6):508-516.
4. Mora S, et al. *AHAJournals.* (2013):1189-1197. doi: 10.1161/circulationaha.113.002671.

HDL Complexity: Anti-Atherogenic Actions



Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = high-density lipoprotein cholesterol; NOS = not otherwise specified.

Modified from Chapman M, et al. *Curr Med Res Opin*. (2004) 20:1253-1268.
Assmann G, et al. *Annu Rev Med*. (2003) 53:321-341.

Non-HDL Cholesterol and Apo B

AACE 2017 Non-HDL-C Risk Categories and Treatment Goals

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

NR=not recommended.
AACE = American Association of Clinical Endocrinologists; ACS = acute coronary syndrome;
ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease;
CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein;
HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

1. Garber AJ et al. *Endocr Pract*. (2017) 23:207-38;
2. Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497.

Possible Explanations for Superiority of Non–HDL-C Over LDL-C for Predicting ASCVD Event Risk

- Like LDL-C, some TG-rich lipoprotein remnants enter the arterial wall and contribute to atherosclerosis initiation and progression.
- Non–HDL-C correlates more closely than LDL-C with apo B and, thus, more closely correlates with the total burden of atherogenic particles.
- Elevated levels of TG and VLDL-C reflect hepatic production of particles with greater atherogenic potential (such as those with poor interactivity with hepatic receptors); this results in a longer residency in circulation.

ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; VLDL-C = very-low-density lipoprotein cholesterol.

Bays H, et al. *J Clinical Lipidology*. (2014) 8:S1-S36.

NLA Recommendations: Non-HDL-C as a Target of Lipid-Altering Therapy

- Non-HDL-C treatment goal for participants at low, moderate and high ASCVD risk is <130 mg/dL.
- Non-HDL-C treatment goal and is <100 mg/dL for participants with ASCVD and very high risk.
- Non-HDL-C comprises cholesterol carried by all potentially atherogenic particles:
  - LDL
  - IDL
  - VLDL and VLDL remnants
  - chylomicron remnants
  - lipoprotein (a)

ASCVD = atherosclerotic cardiovascular disease;
HDL-C = high-density lipoprotein cholesterol;
IDL = intermediate-density lipoprotein;
LDL-C = low-density lipoprotein cholesterol;
VLDL = very-low-density lipoprotein.

Jacobson T, et al. *J Clin Lipidol.* (2014) 8:473-488.

Targets of Therapy: Apo B

- Provides an assessment of total atherogenic particle burden that is equivalent or superior to LDL-C, non-HDL-C, or other cholesterol ratios in predicting ASCVD risk
- More closely associated with insulin resistance syndrome than LDL-C or non-HDL-C, and more closely associated with central adiposity, thrombosis, and inflammation than non-HDL-C
- Potential contributor to lipoprotein-related residual risk; may remain elevated in some individuals at LDL-C and/or non-HDL-C goal
- Apo B and/or an Apo B/Apo A1 ratio is useful to assess residual risk in at-risk individuals: TG ≥150, HDL-C <40, prior ASCVD event, T2D, and/or insulin resistance syndrome
- Can be accurately measured in the non-fasting state

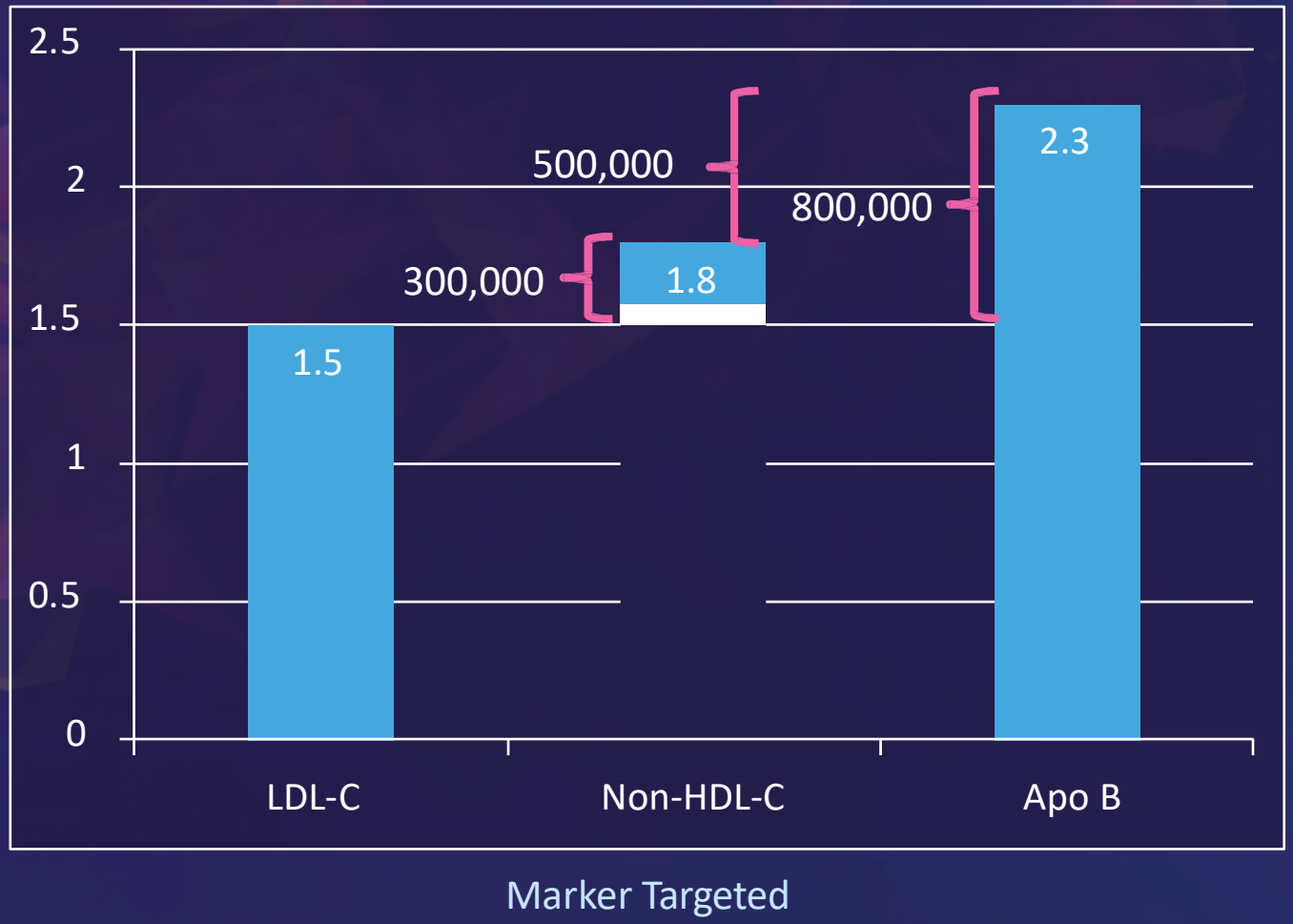
Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; T2D = type 2 diabetes.

Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497.

CVD Events Prevented in High-Risk U.S. Adult Population, According to Atherogenic Marker (LDL-C, Non-HDL-C, and Apo B)

Meta-analysis of CV risk markers in 15 independent published analyses (N=233,455)
CVD events over 10 years prevented by a high-risk treatment regimen

Over a 10-year period, a non-HDL-C strategy would prevent 300,000 more events than an LDL-C strategy; an Apo B strategy would prevent 500,000 more events than a non-HDL-C strategy



Apo = apolipoprotein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Sniderman A, et.al. *Circ. Card. Qual. Outcomes.* (2011) 4:337-345.

AACE 2017 Apo B Risk Categories and Treatment Goals

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

NR = not recommended.
AACE = American Association of Clinical Endocrinologists; ACS = acute coronary syndrome; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

1. Garber AJ et al. *Endocr Pract*. (2017) 23:207-38;
2. Jellinger P, et al. *Endocr Pract*. (2017) 23(4):479-497.

Summary

- Multiple ‘lipid’ risk factors contribute to a patient's total CV risk profile, including residual risk.
- LDL-C remains the primary target for reducing CV risk, but it should not be the sole focus of lipid management.
- There is merit in reducing TG, but by how much TG should be lowered remains to be determined.
- Low HDL-C is an important but complex risk factor; raising HDL-P cholesterol content appears to have no benefit; increasing the number of functional HDL-P may have benefit.
- Lowering LDL-C (and non-HDL-C, Apo B, and LDL-P) have the greatest proven benefit, but by how much needs to be determined.

Apo = apolipoprotein; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HDL-P = high-density lipoprotein particle; LDL-C = high-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle.